Editorial

Solitary pure ground-glass nodules measuring 5 mm or less: current imaging management, question and suggestion

Li Fan, Shi-Yuan Liu

Department of Radiology, Changzheng Hospital, Second Military Medical University, Shanghai 200003, China

Correspondence to: Shi-Yuan Liu, M.D. Department of Radiology, Changzheng Hospital, Second Military Medical University, No. 415 Fengyang Road, Shanghai 200003, China. Email: cjr.liushiyuan@vip.163.com.

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With great interest we read the article by Dr. Kakinuma *et al*. (1) entitled 'solitary pure ground-glass nodules 5 mm or smaller: frequency of growth', which was published on *Radiology* on Apr 23, 2015. During consecutive 46 months of lung cancer screening with computer tomography (CT), 439 solitary pure ground-glass nodules (SPGGNs) 5 mm or smaller were identified at baseline screening among 7,249 participants. Through no less than 5-year CT follow-up, they concluded that approximately 10% (45 of 439) of SPGGNs 5 mm or smaller detected at CT screening would grow. Approximately 1% (4 of 439) of these SPGGNs 5 mm or smaller would develop into invasive adenocarcinomas or minimally invasive adenocarcinomas. They also recommended that SPGGNs 5 mm or smaller should be rescanned 3.5 years later to look for development of a solid component. They provide an evidence-based follow-up time point for patient care.

With the development of lung cancer screening using low-dose CT, more and more small ground glass opacity (GGO) have been detected (2). GGO is defined as an area of a slight homogeneous increase in density, which does not obscure underlying bronchial structures or vascular margins on high-resolution CT (HRCT) (3). Pathologically, GGO may be caused by partial airspace filling, interstitial thickening with inflammation, edema, fibrosis, neoplastic proliferation, the normal respiratory condition or increased pulmonary capillary blood volume (4). According to the presence of solid components, GGO can be classified into pure GGO (pGGO) and mixed GGO (mGGO). Both of them can be called subsolid lesion. Appropriate and effective management of GGO is very important to increase survival rate, improve life quality of patients, and reduce lung cancer mortality.

Based on the new IASLC/ATS/ERS classification of peripheral pulmonary adenocarcinomas (5), the majority of pGGNs 5 mm or less is atypical adenomatous hyperplasia (AAH). AAH maybe progress to adenocarcinoma *in situ*, and to invasive carcinoma stepwisely. However, the frequency of AAH progressing into MIA or IA is unknown. Moreover the doubling time of pGGO is on the order of 3-5 years on average. Due to the small size, the precision measurement of interval growth is limited with current measuring methods. Based on above three reasons, the Fleichner Society recommends SPGGNs measuring 5 mm or less do not require follow-up surveillance CT examinations (6). Although the Fleichner Society recommendations for the management of subsolid nodules were based on more than a decade's studies; it does not apply to the lung cancer screening (6). Moreover, further data from National Lung Cancer Screening Trial that may affect management strategies for subsolid nodules have yet to be analyzed (6). In the study by Dr. Kakinuma (1), the cohort was the lung cancer screening population and the frequency of SPGGN progressing to adenocarcinoma was 1%, which may be overestimated. Some participants were excluded due to without follow up or follow-up period less than 5 years. This finding indicates that SPGGN 5 mm or smaller detected on lung cancer CT screening requires CT follow-up 3.5 years later, which is helpful to provide the evidence-based data to the following revision of the recommendation. A worldwide big data of lung cancer CT screening is necessary. However, the management of SPGGN 5 mm or less depends on the national medical environment to some extent. In the consensus on the imaging management of subsolid nodules of Chinese Society of Radiology (7), SPGGN 5 mm or less

requires low dose CT follow-up 2 years later, if no change, recommend low dose CT follow-up 4 years later since the baseline scanning. If the patient is very nervous, the follow-up period can be shortening. It is recommended 1st round is about 6-12 months, if no change, the 2nd round is 2 years later. However, the results of this management have not been evaluated in China.

Fleichner Society defined nodule size as the average of the long and short axial dimensions on transverse CT sections (6). In the materials and methods part of the article by Dr. Kakinuma (1), they evaluated three dimensional diameter of nodule and found transverse size did not always reflect the growth of nodule. This finding indicates that any dimensional change should be considered on the evaluation of nodule interval growth. Nodule volume is more precise on the assessment of interval growth. However, measurement of such small size may be some discrepancies using current technique. Automatic volumetric measurement is expected to overcome the discrepancies in the near future. At present, the Chinese expert consensus recommends the average of longest and perpendicular diameter on the maximum plane of any dimension may be more meaningful to evaluate nodule size (7).

GGN is heterogeneous entity, even the pure ground-glass nodule (pGGN). The mGGO is defined as the presence of solid component. The solid component can be viewed with mediastinal window settings (WW 350, WL 40). However, in clinical routine work, many GGNs manifest as'solid' component obscuring the underlying lung structure with lung window settings (WW 1500, WL −450), but cannot be viewed with mediastinal window settings. The classification of such GGNs is controversial. According to Fleichner Society definition, these nodules should be classified into pGGNs. The current guidelines of the Japanese Society for CT screening define the size of a solid component in a part-solid nodule as the maximal diameter when viewed with the lung window setting (8), which is different from that of Fleichner Society with mediastinal window settings. The size of solid component may be different at different window settings. Therefore, the heterogeneous entity or solid component has not been reached consensus. The density of GGNs should be evaluated comprehensively. The subjective visual evaluation of the solid component may be not reliable. How to quantitate the density distribution and proportion within a special density range is very important for the classification of GGNs. The Chinese lung cancer screening trial in Shanghai is performing the quantitative GGN density analysis, trying to make a quantitative standard for the classification of GGNs based on the density at different window settings and the pathological types. Other lung cancer screening trials will also provide more data and help to evaluate GGNs comprehensively.

We would like to congratulate Dr. Kakinuma *et al*. for their work, which indicates the controversy and indeterminacy on the management and evaluation of GGNs. Ongoing and future big data research on GGNs will draw a more consistent and determinate guidelines or recommendation.

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Footnote

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