Persistent pulmonary subsolid nodules: How long should they be observed until clinically relevant growth occurs?

Eui Jin Hwang[1], Chang Min Park[1,2]

[1]Department of Radiology, Seoul National University College of Medicine, and Institute of Radiation Medicine, Seoul National University Medical Research Center, Seoul, Korea; [2]Cancer Research Institute, Seoul National University, Seoul, Korea
Correspondence to: Chang Min Park, MD, PhD. Department of Radiology, Seoul National University College of Medicine, 101, Daehak-ro, Jongno-gu, Seoul 03080, Korea. Email: cmpark.morphius@gmail.com.
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During the first two decades of 21st century, there has been remarkable advance in the knowledge about lung cancer. One of the most important advances is persistent pulmonary subsolid nodules (SSNs) including pure ground-glass nodules (GGNs) and part-solid nodules (PSNs). Pulmonary SSNs, when persistent, have high probability of being pulmonary adenocarcinomas spectrum pathologically, and ironically show very indolent clinical courses over follow-ups (1-3). Many researchers investigated the natural history of persistent pulmonary SSNs, which included the frequency and pattern of interval growth, and the growth rate, to determine optimal management plan of patients with these nodules (4-8). However, uncertainty still remains on the natural course of persistent SSNs, especially with respect to the long-term consequences and ideal timing for surgical resection.

Recently, Tang *et al.* reported a noteworthy article regarding the natural history of SSNs (9). In this single-center, retrospective study, the authors included 128 persistent SSNs (93 pure GGNs and 35 PSNs) 3 cm or smaller from 128 participants, and reported their observation during long term follow-ups (average of 3.6 years, maximum follow-up period of 12 years). This study was novel in that the authors subdivided the growth of SSNs into three categories: (I) true SSN growth, defined as increase of whole lesion diameter or solid component diameter of ≥2 mm, or new solid component of ≤2 mm

within the previous pure GGN, from the baseline CT scan; (II) substantial SSN growth, defined as increase of whole lesion diameter or solid component diameter of ≥5 mm, from the baseline CT scan; and (III) stage shift, defined as detection of the specific shift to different T-categories or TNM stages according to the seventh edition of TNM staging system on follow up CT scan (10), compared with the initial CT scan. Determination of the growth of SSNs is not a simple task because there is considerable intra- and inter-observer variability in measurement of SSNs, not only for the size of whole lesion, but also for the size of solid component (11-13). Most of previous studies investigating natural history of SSNs defined the threshold of growth as 2 mm increase in size, either for whole lesion diameter or solid component diameter (4-8,13,14). By extending the threshold of growth to 5 mm and shift in T-categories/cancer stages, Tang *et al.* provided new and interesting insight in natural history of SSNs, because minimal growth of 2 mm of SSN may not necessarily indicate progression to invasive disease or necessity of surgical intervention, especially for pure GGNs.

In this study, pure GGNs exhibited median progression times of 7, 9, and 12 years for true growth, substantial growth, and stage shift, respectively, which may justify longer follow-up intervals for pure GGNs than those suggested by guidelines (15,16). Fleischner Society guideline for management of incidental pulmonary nodules

recommends biennial CT follow-up for pure GGNs (15). However, the interval can be further delayed without concern of substantial growth or stage shift, considering the results of this study. Actually, in a recent study, simulation analyses with follow-up CT intervals of 1-, 2-, and 3-year for pure GGNs showed similar outcome in terms of survival (17). For PSNs, the study reported median progression times of 3, 3, and 9 years for true growth, substantial growth, and stage shift, respectively, which is much shorter than those of pure GGNs, but still indicating indolent behavior. Several previous studies reported more indolent behavior of PSNs with small solid component (i.e., solid part size of 5 mm or smaller) (8,18), and they suggested more conservative management strategy with biennial follow-up after first annual follow-up CT can be applied in those PSNs with small solid components in this context (8,19).

Another important information in this kind of research is risk factors or predictors of growing SSNs. Although it is now generally accepted that adenocarcinomas manifested as SSNs have indolent natural course (14,19,20), the clinical behavior of individual SSN can be diverse. In this study, for example, the time interval to substantial growth varied from 3 to 12 years for pure GGNs, and from 1 year to 7 years for PSNs. Therefore, identification of SSNs with high risk for growth and progression to higher stages is critical in the clinical decision making of these nodules. Risk factors for SSNs' growth have been reported to include old age, male, larger whole lesion size or larger solid component size, presence of solid component, and history of previous lung cancer (5,6,8,21,22). The current study also demonstrated PSNs showed interval growth more frequently and their time to progression was much shorter.

The authors claimed that reaching threshold of substantial growth can be the optimal timing for surgical resection. This is an interesting suggestion, however we have a somewhat different opinion on this issue. Actually, we believe the size of solid component is more critical determinant for surgical resection rather than the occurrence of growth. The solid component within PSNs reflects the pathological invasive component of adenocarcinoma (23), and is one of the most important prognostic indicators in lung cancers manifested as PSNs (11), which was incorporated in the recent version of TNM staging system (24). The current management guidelines also indicate PSNs with solid component of 6mm or greater as highly suspicious lesions (15,16).

Possibility of underlying selection bias should be

considered when interpreting this kind of retrospective study. In this study, 5-year growth rate in terms of true growth (35.5% for pure GGNs and 67.3% for PSNs) was much higher compared with a previous multicenter prospective study [14% for pure GGNs and 48% for PSNs (only including lesions with visible solid component on mediastinal window)] (6). SSNs included in this study may have been more aggressive in nature, compared with previous studies. Furthermore, surgical excision rate (48.4%, 62/128) was quite high, exceeding the number of cases exhibited true SSN growth. Due to the resected cases of SSNs before growth, there can be possibility of underestimation of their time to growth and overestimation of the growth rate of included SSNs.

Another important pitfall in interpreting the time to growth in a retrospective study is that CT follow-up intervals are not standardized or uniform. Sometimes, it may be impossible to know the exact time point of growth. In this context, calculation of the growth rate based on follow-up CTs can be an alternative method to evaluate the growth of SSNs (18).

Lastly, it should be mentioned that the stage shifts of SSNs in this study was defined according to the 7th edition of TNM staging system, which measures entire nodule size of SSNs, rather than solid component (10). Therefore, the results regarding the time to stage shift cannot be directly applied in the current standard of management.

In spite of various researches to answer the questions about the natural history of SSNs, generalization of their results is still limited because they were mostly retrospective, single-center studies, which could be biased by different population, imaging and follow-up protocols, and definition of outcomes. Although there was a prospective, multi-center study, the population size was relatively small, especially for PSNs and surgically resected lesions, and management protocol was not fully standardized (6). To further investigate the natural history SSNs and to predict SSNs at risk of progression, large-scaled, multi-center prospective cohort study is definitely warranted.

In conclusion, to support the ideal clinical decision making in management of patients with SSNs, a thorough understanding of their natural history is essential, however several important questions remained unanswered.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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