

# Growth of pure ground-glass lung nodule detected at computed tomography

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**Abstract:** The natural history of pure ground-glass nodules (GGNs) of the lung has been gradually revealed. Approximately 10-25% of pure GGNs increases in size or grow the solid component, while others remain unchanged for years. Further investigations including the relationship between the successive change on computed tomography (CT) and the molecular change may be necessary to determine the appropriate management strategy of pure GGNs.

**Keywords:** Lung cancer; computed tomography (CT); adenocarcinoma; ground-glass opacity (GGO); screening

Submitted Aug 19, 2015. Accepted for publication Aug 21, 2015.

doi: 10.3978/j.issn.2072-1439.2015.08.27

View this article at: <http://dx.doi.org/10.3978/j.issn.2072-1439.2015.08.27>

## Introduction

Ground-glass opacity (GGO) on computed tomography (CT) is defined as hazy increased attenuation of the lung, but with preservation of bronchial and vascular margins (1). Currently, adenocarcinoma is the most predominant histologic type of lung cancer in many countries and often appears as localized GGOs on CT (2,3). The adenocarcinoma GGO component can be a good predictor of histologic prognostic factors and the greater GGO on CT in peripheral adenocarcinoma correlates with the favorable prognosis (4,5).

A close relationship between lung adenocarcinoma CT findings and pathologic findings has previously been reported. The GGO at CT in pathologically proved lung adenocarcinomas mostly reflects a lepidic growth pattern with a relative lack of acinar filling (6). According to the new IASLCA/ATS/ERS lung adenocarcinoma classification (7), a tumor with a pure GGO component is likely preinvasive lesions (atypical adenomatous hyperplasia, adenocarcinoma in situ) and minimally invasive adenocarcinoma. Lepidic predominant invasive adenocarcinoma is usually characterized on CT as nodules with both GGO and solid components (part-solid GGO nodules) or solid nodules (8). However, confident CT differentiation between these adenocarcinoma histologic subtypes is not yet possible.

The doubling time for most malignant nodules is between 30 and 400 days. The absence of growth of solid nodule over at least a 2-year period is generally considered to be a reliable indicator of benignity. However, lung adenocarcinomas showing a large GGO lesion on CT often doubles more slowly than most malignant nodules. Small adenocarcinomas showing as pure ground-glass nodules (GGNs) often exhibit no change in size over a 2-year period.

Recognition of the natural history of pure GGN is essential to discuss the appropriate management because it is unclear whether pure GGN should be surgically resected and the conservative follow-up is the main management option of them. Recently several interesting studies were published regarding with growth of pure GGNs.

## Natural history of pure GGN on CT

Kakinuma *et al.* investigated 7,294 participants who underwent screening for lung cancer with CT imaging, and reported that 438 solitary pure GGNs 5 mm or smaller were identified in baseline screening, and one new solitary pure GGN 5 mm or smaller developed *de novo* (9). Of the 439 pure GGNs, 45 (10.3%), including newly developed pure GGN, grew and 4 (0.9%) developed into adenocarcinomas. In all

4 adenocarcinomas, the appearance of the solid component (non GGO area) occurred on follow-up CT. The mean period between baseline CT screening and the appearance of solid components in the 4 adenocarcinomas was 3.6 years. They concluded that solitary pure GGNs 5 mm or smaller detected by using CT screening should be rescanned 3.5 years later to look for development of a solid component.

Although the inclusion criteria and the definition growth are not identical, there are other recent reports regarding growth of pure GGNs. Chang *et al.* evaluated 122 pure GGNs with a median size of 5.5 mm (range, 3-20 mm) and the frequency of growth was 9.8% (12 of 122 nodules; 5 of the 12 pure GGNs had a maximal diameter that was 5 mm or smaller) (10). In this study, the median volume doubling time was 769 days (2.1 years) for growing pure GGNs. In 2 of the 12 nodules, the appearance of the solid component (non GGO area) occurred on follow-up CT. A total of 11 growing GGNs were surgically validated, and all lesions were confirmed as primary lung cancer. Matsuguma *et al.* assessed 98 pure GGNs less than 20 mm and the frequency of growth was 14.2% (14 of 98 nodules) (11). In this study, the appearance of the solid component (non GGO area) was occurred on follow-up CT in 9 of the 14 nodules. All resected GGNs which showed growth and appeared as part-solid nodules on final CT, were malignant tumors with only one exception of an atypical adenomatous hyperplasia case. Kobayashi *et al.* estimated 82 pure GGNs less than 30 mm and the frequency of growth was 25.6% (21 of 82 nodules) (12). In this study, the appearance of the solid component (non GGO area) was occurred on follow-up CT in 13 of the 21 nodules and all the growing GGNs began to grow within 3 years of their first observation. Lee *et al.* investigated 143 pure GGNs (mean size 7.0±3.4 mm) and the frequency of growth was 19.6% (28 of 143 nodules) (13). In this study, the appearance of the solid component (non GGO area) occurred on follow-up CT in 11 of the 28 nodules. The authors stated that GGOs which persisted for several years showed an indolent course and resection should be considered if GGOs show character changes from pure to part-solid, as these may be associated with rapid size progression.

### Summary and comments

As described above, the natural history of pure GGNs has been gradually revealed. Approximately 10-25% of pure GGNs increases in size or grow the solid component, while others remain unchanged for years. At least 3 to 4 years

observation seems to be necessary to determine whether GGN with tendency of growth or that without growth. When evaluating the growth of pure GGNs on CT, careful assessment of the GGO size and the solid component appearance is necessary.

Factors affect the progression of pure GGN have not been fully clarified until now and it is unclear whether all pure GGNs should be followed. The Fleischner Society does not recommend follow-up for incidentally detected solitary pure GGNs 5 mm or smaller if the CT image reconstructed in contiguous 1-mm-thick sections to establish the lesions as true GGNs at this time, and the main reason for this is that many of these GGNs probably represent atypical adenomatous hyperplasia which is typically stable or very indolent over many years and the morphological change assessment of small GGNs is problematic (14). On the other hand, invasive adenocarcinoma is believed to progress from preinvasive lesions including atypical adenomatous hyperplasia possibly by a stepwise progression (7). We reported that lung adenocarcinomas with a predominant GGO often possess EGFR mutations, and interval increase in the solid component is linked to P53 alteration (15). Further studies regarding the relationship between the successive changes on CT and the molecular changes in greater depth may help to determine the appropriate management strategy of pure GGNs.

### Acknowledgements

None.

### Footnote

*Provenance:* This is a Guest Editorial commissioned by the Guest-Editor Lihua Chen [Department of Radiology, Taihu Hospital (PLA 101Hospital), Wuxi, Jiangsu, China].

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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**Cite this article as:** Aoki T. Growth of pure ground-glass lung nodule detected at computed tomography. *J Thorac Dis* 2015;7(9):E326-E328. doi: 10.3978/j.issn.2072-1439.2015.08.27