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# The association between baseline clinical–radiological characteristics and growth of pulmonary nodules with ground-glass opacity

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ABSTRACT

*Introduction:* Pulmonary nodules with ground-glass opacity (GGO) are frequently encountered; there is little consensus on appropriate monitoring of them. The purpose of this study was to clarify which baseline clinical and radiological characteristics were associated with growth of these nodules.
*Methods:* We retrospectively studied patients with pulmonary nodules that met the following criteria: (1) lesion diameter of ≤3 cm, (2) GGO proportion of ≥50%, and (3) observation without treatment in the prior 6 months. Between 1999 and 2013, 120 pulmonary lesions in 67 patients fulfilled inclusion criteria. We evaluated changes in lesion size on serial computed tomography. Two endpoints, "time to 2-mm growth" and "incidence of 2-mm growth", were analyzed using Cox proportional hazards and logistic regression models, respectively.
*Results:* At the median observation period of 4.2 years, 34 lesions exhibited growth by ≥2 mm, whereas 86 remained unchanged. Smoking history and initial lesion diameter were statistically significant variables in both time-to-event and regression analyses. Hazard ratio (HR) for smoking history was 3.67 ($P < 0.01$). Compared with those ≤1 cm, HRs for 1.1–2 cm and 2.1–3 cm lesions were 2.23 ($P = 0.08$) and 5.08 ($P = 0.04$), respectively. Odds ratio (OR) for smoking history was 6.51 ($P < 0.01$); OR for lesion diameter of 1.1–3 cm (versus ≤1 cm) was 4.06 ($P = 0.02$).
*Conclusion:* Smoking history and initial lesion diameter are robustly associated with GGO growth. These results suggest that large GGOs, especially in smokers, warrant close follow-up to accurately monitor lesion growth.



## 1. Introduction

Pulmonary nodules with ground-glass opacity (GGO), hazy lesions seen on high-resolution computed tomography (CT) that obscure neither underlying bronchial structures nor pulmonary vessels [1], are frequently observed on both diagnostic and screening images. Anticipated increases in CT use, promoted by recent results from studies such as the National Lung Screening Trial, will likely result in more identification of GGOs [2]. These lesions are observed in a wide variety of clinical contexts, including both malignancy, as well as benign conditions such as focal interstitial fibrosis, inflammation, and hemorrhage [3]. In addition to those that are small or technically inaccessible, lesions may be multiple, and are often not amenable to comprehensive resection.

Several recent reports on the natural history of GGO have clarified that 10 to 27% of lesions exhibit gradual growth, while others persist unchanged for years [4–7]. In order to identify only those malignant lesions which require surgical resection, avoiding unnecessary surgery for stable, benign lesions, it is important to optimize monitoring and follow-up. A GGO proportion of 50% or more has been suggested as a cutoff value for pathological non-invasiveness; several retrospective studies reported that, in ≤3 cm lesions with GGO component <50%, the rate of lymph node metastasis ranges from 21 to 26% [8–10], while one multi-institutional prospective study reported that the specificity for the diagnosis of

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pathological invasiveness were 96.4% for adenocarcinoma ≤3 cm with GGO component >50% [11]. Therefore, we focused on pulmonary nodules with GGO proportion ≥50%. Based on a sample of 108 pulmonary nodules of ≤3 cm and exhibiting a GGO component of ≥50%, we previously reported that GGO lesions meeting these specifications require at least 3 years of follow-up to accurately evaluate growth [7].

However, it remains unclear whether all GGOs should be followed for as long as 3 years. To establish a reasonable monitoring plan, it is useful to be able to predict which GGO lesions may be predisposed to growth by any of clinical–radiographic characteristics. The purpose of this study was to clarify which baseline clinical and radiological characteristics were associated with subsequent GGO growth.

## 2. Patients and methods

### 2.1. Patient cohort

We retrospectively studied patients with pulmonary nodules who met the following criteria: (1) lesion diameter of ≤3 cm; (2) GGO proportion of ≥50%; and (3) observation without treatment in the prior 6 months. First, we collected list of outpatients with GGO from all physicians in our department and identified 31 patients who met inclusion criteria. Next, we extracted 36 candidates from a database of surgery patients with lung cancer, in which 2331 cases were registered between January 1999 and February 2013. In total, we identified 120 pulmonary lesions in 67 patients fulfilling the inclusion criteria in our institution. These lesions were initially detected from a variety of clinical situations: 40 lesions were found during routine screening, 27 were found on preoperative CT examination of an unrelated pulmonary lesion, 14 were found on routine follow-up CT after pulmonary resection, and 39 were found during CT examination for unrelated extrapulmonary disease. In addition to radiologic characteristics of these lesions, we collected and reviewed baseline clinical characteristics of these patients. The institutional review board at our institution approved all aspects of this study; as all CT imaging was performed during routine medical care, requirements for individual patient consent were waived.

### 2.2. Radiological evaluation of the lesions

CT examinations were performed with a window level of 500 to 700 Hounsfield units (HU) and a window width of 1000–2000 HU on lung window settings. Images were acquired with the use of a multi-detector CT at 2-mm thicknesses, except in 9 lesions, in which single-detector CT imaging at 5-mm thicknesses was performed during early follow-up. In patients with multiple lesions at first presentation, only those lesions meeting the above-mentioned criteria were included.

The maximum diameter of each lesion on lung window was measured. We defined growth as a ≥2 mm increase in diameter, based on a prior report by Kakinuma et al. stating that a diameter increase of >1.72 mm is necessary to reliably identify growth considering interobserver measurement errors [12]. We scored the GGO ratio by visually estimating the proportion of GGO component in each lesion without measuring the diameter; solid proportions were categorized into 3 groups: 0%, 1–25%, or 26–50% [13]. GGO was defined as an area with a slight, homogenous increase in density, not obscuring underlying vascular markings [11]. We evaluated all CT images during the follow-up period and analyzed changes in size over time. Intervals between CT examinations were at the physician's discretion, ranging from 3 to 12 months.

### 2.3. Statistical analyses

To evaluate the association of baseline clinical and radiological characteristics with GGO growth, we performed two independent analyses. First, "time to 2-mm growth" was assessed for each lesion; univariate and multivariate analyses using the Cox proportional hazards model were performed. Measures of association were reported as hazard ratios (HR) with 95% confidence interval (CI). Time to 2-mm growth curves were estimated using Kaplan–Meier method and differences were compared using the log-rank test. Variables for univariate analysis were as follows: age, dichotomized at a median of 60 years; gender; smoking history (ever versus never); past history of lung cancer; lesion multiplicity (single versus multiple); lesion diameter (≤1 cm versus 1.1–2 cm or 2.1–3 cm); and solid proportion (0% versus 1–25% or 26–50%). Lesion diameter was dichotomized at the median value, as well as by tumor–node-metastasis classification of the International Union Against Cancer, 7th edition [14]. Except for lesion diameter and solid proportion, other variables were defined in the same fashion as those in previous reports on predictors of GGO growth [4,5]. Factors for which *P*-value was <0.05 in univariate analysis, as well as past history of lung cancer which has been previously reported as a predictor, were included in multivariate analysis [4,5]. Given that patients with multiple lesions would be overrepresented, we subsequently performed a subanalysis including only the largest lesion per patient.

Next, "incidence of 2-mm growth" was defined as an outcome, and univariate and multivariate analyses using the logistic regression model were performed. Measure of association was reported as odds ratio (OR) with 95% CI. To strictly define "no growth", we excluded lesions which had been observed for less than 3 years based on our previous report [7]. Given a consequently decreased number of lesions, two variables were changed as follows: lesion diameter was divided at the median (≤1 cm versus 1.1–3 cm), and solid proportion was dichotomized (0% versus 1–50%). Univariate analysis was performed between lesions with and without growth by the Chi-square test or the Fisher's exact test, as appropriate. Factors for multivariate analysis were determined via the same method as stated above.

All statistical analyses were performed with JMP version 8.0.2 (SAS Institute Inc., Cary, NC, USA). Differences were considered significant at a two-sided *P*-value of ≤0.05.

### 2.4. Pathological diagnosis

Pathological diagnosis was classified according to the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma [15].

## 3. Results

### 3.1. Baseline characteristics of patients and pulmonary lesions

Characteristics of 120 pulmonary lesions observed at initial presentation in 67 patients are shown in Table 1. Approximately two-thirds of patients were women and never-smokers. At the time of initial observation, 18 patients (27%) had a past history of lung cancer. The histologic diagnoses of previously resected lesions included adenocarcinoma in 13 patients and preinvasive lesions, including atypical adenomatous hyperplasia (AAH) and adenocarcinoma in situ (AIS), in 5 patients. Median lesion size was 0.9 cm (range, 0.4–2.4 cm). Approximately three-fourths of lesions were purely GGO, exhibiting no solid component.