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# Computed tomography attenuation predicts the growth of pure ground-glass nodules

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ABSTRACT

*Objectives:* Cases of lung cancer with pure ground-glass nodules (GGNs) have been detected with increasing frequency since the advent of computed tomography (CT), and growth is sometimes noted during follow-up. The objective of this study was to evaluate the potential predictive factors for pure GGN growth.

*Materials and methods:* We retrospectively examined 124 cases involving pure GGNs. Patients were monitored for >2 years using high-resolution CT. After a median follow-up period of 57.0 months, GGNs showed growth in 64 of the 124 cases. We compared the patient characteristics and tumor properties of cases with and without growth. The predictive value of the mean CT attenuation for GGN growth was evaluated using receiver operating characteristic curve analysis.

*Results:* Univariate analysis revealed significant differences between mean CT attenuation values in patients with and without growth ($-602.9 \pm 90.7$ Hounsfield units [HU] vs $-705.7 \pm 77.7$ HU, $P < 0.0001$). The final incidence of growth was estimated to be significantly higher for lesions with a mean CT attenuation value of $\geq -670$ HU ($n = 62$; 93.2%) than for lesions with values of $< -670$ HU ($n = 62$; 31.6%; $P < 0.0001$). The sensitivity and specificity for predicting tumor growth using this cutoff value were 78.1% and 80.0%, respectively (area under the curve, 0.81).

*Conclusion:* The mean CT attenuation value could be useful in predicting the growth of GGNs.



## 1. Introduction

We previously evaluated the usefulness of computed tomography (CT) as a screening tool for lung cancer [1,2]. Cases of lung cancer involving ground-glass nodules (GGNs) have been detected with increasing frequency since the advent of CT. However, the natural history of GGNs has not yet been fully elucidated. Pulmonary adenocarcinomas, which often present with GGNs during radiologic investigation, regularly show involvement of neoplastic cells on histologic examination. These neoplastic cells are usually distributed along pre-existing alveolar structures in a pattern referred to as a "lepidic growth pattern" [3]. It is thought that pulmonary lepidic growth tumors progress in a stepwise fashion from adenocarcinoma in situ to invasive adenocarcinoma [3,4]. Previous studies have reported cases in which pure GGNs progressed [5–7], and long-term follow-up investigations gradually elucidated the natural history of pure GGNs [8–11]. Recently, the Fleischner Society published recommendations for the management of subsolid pulmonary nodules detected on CT [12]. However, it is not yet possible to ascertain which GGNs will progress to solid tumors, and there are no known prognostic factors that can predict the growth of adenocarcinoma from a non-invasive to an invasive type.

To address the current lack of knowledge regarding the natural history of GGNs, we retrospectively reviewed the characteristics

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and CT findings of patients with pure GGNs who were followed up for a long period of time (>24 months).

## 2. Patients and methods

### 2.1. Patients

This retrospective study was approved by the institutional review board of Shinshu University Hospital, Matsumoto, Japan, and conducted in accordance with principles outlined in the Declaration of Helsinki.

Between September 1998 and September 2013, we identified 152 patients who were diagnosed with pure GGN at the Shinshu University Hospital, and these patients were followed up for more than 24 months after the initial diagnosis. During this period, we used three types of CT scanners for the diagnosis of GGNs: Hispeed Advantage RP (GE Healthcare), from September 1998 to January 2003; Light Speed Ultra (GE Healthcare), from January 2003 to December 2007; and then Light Speed VCT Vision (GE Healthcare), from December 2007 onwards. GGNs were detected either by low-dose CT screening (45 patients), routine follow-up CT for previously resected lung cancer (70 patients), routine follow-up CT for other malignant diseases (13 patients), or CT for the investigation of a non-malignant disease (24 patients). Of these 152 patients, 28 patients were excluded from our analyses because GGNs in these cases were analyzed using CT slices thicker than 1.25 mm. The remaining patients ($n = 124$) were enrolled in this retrospective investigation. The GGNs of these 124 patients were detected between February 2003 and July 2011 and could be analyzed by 1.25-mm-slice, high-resolution CT (HRCT). HRCT surveillance was repeated annually, or more frequently in some cases.

The follow-up duration was defined as the period from the date of pure GGN confirmation by HRCT to the date of the most recent HRCT. In total, 34 of the enrolled patients received surgical or radiological therapies for the treatment of GGN. The follow-up period for these patients was defined as the time from the first confirmation of pure GGN to the date of the CT procedure immediately prior to the start of treatment.

### 2.2. Radiological definition

All CT procedures were performed at our institute, and full resolution of 1.25-mm-thick sections was obtained without the use of contrast media. CT scans were viewed at WL-550 Hounsfield units (HU) and WW1500 HU at a computer workstation. Two experienced radiologists, who were unaware of the patients' clinical information, interpreted the scans independently (the radiologists ST and MM had 17 and 10 years of experience as specialists, respectively). Pure GGN was defined as a hazy increase in lung attenuation with a diameter of $\geq$3 mm, but without a solid component. The latter was defined as a portion that could be detected in the mediastinal window setting (WL30 HU and WW400). The size of each lesion was defined as the average length of the long and short diameters [13] measured using the caliper tool of the software program. The growth of GGNs was defined as (1) an increase from baseline in the size of the GGN by at least 2 mm or (2) an emergence of a solid component. We decided to use a cutoff diameter value of 2 mm, in accordance with the value used in previous studies investigating GGNs [8,10]. In cases that presented with 2 or more GGNs, detected in both lungs and with diameters of $\geq$3 mm, the GGN lesion with the largest diameter or the lesion that showed changes on follow-up was included in our analyses. The mean CT attenuation value was measured using the region-of-interest (ROI) cursors, which traced the edge of the tumor using manual tracing juts along its internal edge, on the slices containing the region of the lesion with the greatest diameter (Fig. 1) [14]. Volume-doubling time (VDT) was based on the first and the last CT scans, calculated using the modified Schwartz equation [15,16]. The average values of the data recorded by the two radiologists were used for our statistical analyses. If the data differed between two radiologists by >2 mm in size or >50 HU in CT attenuation, the CT findings were reviewed and re-examined by two radiologists and a third investigator (TE).

### 2.3. Statistical analysis

To identify factors associated with tumor growth, the patients were divided into two groups. Patients in Group 1 had a GGN that enlarged and patients in Group 2 had a GGN that consisted of a non-solid nodule or that grew by less than 2 mm during the follow-up period. The two groups were compared with respect to the follow-up period, age, sex, smoking history, lung cancer history, tumor size, mean CT attenuation value, and the multiplicity of GGNs. Continuous variables were compared using the Mann–Whitney *U*-test, and categorical data were compared using Chi-square analyses. Multivariate analysis was performed using a multinomial logistic regression model.

Independent factors associated with the time to GGN growth were identified using a Cox proportional hazard model with a stepwise selection process. For this analysis, the original continuous variables were dichotomized at cutoff values for age (60 years), tumor size (7 mm), and mean CT attenuation value (−670 HU). The curve of the time to GGN growth for all patients was derived using the Kaplan–Meier method. The time-to-growth curves were derived for smoking history, tumor size, mean CT attenuation value, and GGN multiplicity. Differences between curves were evaluated using the log-rank test. Finally, a receiver operating characteristic (ROC) curve analysis was used to verify whether tumor size and the initial mean CT attenuation value could predict GGN growth.

All data are reported as the mean ± standard deviation, except for the observation period, VDT, and the time to tumor growth, which are presented as median values and ranges. Statistical significance was set at $P < 0.05$.

## 3. Results

### 3.1. Patient characteristics and tumor properties

GGNs were detected either by low-dose CT screening (32 patients), routine follow-up CT for previously resected lung cancer (58 patients), routine follow-up CT for other malignant diseases (13 patients), or CT for the investigation of a non-malignant disease (22 patients). Of the 124 patients enrolled in the study, 64 patients had GGNs that showed growth (Group 1), and 60 patients had GGNs that did not show signs of growth (Group 2) during the follow-up period. In Group 1, 40 GGNs showed emergence of a solid component with or without size increase, and 24 GGNs showed size increase without emergence of a solid component. The median follow-up period, age at GGN detection, sex, smoking history, lung cancer history, initial tumor size, and initial mean CT attenuation value for all patients are summarized in Table 1. For Group 1 patients, the VDT was 1203 days (range −61,075 to 4,344,231 days), and the median time from tumor detection to tumor growth was 38.0 months (range 3.1–80.0 months).

Thirty-four patients received treatment for GGNs. The median follow-up period for this group was 38.9 months (range 24.1–113.0 months). Surgical resection was performed in 33 cases (26 in Group 1 and 7 in Group 2). For the 26 patients in Group 1, the median duration from the confirmation of the tumor until surgery was