Pulmonary Ground-Glass Opacity (GGO) Lesions–Large Size and a History of Lung Cancer are Risk Factors for Growth

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Objective: Ground-glass opacity (GGO) of the lung is being frequently detected by thin section computed tomography scan. However, the long term management of detected GGO is still unclear. To establish follow-up plans, we performed the clinical and radiological review to identify the factors that are closely associated with GGO growth.

Methods: We retrospectively analyzed computed tomography images of 125 GGOs that were stable for 3 months between 1999 and 2006 at the Cancer Institute Hospital, Tokyo. To identify factors that affect the roentgenological growth, the time to GGO growth curve by Kaplan-Meyer method was evaluated in terms of gender, age, smoking, initial size, existence of a solid part, GGO density, location, multiplicity, and lung cancer history by univariate and multivariate analyses.

Results: The median observation period was 1048 days (177–3269) and 26 of 125 GGOs (21%) grew. The estimated growth population for 5 years was 30%. The growth was more frequently seen in the elderly ($p = 0.017$), in part-solid GGO ($p < 0.01$) and in GGO of larger than 10 mm ($p < 0.01$, logrank test). By multivariate analysis, initial size ($p < 0.01$, Cox's model) and history of lung cancer ($p = 0.017$, logistic model) were independent factors that were significantly associated with GGO growth. Fifty GGOs that were 10 mm or smaller and without a lung cancer history did not grow within 3.5 years.

Conclusions: After initial management and 3 month follow-up, larger size (more than 10 mm) and a history of lung cancer are risk factors for GGO growth, and therefore should be considered when making a follow-up plan.

Key Words: Lung Adenocarcinoma, Ground-glass, Follow-up, Thin-section CT.

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Recent studies have demonstrated that screening with low-dose computed tomography (CT) can improve detection of lung cancer at an early and potentially curable stage.[1,2] Since CT screening has become more widely accepted and with advances in technique, very faint and smaller lesions called ground-glass opacities (GGOs) are now frequently encountered. GGO is a roentgenological term for lesions in the lung on thin section CT (TSCT), defined as a homogeneous hazy increase in density in the lung field that does not obscure the bronchiolovascular structure.[3,4] Recently GGOs were found in 0.2 to 0.5% of screened populations.[5] Pathologically, localized GGOs existing for months have been reported to correspond to precancerous lesions or early stage adenocarcinomas.[6–10] These pathologic conditions include atypical adenomatous hyperplasia (AAH) and bronchioloalveolar carcinoma (BAC) which replace alveolar epithelial cells according to the World Health Organization definition.[11] Although GGOs are generally reported to grow slowly, details of natural history remain limited.[12,13]

In this study, we therefore examined GGOs and part-solid GGOs that existed for more than 3 months on chest TSCT in our hospital. The purpose was to clarify factors that are likely to affect the growth of a GGO and to gain a better understanding to facilitate appropriate GGO follow-up planning.

PATIENTS AND METHODS

Patients

Between 1999 and 2006, 184 patients were referred to the Department of Thoracic Surgical Oncology, the Cancer Institute Hospital, Tokyo, for further examination of lung lesions that seemed as a GGO on chest TSCT. Among these, 17 patients (9%) had an immediate diagnostic work-up including surgical intervention and 10 patients were lost to

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follow-up. Although the remaining 157 patients were then followed-up for 3 months by CT scan, it was terminated in 32 patients for the following reasons (number of patients); vanished, (6) gross growth, (3) rapid increase in number and recognition as pulmonary metastasis, (4) advance in other malignancy, (1) patient's request, (3) and lost to follow-up. (11) TSCT was repeated and 125 patients, who showed no change in the repeat CT images, were finally enrolled in the study. Their clinicopathologic background and CT findings are shown in Table 1. Although 45 patients (36%) had multiple GGOs (range of number, 2–20), we only considered the largest lesions. Follow-up consisted of periodic TSCT at a 6-month intervals. The mean observation period was 1048 days (ranged, 177–3269), and follow-up CT scans were performed an average of 6 times in each case. In 59 cases, GGOs were detected at a health check-up or were found incidentally, and the others were detected during follow-up of prior malignancy (51 patients with lung adenocarcinoma (stage I, 48; stage II, 1; stage III, 2), 9 with breast cancer, 2 with gynecologic cancer, 2 with urologic cancer, and 2 with sarcomas). Nine patients with a history of lung cancer also had other cancers in other organs. The interval between the prior malignancy treatment and detection of the current GGO varied from 0 to 168 (mean 36) months among these 66 patients.

TABLE 1. Patient Background and CT Findings

	Total $n = 125$	With Growth $n = 26$ (%)
Patient background		
Gender		
Men	51	13 (25)
Women	74	13 (18)
Age (36–88, mean 62)		
≤60	44	5 (11)
60<	81	21 (26)
Smoking habit		
Never	58	10 (17)
Ever	41	10 (24)
Unknown	26	6 (23)
History of lung cancer		
Without	74	11 (15)
With	51	15 (29)
CT findings		
Initial size (3–17 mm, mean 8.3)		
≤10	87	8 (9)
10<	38	18 (47)
Existence of solid part		
Without (GGO)	95	14 (15)
With (part-solid GGO)	30	12 (40)
CT density (−810 to −10 HU)[a]		
≤−500	67	10 (15)
−500<	58	16 (28)
Location[b]		
Above	79	19 (24)
Below	46	7 (15)
Multiplicity		
Solitary	80	17 (21)
Multiple	45	9 (20)

[a] The mean CT density (HU) of 3 spots within the GGO.
[b] With reference to the major fissure of the lung.
GGO, ground-glass opacity; CT, computed tomography.

This retrospective study was approved by the institutional review board of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research.

Radiologic Definition of GGOs and Their "Growth" on TSCT

CT scan was performed with a GE Yokogawa Medical System, Light Speed QXi or High Speed DXi (Hino, Tokyo). For screening of the whole lung field, the scanning parameters were as follows: 120 kV, 230 mA, beam width of 7.5 mm, rotation speed of 1 revolution/s, table speed of 15 mm/s (pitch 2:1), and a reconstruction interval of 7.5 mm. When the presence of GGO was suspected, targeted axial scanning was repeated only for the suspected area based on the previous scanning. The scanning parameters were 120 kV, 280 mA (or 180 mA), clustered axial scanning of 1.25 mm or 2.0 mm slice and the largest diameter of the lesion was evaluated at WL-585HU and WW1800HU.[14] All scans were obtained in full inspiration without any contrast material and viewed in cine format on a computer workstation. All radiologic images were evaluated by 2 of the specialists who had 5 and 17 years of experience (MH, YS), respectively and a final consensus was obtained by plenary reading. The size of each lesion was recorded by evaluating the largest diameter using a caliper tool in the software. In this study, we discriminate "part-solid GGO" from "GGO." The definition of them was based on that of Henschke et al.,[15] in which the subcategories "nonsolid" and "part-solid" were recognized according to the absence/presence of solid parts in the GGO lesion. We prefer the term "GGO" to "nonsolid nodule" because a finding of GGO on TSCT corresponds specifically to a pathologic alveolar condition with noninvasive tumor-spreading, while "nonsolid nodule" does not. The remainder (24%) had a solid part, the diameter of which as a proportion of the diameter of the whole lesion was (solid part/ GGO) from 0.13 to 0.42 (2/16 mm–2.5/6 mm) and we used the term "part-solid GGO" for them in this study. All GGOs with extra findings (6 GGOs with cystic components and 12 GGOs with heterogeneous ground-glass density) were included as "GGO." The "CT density" was defined as the mean density (HU) measured at three spots within the GGO part of each lesion with the software tool. "Growth" of a GGO was concluded when any of the following were recognized: gross increase in the greatest dimension by at least 2 mm from the initial TSCT (Figure 1), gross increase in the size of the solid part by at least 2 mm, or a new solid part of any size (Figure 2).

Statistical Analysis

The follow-up time was defined from the date of the initial TSCT to the latest TSCT. To clarify the factors that may affect GGO growth, univariate and multivariate analyses were performed with regard to the growth incidence (numbers of GGO with concluded growth/numbers at risk). In this retrospective investigation, multivariate analyses were ap-