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The long-term course of ground-glass opacities detected on thin-section computed tomography

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Follow-up

Summary
Background: Focal ground-glass opacity (GGO) is becoming a major concern because of its possible association with lung cancer. In this study, we analyzed the long-term progression of GGOs that persisted for more than 2 years.
Methods: We reviewed focal GGOs identified by thin-section computed tomography that persisted for more than 2 years.
Results: We enrolled a total of 114 patients with 175 GGO lesions. The median patient age was 61 years (range, 37–92 years) and 42 (36.8%) patients were male. Mean initial GGO size was 7.8 ± 4.4 mm. Median follow-up duration was 45 months. Forty-six (26.3%) GGOs had significant size increases (≥2 mm in the longest diameter) with a mean volume doubling time of 1041 days. In a multivariate analysis, large size (≥10 mm), the presence of a solid portion

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(mixed GGO) and old age (≥65 years) were risk factors for significant size increase, with odds ratios (95% CI) of 6.46 (2.69—15.6), 2.69 (1.11—6.95) and 2.55 (1.13—5.77), respectively. GGOs with character changes from pure to mixed or mixed to solid showed more rapid volume expansion.

Conclusions: GGOs which persisted for several years showed an indolent course. Large lesions with a solid portion and GGOs in male or elderly individuals may be cause for more concern, as these factors were associated with size increase. Resection should be considered if GGOs show character changes, as these may be associated with rapid size progression.

Introduction

As a result of the recent expansion in the availability of computed tomography (CT),[1—4] focal ground-glass opacity (GGO) has become a major concern, due to an increase in detection.[5] GGO lesions cannot be ignored, as they are frequently associated with lung cancer.[6—11] Given the malignant potential of GGO, patients are often subjected to short interval CT; however, such management is not reasonable, considering the cumulative radiation associated with frequent CT[12] and the indolent course of most GGOs.[13] Furthermore, some GGOs show no progression over the course of several years.[14] For those cases, resection may not be necessary, even if malignancy is suggested. A universal and appropriate follow-up plan for GGO patients is still under debate, and no surveillance guidelines have existed until recently.

When focal GGO lesions with malignant potential are identified, physicians recommend either resection or close observation. Larger GGOs and/or those with solid components are typically resected, whereas small and/or non-solid lesions are subject to short interval follow-up.[15,16] Some GGOs remain persistent for several years without the need for resection, which can cause concern for physicians, as it is unknown whether or not these lesions will progress to incurable malignancies. Therefore, it is imperative to understand the natural course of GGOs. Only a few reports have been published on this subject. The doubling time for mixed GGOs has been reported to be greater than 1 year.[17] Only a fraction of persistent GGOs demonstrate rapid size progression, which is evident several months or years after detection.[18] The typical course for a GGO appears to be indolent; however, definite evidence of the long-term natural history of GGOs is lacking.

Previously, we reported the short-term natural course of GGOs.[19] In this study, we analyzed the long-term course and progression of GGOs persistent for more than 2 years without resection. We also sought to elucidate the risk factors for size increases of lesions to help inform proper management.

Patients and methods

Patients

We enrolled patients with GGO lesions that were confirmed by thin-section CT (slice size 1—3 mm) and were persistent for more than 2 years without resection between April, 2004, and July, 2011, at Seoul National University Bundang Hospital in Seoul, Korea. GGO lesions that were only detected by low-dose CT or disappeared within 2 years were excluded from this study. GGO lesions were identified on CT images by experienced pulmonologists, and size changes and characters were defined by consensus of a pulmonologist and experienced radiologists. Follow-up periods were from the date of the initial CT scan until the last CT scan still showing the GGO lesion. The study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Bundang Hospital (B-1110/138-109).

Radiologic features of GGO lesions

GGO lesions were classified as pure GGO (pGGO) or mixed GGO (mGGO) at initial detection, according to the presence of a solid component within the nodule by thin-section CT at a lung window setting. GGO size was defined by its longest diameter. Size increases of 2 mm or more were considered significant, as changes < 2 mm are subject to measurement error.[16] Volume changes were estimated by the cube of the longest diameter.

CT scans were performed using various instruments, including the Brilliance-64, MX-8000 IDT, and iCT 256 (Philips Medical Systems, Cleveland, OH, USA). Scanning was performed from the thoracic inlet to the upper portion of the kidneys. Images were obtained using a level of −600 Hounsfield units (HU) and width of 1500 HU (lung window) and a level of 30 HU and a width of 400 HU (mediastinal window). Conventional CT images were reconstructed into 3 mm section thickness, and high-resolution CT images were reconstructed into 1 mm section thickness.

Pathological examination

Resected surgical specimens were cut at 3 mm intervals and fixed in 10% buffered formalin. After fixation, all sections were embedded in paraffin and stained with hematoxylin and eosin for histologic examination. All sections of tumors and suspicious lesions were submitted for microscopic examination. Histopathologic diagnoses were based on the 2011 adenocarcinoma IASLC/ATS/ERS classification system.[20]

Statistical analyzes

The relationship between clinical characteristics and increases in GGO size was evaluated using the χ^2 test for

categorical variables and logistic regression analysis for continuous variables. Time to GGO growth was also analyzed using a Cox's proportional hazard model. In the multivariate analysis, the backward selection method was used to exclude multicollinearity. Volume increases were compared by Student's *t*-test or analysis of variance. Statistical significance was defined as a two-tailed *p* value of <0.05. All data are presented as mean $\pm$ standard deviation. All statistical analyzes were conducted using PASW software (v18.0; SPSS, Inc., Chicago, IL, USA).

Results

Demographic characteristics

A total of 175 GGO lesions in 114 patients were included in our analysis. Median patient age was 61 years (range, 37—92 years) and 42 (36.8%) patients were male (Table 1). The condition of initial detection was most often at routine checkup (84/175, 48.0%), followed by evaluation for respiratory symptoms (40/175, 22.9%), and regular follow-up for lung cancer or other nodule (27/175, 15.4%). Median follow-up time after initial detection was 45 months (range, 24—99 months). Of the 175 GGOs, 143 (81.7%) were pGGO and 32 (18.3%) were mGGO, initially. Mean GGO size was 7.8 $\pm$ 4.4 mm on initial detection, with mean mGGO and pGGO sizes of 11.2 $\pm$ 6.5 mm and 7.0 $\pm$ 3.4 mm, respectively ($p < 0.001$). Twenty-eight patients had a history of lung cancer, including 22 (78.6%) GGOs and 6 (21.4%) solid tumors. All of these previous cancer lesions were resected and pathologically confirmed as adenocarcinoma.

Progression of GGO lesions

Forty-six (26.3%) GGOs showed significant increases in size ($\geq$2 mm) during the follow-up period. Twenty-eight (19.6%) of 143 pGGOs and 18 (56.3%) of 32 mGGOs had significant size increases. Eleven pGGOs (7.7%) changed to mGGOs during follow-up, nine (81.8%) of which had significant size increases. Three mGGOs increased significantly in size and became solid masses. There was no difference in the length of follow-up between GGOs with and without size increases (48.8 $\pm$ 19.4 mo versus 51.5 $\pm$ 20.9 mo, respectively, $p = 0.44$). Most GGOs, even those with significant size increases, showed an indolent course and linear increases in diameter. The mean size increase rate of the 45 GGOs that showed significant increases was 2.2 $\pm$ 2.9 mm/yr. Only three (2.2% of total GGOs) mGGOs had size increase rates of $>$5 mm/yr at least once during the 7 year follow-up period (Fig. 1). Among 45 GGOs with significant size increases (27 pGGOs and 18 mGGOs), the size increase rate and volume doubling time were not different according to their initial character (pGGO, 1.8 $\pm$ 2.3 mm/yr and 872 $\pm$ 649 days versus mGGO, 2.6 $\pm$ 4.1 mm/yr and 1005 $\pm$ 732 days; $p = 0.35$ and $p = 0.19$, respectively). A total of 29 lesions were pathologically confirmed, including 11 (37.9%) invasive adenocarcinoma (ADC), 11 (37.9%) minimally invasive adenocarcinoma (MIA), three (10.3%) adenocarcinoma *in situ* (AIS, formerly known as bronchioloalveolar carcinoma), one (3.4%) atypical adenomatous hyperplasia (AAH), one (3.4%) pleomorphic carcinoma, and two (6.9%) interstitial fibrosis.[20] Most mGGOs were MIA or invasive adenocarcinoma, whereas pGGOs included various pathologic types (Table 2). Twenty (80%) of 25 adenocarcinoma (*in situ*) showed size increase, as did one pleomorphic carcinoma and one AAH.

A total of 90 GGOs were tracked for more than 4 years, with a median follow-up time after 4 years of 13 months (range, 1—51 months). Among these, 25 (27.8%) had size increases during the total follow-up period, but only two (2.2%) had a significant size increase after 4 years, except four GGOs without follow-up for several years. Thirteen GGOs were confirmed as adenocarcinoma (including two AISs, five MIAs, and six invasive ADCs). Eleven of them had significant size increases, but one invasive ADC and one AIS demonstrated no size increase for as long as 57 and 72 months, respectively.

Table 1 Baseline characteristics of enrolled patients.

Character	*n* = 114
Age, years; median (range)	61 (37—92)
Male sex, *n* (%)	69 (60.5)
Smoking history, *n* (%)	
Never smoker	63 (55.3)
Former smoker	26 (22.8)
Current smoker	25 (21.9)
GGO lesion per a patient, *n* (range)	1 (1—4)
Previous lung cancer, *n* (%)	28 (24.6)
GGO	22 (78.6)
Solid	6 (21.4)
Initial GGO size (mm), mean $\pm$ SD (range)	7.8 $\pm$ 4.4 (2.5—31.0)
Initial character of GGO, *n* (%)	175 (100)
Pure	143 (81.7)
Mixed	32 (18.3)
Follow-up duration, mo; median (range)	48 (24—99)

GGO, ground-glass opacity.

Risk factors for GGO size increase

According to univariate analysis, age, male sex, larger initial lesion size, mGGO, bubble lucency (pseudocavitation

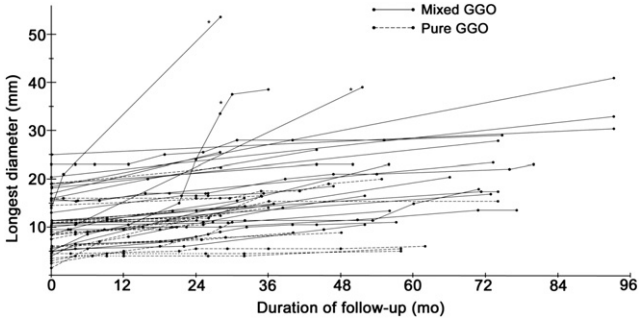

Figure 1 Progression of 45 GGOs with significant size increases ($\geq$2 mm).
*Three GGOs with size increase of more than 5 mm/yr at least once.

Table 2 Pathologic findings from resected GGOs according to preoperative radiologic findings.

Pathology, *n* (%)	Radiologic finding		Total
	Pure GGO	Mixed GGO	
Benign	0 (0)	2 (100.0)	2
Atypical adenomatous hyperplasia	1 (100.0)	0 (0)	1
Adenocarcinoma *in situ*	2 (66.7)	1 (33.3)	3
Minimally invasive adenocarcinoma	3 (27.3)	8 (72.7)	11
Invasive adenocarcinoma	3 (27.3)	8 (72.7)	11
Other malignancy	0 (0)	1 (100.0)	1
Total	9	20	29

associated with nodules of varying density),[21–23] and smoking history (≥10 pack years) were significant risk factors for GGO size increase. Meanwhile, follow-up duration, previous lung cancer history, and multiple GGOs were not associated with size increase (Table 3). Initial large size (≥10 mm), mGGO and old age remained significant risk factors for significant size increase (adjusted odds ratio [95% CI] = 6.46 [2.69–15.6], 2.69 [1.11–6.95] and 2.55 [1.13–5.77], respectively), in a multivariate analysis using the covariates age, sex, initial size, mGGO, smoking history, bubble lucency and previous lung cancer history. Bubble lucency, previous lung cancer and smoking history were excluded from our final analysis due to multicollinearity (Table 4). In a Cox's proportional hazard model, mGGO, initial size (≥10 mm) and single lesion (compared with multiple lesion) were significant factors for size increase (adjusted hazard ratio = 3.13 [95% CI, 1.58–6.20], 2.06 [95% CI, 1.08–3.92] and 2.88 [95% CI, 1.41–5.88], respectively). When we stratified GGOs into the three groups, pGGO ($n = 134$), mGGO ($n = 27$), and change from pGGO to mGGO or mGGO to solid mass ($n = 14$), the latter group demonstrated the fastest volume expansion (Fig. 2, $p < 0.001$).

Discussion

This study was designed to characterize the natural course of GGOs that were present, but not resected, for several years in real practice. According to our enrollment criteria, we collected distinct GGOs that initially appeared indolent then undertook image follow-up for several years without resection. Chest physicians typically identify these lesions in the clinic, but treatment management plans, including CT interval and resection, can be somewhat arbitrary and

Table 3 Relationship between initial character and significant size increase (≥2 mm).

	Number $n = 175$	Significant size increase $n = 45$ (%)	Odds ratio (95% CI)	*p* value
Sex				
Female	71	9 (12.7)	1.00 (reference)	0.002
Male	104	36 (34.6)	3.64 (1.62–8.17)	
Age				
<65	114	21 (18.4)	1.00 (reference)	0.003
≥65	61	24 (39.3)	2.87 (1.43–5.78)	
Initial size				
<10 mm	137	21 (15.3)	1.00 (reference)	<0.001
≥10 mm	38	24 (63.2)	9.47 (4.23–21.2)	
GGO character				
Pure GGO	142	27 (19.0)	1.00 (reference)	<0.001
Mixed GGO	33	18 (54.5)	5.11 (2.29–11.4)	
Bubble lucency				
Absent	161	36 (22.4)	1.00 (reference)	0.002
Present	14	9 (64.3)	6.25 (1.97–19.8)	
Smoking history				
<10PY	119	22 (18.5)	1.00 (reference)	0.002
≥10PY	56	23 (41.1)	3.07 (1.52–6.22)	
Multiplicity[a]				
Multiple	108	25 (23.1)	1.00 (reference)	0.33
Single	67	20 (29.9)	1.41 (0.71–2.81)	
Lung cancer history				
Absent	122	32 (26.2)	1.00 (reference)	0.81
Present	53	13 (24.5)	0.91 (0.43–1.92)	
Follow-up duration				
<4 years	85	20 (23.5)	1.00 (reference)	0.52
≥4 years	90	25 (27.8)	1.25 (0.63–2.47)	

GGO, ground-glass opacity; PY, pack year.
[a] Defined as when more than one GGO was present at the same time.

Table 4 Risk factors for GGO lesion size increase.

	Multivariate analysis	
	Adjusted OR (95% CI)	*p* value
Initial size ≥10 mm	6.46 (2.69–15.6)	<0.001
Presence of solid portion (mixed GGO)	2.69 (1.11–6.95)	0.03
Age ≥65	2.55 (1.13–5.77)	0.03
Male sex	2.43 (0.96–6.15)	0.06

GGO, ground-glass opacity; PY, pack year.

differ according to the physician. In this study, we sought to guide appropriate treatment plans for GGO lesions. We found that a small portion (26.3%) of GGOs showed size increases during a relatively long follow-up period (median, 48 months). Most GGOs, however, displayed an indolent course, and only three had relatively rapid size increases (>5 mm/yr). The presence of a solid portion (mGGO), male sex, large size, and old age were risk factors for size increases, but pGGO also showed rapid volume expansion if it changed to mGGO.

In a previous study, mGGO, old age, and large lesion size were associated with size increases of GGOs in a univariate analysis; male sex was also associated with marginal significance.[16] This is similar to the findings of our study; however, the results of the multivariate analyzes were somewhat different, as the previous study found history of lung cancer as a significant risk.[16] In our study, initial GGO size was also associated with size increase, but our finding

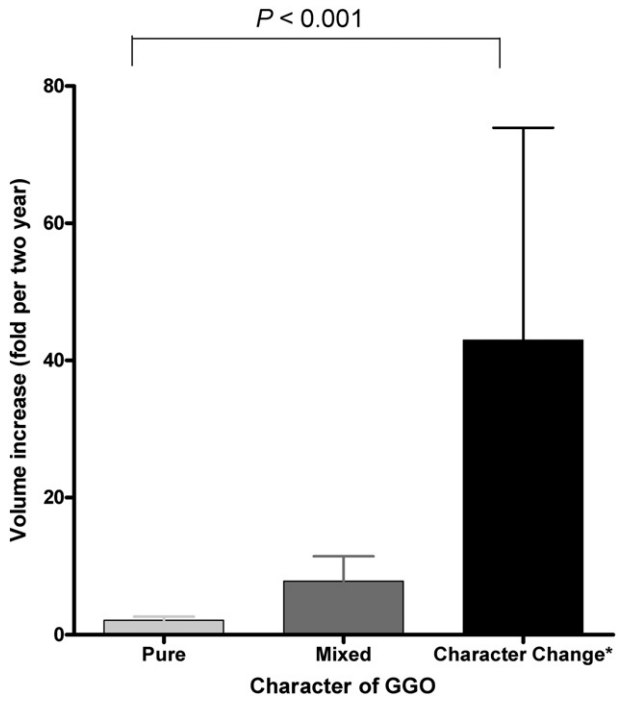

Figure 2 Volume increase per 2 years, according to GGO character.
*pGGO to mGGO or mGGO to solid mass.

of age and sex as factors have not been reported previously. Male sex showed marginal significance in for size increase. One possible explanation is the different presentation of GGO by sex. A previous study reported that adenocarcinoma is more prevalent in males and AAH more prevalent in females.[6] In our study, the proportion of mGGOs was slightly greater in males, although it did not reach statistical significance (21.2% versus 14.1%, $p = 0.32$). Old age was also an independent risk factor for size increase. It is not easy to explain this observation; GGOs in younger patients seem to have a relatively indolent course, due to lead-time bias and they can progress in old age. Some previous studies reported that bubble lucency was associated with malignancy.[21] Bubble lucency was also associated with significant size increase in univariate analysis in this study; however, it was also associated with mGGO ($p = 0.001$) and thus excluded from the multivariate analysis due to multicollinearity.

We did not find lung cancer history to be a risk factor for GGO progression. Only 14 (26.4%) of the 53 lesions in 28 patients with a history of lung cancer had significant GGO size increases. This rate is consistent with the findings of previous studies.[14,16] Size is a suggested predictor of malignancy,[24] and we determined that the initial mean GGO size in patients with lung cancer history was 7.4 ± 5.2 mm; only nine (17.0%) patients had GGO lesions ≥10 mm. The small size of GGOs in patients with a history of lung cancer may explain the indolent course. Multifocal GGOs arise as independent events rather than by intrapulmonary spread or systemic metastasis.[25] Therefore, operable lung cancer should be considered for resection, even when other GGO sites are difficult to resect at the same time. Regular follow-up is sufficient for those GGOs, especially when the lesion is small. This recommendation is supported by one report stating that the prognosis of GGO is favorable.[26] In our study, only one patient, who went without follow-up for several years, died due to a GGO.

GGO lesions with character changes from pGGO to mGGO, or mGGO to solid showed rapid size increases. Atypical adenomatous hyperplasia has been reported to be the precursor of adenocarcinoma.[27,28] Therefore, character changes of pGGOs may indicate rapid progression from AAH to adenocarcinoma. GGO lesions with significant size increases were more prevalent in mGGO than pGGO. A recent report based on screening low-dose CT also indicated that new development of an internal solid portion was significantly nodule growth.[29]

AAH and AIS typically appear as pGGOs; those of AIS are usually slightly larger and have higher attenuation than the very faint GGOs of AAH.[30,31] MIA has a variable[32,33] and not yet fully understood pathology. Invasive adenocarcinoma is usually a solid nodule, but may also present as a GGO.[14,34,35] In our study, resected pGGO had a variety of pathologic diagnoses including AAH, AIS, MIA, or invasive adenocarcinoma. Meanwhile, most mGGOs proved to be MIA or invasive adenocarcinoma. These included only resected cases. Therefore, small GGOs with an indolent course were excluded from the analysis, which may explain the small number of AAH and AIS cases. Among invasive adenocarcinomas, three (27.3%) presented as pGGO, two of which contained bubble lucency. These results indicate an overlap among the imaging features of GGOs.

Decisions regarding CT intervals and the termination of CT follow-up are challenging and important issues. Although most GGO lesions did not increase in size after 4 years in this study, 13 (including six invasive ADCs) were diagnosed as adenocarcinoma. Predictions of whether such adenocarcinomas will develop into clinically meaningful malignant lesions are difficult. Some reports have suggested that pulmonary nodules can be generally considered benign if they maintain their size over a 2-year observation period.[36,37] However, this assumption cannot be applied to GGOs, as one GGO lesion without a size increase for 57 months in our study was later confirmed as invasive ADC. Rapid progression was also noted in two GGO lesions without follow-up for several years. Therefore, regular CT follow-up, for example, yearly, should be continued for an indefinite period, until longer-term data can be obtained. Resection or shorter CT intervals, such as 6 months, should be considered when a pGGO develops a solid component, which can suggest rapid size progression. Longer follow-up CT intervals, such as 2 years, could be sufficient in the case of pGGOs with a size $<$10 mm or no change for more than 4 years, which suggests slow progression and good prognosis.[23,38]

Whether or when persistent GGO should be resected is also controversial. Based on observational data, close follow-up without resection until the appearance of a solid component was suggested for pGGO.[39] Our data support this suggestion. Only a small portion of pGGO lesions (19.6%) showed size increases. Most mGGOs had an indolent course, and no deaths have been reported due to lung cancer for those with regular follow-up. Even among GGO lesions with size increases, the rate of increase was very slow (2.2 ± 2.9 mm/yr) and their volume doubling time was more than 2 years. Favorable prognosis and slow progression have been reported by others.[17,34,40,41] Considering the radiation hazard of CT, indolent course, and favorable prognosis, annual follow-up with CT may be sufficient for GGO lesions. However, resection should be considered when pGGO lesions develop a solid portion, as this may be associated with rapid progression.

Some studies, including research from our group, report that GGO lesions can decrease in size or even disappear; however, shrinkage of GGO lesions usually occurs within 3 months.[19,39] Blood eosinophil counts in transient GGO cases are significantly higher than in GGO cases diagnosed with cancer.[19] This suggests that pulmonary infiltration of eosinophils might be the cause of transient GGOs. No GGO lesions had a significant size decrease ($\geq$2 mm) in this study. This may be attributable to our enrollment criteria, as we only included individuals with GGOs persistent for more than 2 years.

This study had limitations. First, this was a retrospective study, and CT intervals varied among the patients. Therefore, an accurate size increase rate was hard to estimate. Second, all enrolled patients were Koreans. Racial and epidemiologic factors should be considered when interpreting our findings. Third, although lesion size increase was used as the main outcome measure, invasive cancer or carcinoma may be a more appropriate outcome. In this study, only 29 (16.6%) lesions were confirmed pathologically and most of them (26 [89.6%]) were adenocarcinoma (*in situ*). Therefore, it was not possible to use this as a measure of outcome. We considered that size increase was at least as, if not more, important as pathology in real clinical practice, because even adenocarcinoma may not progress for several years, as proven in this study. Finally, it is possible to classify GGOs in a different way, which may have permitted a more detailed analysis.[41,42] However, we chose a method used in previous reports[16,20,24,25] to simplify the results and to maintain statistical power.

In conclusion, a significant fraction of GGO lesions persistent for more than 2 years progressed slowly. However, larger GGOs with a solid component observed in males or older patients may be cause for more concern and closer follow-up, as these were risk factors for lesion size increase. If GGO lesions show character changes, such as from pure to mixed, early resection should be considered, as it may indicate rapid progression in size.

Conflict of interest statement

All authors have no conflicts of interest.

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