Editorial Commentary

Optimal management of pulmonary ground-glass opacity nodules

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On the basis of the promising results of lung cancer screening in recent large trials, low-dose chest computed tomography (CT) has been widely introduced in clinical practice for the early detection of lung cancer (1,2). The increased use of CT for screening has also led to an increased detection of lung nodules, with a significant proportion of ground-glass opacity nodules (GGNs). Although some GGNs are transient, persistent GGNs have a high likelihood of causing lung adenocarcinoma; also, their nature is different from typical lung cancer, thereby indicating a separate disease entity. Most patients detected with persistent GGNs are never-smokers, women, of Asian origin, and relatively young, of which are in contrast to the classic risk factors of lung cancer. Accordingly, the management of GGNs is important, although it is complicated owing to the indolent course of GGNs and the heterogeneity in growth rates, thereby requiring long-term follow-up and frequent CT screening. Herein, we discuss the appropriate management of GGNs, mainly focusing on the interval and duration of follow-up and the timing and modality of treatment.

Follow-up of GGNs

In real-world clinical settings, a significant proportion of GGNs that clinicians encounter are transient, as they disappear spontaneously (3). Among persistent cases, most GGNs remain stable without any change in size or features for years. However, according to long-term follow-up studies, a considerable percentage of GGNs tend to gradually grow over time. The appearance and growth of a solid component is also an important feature during the follow-up of GGNs in addition to a simple growth in size. We summarized recent studies that analyzed >50 GGNs with available information regarding the follow-up period, change in size or solid component, and diagnostic results (4-18) (*Table 1*). Kobayashi *et al.* reported that approximately 20% of pure GGNs and 40% of part-solid GGNs gradually grew or showed an increase in their solid components (19). They found that all GGNs with a significant increase in size grew within 3 years, and suggested that a minimum of 3 years of follow-up is reasonable (7). In 2016, Kakinuma *et al.* reported the data of a prospective multicenter study that evaluated 1,229 GGNs. They showed that the 5-year probabilities of nodule growth of ≥2 mm were 14% for pure GGNs, 24% for heterogeneous GGNs (defined as a GGN with solid components only in the lung window but not in the mediastinal window setting), and 48% for part-solid GGNs. The 5-year probabilities of the appearance of a solid component were 6% and 22% for pure GGNs and heterogeneous GGNs, respectively (15). The data from that study showed that some GGNs start to grow even after 3 years of stabilization. In a study by our group in 2013, we found that 2 of 90 GGNs (2.2%) showed significant growth after 4 years (9). Moreover, another recent study from our group that evaluated 453 GGNs revealed that

Table 1 Studies that evaluated the natural course of pulmonary ground-glass opacity nodules

Study (author, year, reference no.)	Sample size	Number of GGNs	Inclusion criteria	Follow-up duration	Nodules with growth	Number of nodules with pathologic diagnosis or treatment	Pathologic diagnosis
Hiramatsu, 2008 (4)	125	125	GGNs that were stable for 3 months	Mean of 1,048 days	26/125 (21%)	9 of 26 with growth 5: lobectomy 2: segmentectomy 1: percutaneous biopsy 1: transbronchial biopsy	2 BAC 6 invasive adenocarcinomas 1 organizing pneumonia
Silva, 2012 (5)	56	76	GGNs with a solid component ≤5 mm	Mean of 50.3 months	20/76 (26.3%)	1 of 20 with growth 1: resection	1 invasive adenocarcinoma
Matsuguma, 2013 (6)	171	174	GGNs ≤20 mm with a proportion of GGO >20%	Mean of 29 months	41/174 (23.6%)	56 of 174 21: lobectomy 15: segmentectomy 20: wedge resection	3 AAH 36 AIS 11 MIA 6 invasive adenocarcinomas
Kobayashi, 2013 (7)	61	108	GGNs ≤30 mm with a proportion of GGO ≥50%	Median of 4.2 years	29/108 (26.9%)	26 of 108 (in 21 patients) 5: lobectomy 10: segmentectomy 6: wedge resection	1 AAH 1 AAH/AIS 10 AIS 1 AIS/MIA 8 MIA 5 invasive adenocarcinomas
Chang, 2013 (8)	89	122	Pure GGNs	Median of 59 months	12/122 (9.8%)	11 of 12 with growth 8: lobectomy 3: wedge resection	2 AIS 6 MIA 3 invasive adenocarcinomas
Lee, 2013 (9)	114	175	Any GGNs	Median of 45 months	46/175 (26.3%)	29 of 175 29: pathologic confirm (modalities NA)	1 AAH 3 AIS 11 MIA 11 invasive adenocarcinomas 1 pleomorphic carcinoma 2 interstitial fibrosis
Eguchi, 2014 (10)	124	124	Pure GGNs	Median of 57 months	64/124 (51.6%)	34 of 124 33: resection 1: stereotactic irradiation	5 AIS 15 MIA 12 invasive adenocarcinomas 1 capillary hemangiomatosis
Scholten, 2015 (11)	98	101	Any GGNs	Median of 95 months	79/101 (78.2%)	32 of 101 32: resection	8 AIS 19 invasive adenocarcinomas 5 benign

Table 1 *(Continued)*

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Study (author, year, reference no.)	Sample size	Number of GGNs	Inclusion criteria	Follow-up duration	Nodules with growth	Number of nodules with pathologic diagnosis or treatment	Pathologic diagnosis
Kakinuma, 2015 (12)	NA	439	Pure GGNs ≤5 mm	Median of 6 years	45/439 (10.3%)	5 of 439 5: resection	1 AAH 2 MIA 2 invasive adenocarcinomas
Cho, 2016 (13)	218	453	GGNs that were stable for 3 years	Median of 77.5 months	15/453 (3.3%)	7 of 15 with growth 7: resection	2 MIA 5 invasive adenocarcinomas
Lee, 2016 (14)	213	213	GGNs with 5–30 mm in diameter with solid component ≤5 mm	Median of 849 days	42/213 (19.7%)	58 of 213 58: resection	9 AAH 30 AIS 5 MIA 14 invasive adenocarcinomas
Kakinuma, 2016 (15)	795	1,229	GGNs ≤30 mm with a solid component ≤5 mm	Mean of 4.3 years	5-year probability of growth: 14% for pure-GGNs 24% for HGGNs 48% for part-solid nodules	91 of 1229 (in 80 patients) 25: lobectomy 22: segmentectomy 33: wedge resection	6 AAH 33 AIS 40 MIA 12 invasive adenocarcinomas
Sato, 2017 (16)	187	187	GGNs ≤30 mm with a proportion of GGO ≥50%	Median of 45.5 months	49 (26.2%) at 36 months 13 (7.0%) after 36 months	45 of 187 32: resection 13: radiation therapy	5 AAH/AIS/MIA 25 invasive adenocarcinomas 2 NA
Tang, 2019 (17)	128	128	GGNs ≤30 mm	Mean of 3.6 years	60/128 (46.9%)	62 of 128 62: resection	1 AAH 4 AIS 9 MIA 48 invasive adenocarcinomas
Lee, 2019 (18)	160	208	GGNs ≤30 mm that were stable for 5 years	Median of 136 months	27/208 (13.0%)	3 of 27 with growth 3: pathologic confirm (modalities NA)	1 AIS 1 MIA 1 invasive adenocarcinoma

GGN, ground-glass opacity nodule; GGO, ground-glass opacity; NA, not available; HGGN, heterogeneous ground-glass nodule; BAC, bronchioalveolar carcinoma; AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma.

the frequency of subsequent growth of GGNs after 3 years of stabilization was 6.7% for person-based analyses and 3.3% for nodule-based analyses (13). Based on these recent data, the minimum suggested follow-up period for GGNs was extended to 5 years in the updated Fleischner Society guidelines in 2017 (20). While GGNs have a relatively high prevalence in Asian countries, studies in Caucasians revealed a much lower incidence of GGNs. For example, in the MILD trial from Italy, 76 GGNs were identified in 1,866 individuals who underwent baseline CT (5). In the NELSON trial in a Dutch-Belgian population, 264 GGNs were detected in 7,135 participants who underwent 4 rounds of low-dose CT (11).

Notably, in 2019, Lee *et al.* provided comparative information about the long-term natural course of GGNs after stabilization for 5 years (18). They evaluated 208 GGNs from 160 patients who had been stabilized for 5 years with a total of 10 years of follow-up. Of the evaluated GGNs, 27 (13.0%) showed significant growth during a total follow-up of 136 months. In 8 of the 27 cases, there was a growth in size before the development of a new solid component. Moreover, in that study, approximately 70% of GGNs that showed growth after stabilization for 5 years had an initial size of <6 mm, and the growth was more prevalent in female patients with a smoking history of a few cigarette pack-years. As male sex, larger initial size, and smoking are previously reported risk factors for the growth of GGNs, Lee *et al.* as well as Kobayashi *et al.* (21) suggest that GGNs that grow after a long time of stabilization have clinical features different from those of GGNs in high-risk subjects with growth. The report from Lee *et al.* adds novel information to the field and indicates that a longer period of follow-up would be needed even in GGNs that were stabilized for a long time. Future research should focus on the identification of patients with GGNs who are at risk of showing GGN growth after long-term stabilization as well as optimizing the duration and interval of performing CT scans in such patients.

In 2015, Yankelevitz *et al.* reported the data of the I-ELCAP screening study that evaluated 57,496 participants who underwent repeated CT screenings; they revealed that GGNs of any size could be safely followed with CT at 12-month intervals to assess the development of a solid component (22). Recently, Hammer *et al.* reported simulation results using the data from the NLST trial, suggesting that the follow-up interval for GGNs can be increased from 1 year to 3 years without a significant change in the clinical outcomes (23). Although it seems quite adequate to increase the interval for long-term CT screening for GGNs with no change, clinicians should always be aware of the possibility of growth in such nodules, and even small or stable GGNs should not be neglected. In addition, we have to take into account that the studies by Yankelevitz *et al.* and Hammer *et al.* enrolled mainly Caucasian participants and ever-smokers. Accordingly, different strategies for the optimal follow-up of GGNs might be needed in Asian countries where GGNs are more prevalent and are often observed in never-smokers.

Treatment of GGNs

The current recommendation for the treatment of GGNs is resection. However, the criteria for surgery vary among different guidelines. Results of recent studies indicate the importance of the presence and size of a solid component, of which are known to reflect the pathologically invasive component of adenocarcinoma (24). According to the recent Fleischner Society guidelines, resection is recommended for pure GGNs that grow or show the development of solid portions as well as for persistent part-solid nodules with solid portions of ≥6 mm (20). The guidelines of the American College of Chest Physicians recommend that GGNs that meet any of the following conditions should be resected: (I) GGNs with growth or development of new solid components, (II) pure GGNs >10 mm with confirmed persistence, (III) part-solid GGNs >8 mm with confirmed persistence, and (IV) part-solid GGNs >15 mm without any follow-up (25). However, there is no generally accepted consensus regarding the optimal timing of surgery when GGNs show growth. Accordingly, it is still questionable whether urgent surgery is necessary for all such GGNs. Considering the commonly indolent course of GGNs even after the start of growth and the relatively low mortality of lung cancers presenting as GGNs compared to solid cancers (26), the life expectancy of patients with other medical conditions and the possibility of surgery-related complications should be considered.

The introduction of video-assisted thoracoscopic surgery has resulted in significant advances in the field of management of pulmonary nodules including GGNs. Currently, lobectomy is the modality of choice for resection of early lung cancer. A recent prospective study from the Japan Clinical Oncology Group revealed that the 5-year overall and relapse-free survival rates of patients who received lobectomy and lymph node dissection were 90.6% and 84.7%, respectively (27). Recently, the use of limited

resection such as segmentectomy or wide-wedge resection is increasing. Promising results have been reported regarding the performance of limited resection for relatively smaller GGNs that had outcomes similar to those of standard lobectomy (28). However, as limited resection is often associated with a higher recurrence rate for certain subtypes of early lung adenocarcinomas (29), lobectomy should be indicated for GGNs with a significant solid component; in addition, careful selection of patients who can undergo limited resection for GGNs is essential.

Stereotactic body radiation therapy (SBRT) and percutaneous ablation could be other options for local treatment of GGNs considered for resection. The study by Hammer *et al.* evaluated a simulation model for the treatment of GGNs with SBRT in patients aged >77 years, instead of lobectomy (23). The results revealed that, among patients who developed nodules that require treatment, the overall survival was higher for those treated with SBRT (80%) than for those treated with surgery (79%) and for those with no therapy (74%). However, as the authors noted, we should take into account the fact that only a minority of GGNs had clinically significant malignancy in the study. Therefore, the mortality outcomes would have been driven not by recurrence but rather by treatment-related complication rates, which are higher for lobectomy than for SBRT. To date, there are limited data about the outcomes of SBRT or percutaneous ablation compared to lobectomy or limited resection for the treatment of early lung cancer. Unfortunately, 2 prospective studies that compared the outcomes of surgery and SBRT for early lung cancers were closed owing to slow accrual (30). Therefore, in future, the effects of treatment modalities need to be evaluated in real-world clinical settings rather than simulation models. To achieve this goal, large randomized prospective trials are needed. Another important limitation of SBRT and percutaneous ablation is that the pathologic results of the treated GGNs cannot be obtained, in contrast to resection, which can be used to perform the pathologic diagnosis and treatment simultaneously. This fact should be considered by corresponding clinicians because most patients with GGNs undergo resection without prior pathologic confirmation.

Regarding the proper management of GGNs, the multiplicity is also an important issue that should be taken into account. Approximately one-third of patients with GGNs have multiple nodules, which are usually similar in size and observed in different lobes. Generally, multiple GGNs are considered to be multiple synchronous lung cancer rather than a metastatic disease. A study by our group that investigated the genetic features of multiple GGNs resected from the same patients showed that a high frequency of discordant *EGFR* mutations (17 of 24, 70.8%) could discriminate tumor clonalities (18 of 24, 75%) of multiple neoplastic GGNs (31). Accordingly, multiple GGNs should be treated as independent early lung cancers if they fulfill the criteria for resection, and such patients would have a high probability of undergoing multiple resection of the lungs. In these patients, initial resection of GGNs with limited resection can be an effective strategy to preserve the remnant pulmonary function. Non-surgical treatments such as SBRT or percutaneous ablation can be alternative options for patients with a high risk of complications or those who cannot undergo surgery.

In conclusion, despite the relatively long and indolent course, GGNs are generally heterogeneous, thereby making it difficult to predict the growth or development of a solid portion requiring treatment. In particular, a notable percentage of GGNs tend to grow even after a long time of stabilization. Therefore, understanding the distinct etiology—including the genetic features—along with more cumulative data on the long-term follow-up of such GGNs would allow the development of novel management strategies. In addition, future studies should focus on the selection of the GGNs for invasive treatment, while considering the timing and modality of therapy, especially in patients with multiple nodules. The relevant data regarding these issues would be essential for the optimal management of pulmonary GGNs.

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Footnote

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