Review Article

Ground-glass nodules of the lung in never-smokers and smokers: clinical and genetic insights

Yoshihisa Kobayashi[1,2], Chiara Ambrogio[2], Tetsuya Mitsudomi[1]

[1]Department of Thoracic Surgery, Kindai University Faculty of Medicine, Osaka-Sayama, Osaka 589-8511, Japan; [2]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA

Contributions: (I) Conception and design: Y Kobayashi, T Mitsudomi; (II) Administrative support: Y Kobayashi, T Mitsudomi; (III) Provision of study materials or patients: Y Kobayashi, T Mitsudomi; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Tetsuya Mitsudomi. Department of Thoracic Surgery, Kindai University Faculty of Medicine, 377-2 Ohno-Higashi, Osaka-Sayama, Osaka 589-8511, Japan. Email: mitsudom@med.kindai.ac.jp.

Abstract: Pulmonary ground-glass nodules (GGNs) are hazy radiological findings on computed tomography (CT). GGNs are detected more often in never-smokers. Retrospective and prospective studies have revealed that approximately 20% of pure GGNs and 40% of part-solid GGNs gradually grow or increase their solid components, whereas others remain stable for years. Most persistent or growing GGNs are lung adenocarcinomas or their preinvasive lesions. To distinguish GGNs with growth from those without growth, GGNs should be followed for at least 5 years. Lesion size and smoking history are predictors of GGN growth. Genetic analyses of resected GGNs have suggested that *EGFR* mutations are also predictors for growth but a subset of *KRAS*- or *BRAF*-mutated GGNs may undergo spontaneous regression because the frequencies of *KRAS* or *BRAF* mutations decrease with the advance of pathological invasiveness. Although lobectomy is the standard surgical procedure for lung cancer, limited surgery such as wedge resection or segmentectomy for lung cancers ≤2 cm with consolidation/tumor ratio ≤0.25 can be a viable alternative based on the recent clinical trial. Further genetic analyses and clinical trials can contribute to elucidation of the biological aspects of preinvasive adenocarcinoma and the development of less invasive management strategies for patients with GGNs.

Keywords: Adenocarcinoma; ground-glass opacity (GGO); lung cancer; subsolid nodule

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Introduction

Ground-glass nodules (GGNs) on computed tomography (CT) are hazy lesions that do not obscure underlying bronchial structures or pulmonary vessels. GGNs are manifestations of both malignant and benign lesions, such as focal interstitial fibrosis, inflammation, or hemorrhage (1). However, slowly growing or stable GGNs are early lung cancers or their preinvasive lesions, atypical adenomatous hyperplasia (AAH) or adenocarcinoma in situ (AIS). AAH, AIS, and lepidic predominant lung adenocarcinomas grow along preexisting alveolar structures (2), which maintain the air space. Therefore, these lesions appear as GGNs on CT. GGNs are classified into pure GGNs and part-solid GGNs that have both ground-glass and solid components (*Figure 1A*).

We previously reviewed the pathological features and natural history of the GGN (3). The proportion of solid components of GGNs is closely related to pathological invasive lesions. The longest diameter of consolidation/longest diameter of tumor ratio (C/T ratio) is commonly used to evaluate the proportion of ground-glass components (*Figure 1B*). Empirically, C/T ratio ≤0.5 has been suggested as a benchmark for pathological invasiveness because the incidence of lymph node metastasis in ≤3 cm GGNs with C/T ratio >0.5 ranges

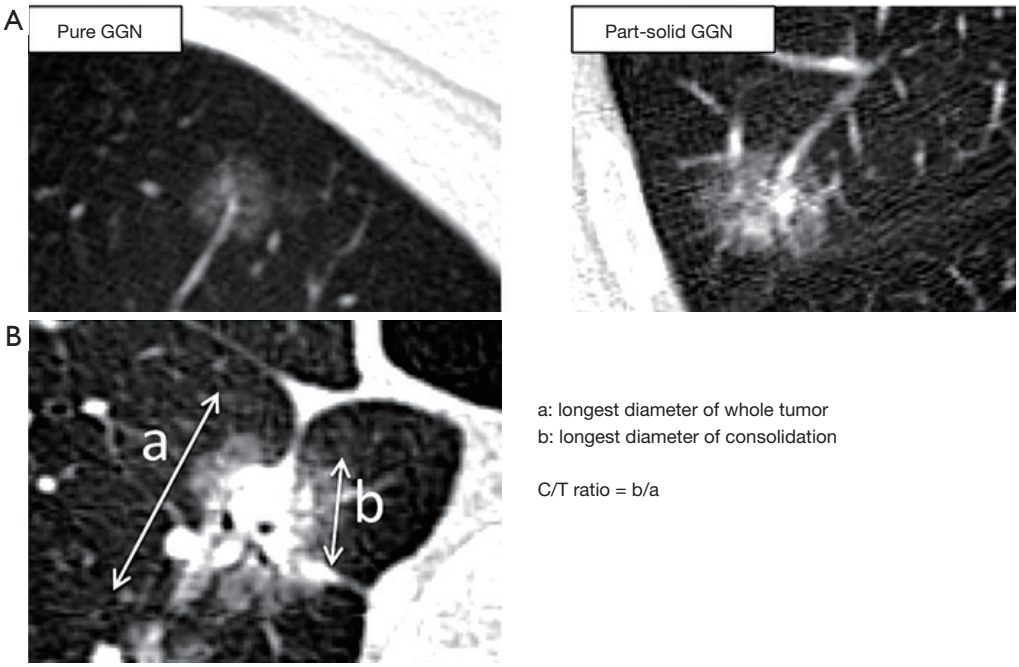

Figure 1 Representative computed tomography images of pure and part-solid GGN and the definition of the consolidation/tumor (C/T) ratio. GGN, ground-glass nodule.

from 21% to 26% (4-6). Solid components of GGN on CT often contain pathologically invasive parts when analyzed under a microscope. Typically, AAH and AIS present as pure GGNs on CT, whereas minimally invasive adenocarcinoma (MIA) and lepidic invasive adenocarcinoma present as part-solid GGNs. Some GGNs exhibit gradual growth, but others remain unchanged for years.

We collected recent reports analyzing more than 100 GGNs with information on smoking history (7-15) (*Table 1*). In total, approximately 60% of GGNs are found in never-smokers. Although there is some inconsistency regarding the incidence of smoking status, 8 of 9 articles reported that GGNs are detected more often in never-smokers. Thus, GGN can be regarded as one of the features of lung cancer in never-smokers. In this review, we have updated recent data on GGNs in terms of smoking and genetic alterations to gain insights into the biological features of lung cancer progression and to suggest clinical management strategies for GGNs.

Follow-up period of GGN

Although GGNs often remain stable without growth for years, about 20% of pure GGNs and 40% of part-solid GGNs gradually grew or increased their solid components in our recent review summarizing four reports (3). We suggested that 3-year follow-up was a reasonable benchmark to distinguish these lesions based on the volume-doubling times of GGNs (9). In 2016, Kakinuma *et al.* reported more extensive results of a Japanese prospective multi-institutional study (13). A total of 795 patients with 1,229 GGNs were assessed, and the mean follow-up period was 4.3 years. In addition to pure GGN and part-solid GGN, the authors defined heterogeneous GGN as a GGN with solid components only in the lung window but not in the mediastinal window setting. The 2-mm growth probabilities at 5 years were 14%, 24%, and 48% for pure, heterogeneous, and part-solid GGNs, respectively. These data are similar to the combined data in our review article (3). However, notably, some GGNs began to grow even after the 3-year follow-up. Based on these prospective data, the minimum follow-up period was extended from 3 to 5 years in the updated Fleischner Society guidelines in 2017 (16).

Predictors of GGN growth

Previously reported predictors and statistical concerns

It would be useful if we could predict which GGNs would

Table 1 Smoking status and gender in patients with pulmonary ground-glass nodules

Author (reference)	Year	GGNs	Patients	Smoking status						Gender			
				Non-smokers		Smokers		Unknown		Female		Male	
				Number	%	Number	%	Number	%	Number	%	Number	%
Hiramatsu (7)	2008	125	125	58	46	41	33	26	21	74	59	51	41
Chang (8)	2013	122	89	30	34	59	66	–	–	16	18	73	82
Kobayashi (9)	2013	108	61	40	66	19	31	2	3	39	64	22	36
Lee (10)	2013	175	114	63	55	51	45	–	–	45	39	69	61
Matsuguma (11)	2013	174*	171	95	56	56	33	23	13	103	60	71	42
Cho (12)	2016	453	218	125	57	84	39	9	4	110	50	108	50
Kakinuma (13)	2016	1229	795	474	60	317	40	4	0	454	57	341	43
Lee (14)	2016	213	213	143	67	59	28	11	5	141	66	72	34
Sato (15)	2017	187	187	125	67	62	33	–	–	118	63	69	37
Total	–	–	1,973	1,153	58	748	38	75	4	1,100	56	876	44

*, only numbers of nodules are linked to information about smoking and gender.

grow and which GGNs would remain stable without any change. Lesion diameter and past history of lung cancer were reported as predictors for the growth of GGNs (7,8,11) (*Figure 2*). However, statistical analyses of the growth of GGNs are subject to two major concerns. First, some patients have synchronous multiple GGNs. When all GGNs are independently counted, patient characteristics, such as gender or smoking status, are overweighed because of double-counting. Second, the definition of "no-growth" as an outcome is difficult because GGNs without growth for a given period might begin to grow afterwards.

Influence of smoking on GGN growth

We conducted two independent analyses considering the above concerns (17). First, the "time to 2-mm growth" was assessed for each lesion, and univariate and multivariate analyses using the Cox proportional hazards model were performed. To avoid possible biases in the case with multiple lesions, we performed a subsequent subanalysis dealing with only the largest lesion per patient. Next, the "incidence of 2-mm growth" was defined as an outcome, and univariate and multivariate analyses using the logistic regression model were performed. To strictly define "no-growth", we excluded lesions that had been observed for <3 years based on our previous report (9). Based on the consistent results of these statistical analyses, we found that smoking, in addition to larger diameter, is a novel predictor of growth (17) (*Figure 2*).

Considering that GGNs are found more often in never-smokers, smoking history as a predictor of growth seems to be paradoxical. We collected recent reports describing smoking status and GGN growth (7,8,10,12,15,17) (*Figure 3*). Combined data from six articles showed that frequency of GGN growth based on data about "growth" or "no-growth" was significantly higher in smokers than that in never-smokers (26% versus 18%, P=0.0045). Among the six articles, 3 reported frequencies of GGN growth at 2, 3, or 5 years based on data on "time to growth" (11,13,17) (*Figure 3*). All data consistently showed that GGNs in smokers were more likely to grow than those in never-smokers. Notably, a prospective multi-institutional study also reported that lesion size and smoking history were factors for growth toward the appearance of solid components by multivariate analysis, although lesion size and male gender were predictors for 2-mm growth (13). Male gender and smoking were closely correlated in our previous analysis (17). Although it is not clear whether smoking cessation after diagnosis of GGN changes the clinical behavior of these GGNs, smoking cessation should be emphasized in this situation as well.

In addition to GGN growth, there is an interesting report about the influence of smoking on the new appearance of GGNs. Remy-Jardin *et al.* examined growth changes in 111 subjects who had undergone sequential CT

Author, year (ref.)	Number of GGNs	Univariate analysis	Multivariate Cox for time to growth	Multivariate logistic for growth incidence
Hiramatsu, 2008 (7)	125*1		Size	Size, PH of lung cancer
Chang, 2013 (8)	122 pure	Size	NE	NE
Matsuguma, 2013 (11)	98 pure		Size, PH of lung cancer	NE
	76 part-solid		NE factor	NE
Kobayashi, 2014 (17)	120*1		Size, Smoking	Size, Smoking
Kobayashi, 2015 (18)	120*1	EGFR	NE	NE
Kakinuma, 2016 (13)	1053 pure		Size, Male, Size*2, Smoking*2	NE
	81 hetero		Size	NE
	106 part-solid		Size	NE

Figure 2 Summary of predictors for the growth of GGNs (7,8,11,13,17,18). *1: pure GGNs and part-solid GGNs; *2: changes in the appearance of the solid component is defined as the outcome. NE, not evaluated; PH, past history; GGN, ground-glass nodule.

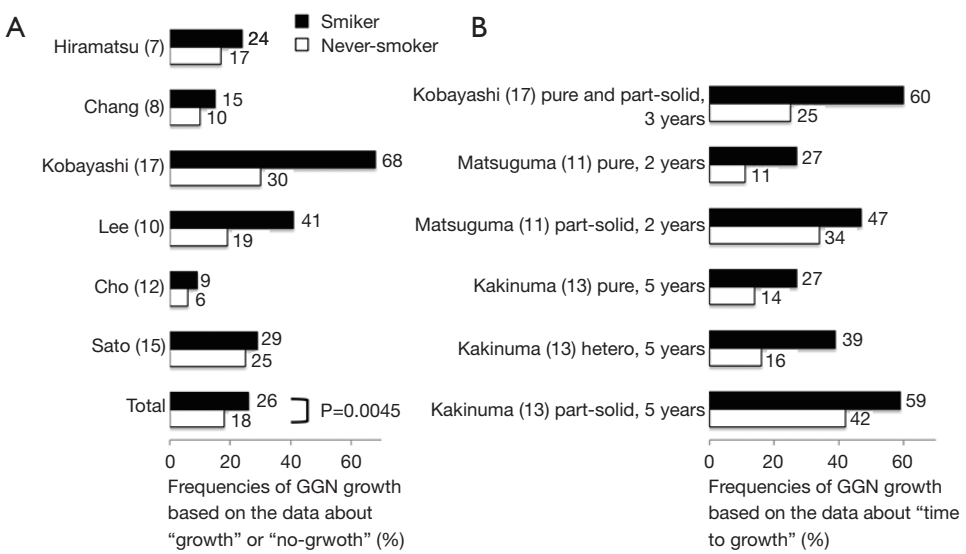

Figure 3 Frequencies of GGN growth in smokers and never-smokers (7,8,10-13,15,17). Previous studies evaluated frequencies of GGN growth via two independent analyses. First, "growth" or "no-growth" was used as an outcome. Combined data from six studies were compared using Chi-square test (A). Second, "time to growth" was used as an outcome and growth rates were estimated using the Kaplan-Meier method. In reference 13, in addition to pure GGN and part-solid GGN, the authors defined heterogeneous GGN as a GGN with solid components only in the lung window but not in the mediastinal window setting (B). GGN, ground-glass nodule.

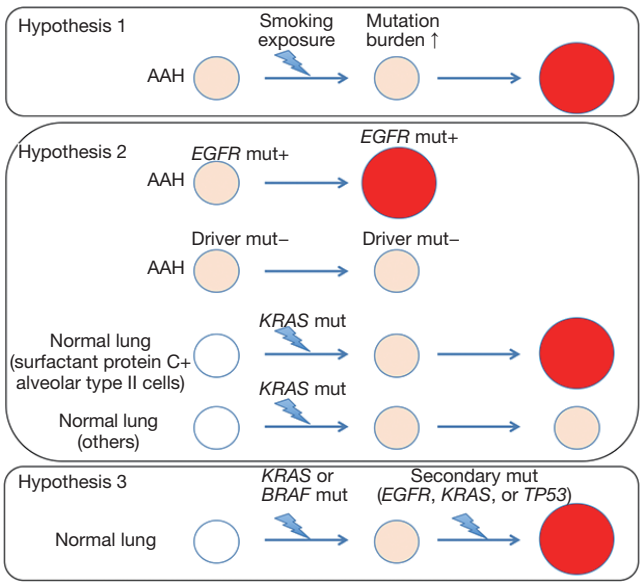

Figure 4 Hypotheses for the progression of preinvasive adenocarcinoma showing as a GGN. Hypothesis 1 suggests that smoking exposure induces a mutation burden, which contributes to the growth of the GGN. According to hypothesis 2, *EGFR* mutation-positive AAHs gradually grow, whereas driver mutation-negative AAHs do not progress. Among *KRAS*-mutant AAH, only those derived from surfactant protein C+ alveolar type II cells may progress to invasive adenocarcinoma. Hypothesis 3 suggests that progression to invasive adenocarcinoma is induced by an initial stimulation by BRAF or *KRAS* mutations and the subsequent secondary mutations. GGN, ground-glass nodule; AAH, atypical adenomatous hyperplasia.

examinations over a mean period of 5.5 years. GGNs were detected in 28% of current smokers by initial evaluations. Interestingly, final evaluations detected GGNs in 42% of persistent current smokers (P=0.02). In contrast, the frequencies of GGNs upon initial and final evaluations were not significantly different in never-smokers (19). These data indicate that a subset of GGNs may be newly developed due to chronic exposure to smoking.

Smoking is thought to cause cancer by inducing DNA damage, which leads to somatic mutations in cancer-related genes. Alexandrov *et al.* collected data on somatic mutations in 5,243 cancers from the Cancer Genome Atlas (TCGA), the International Cancer Genome Consortium (ICGC), and 17 other articles to reveal the association between mutational signatures and tobacco smoking (20). In analyses of samples with information about cumulative exposure to smoking, the total numbers of base substitution mutations were positively correlated with pack-years smoked. For lung adenocarcinoma, the authors estimated that approximately 150 mutations accumulated per genome per pack-year (20). Considering these data, cumulative mutations due to smoking may induce GGN growth.

The association between genetic alterations and GGN growth

EGFR mutation

Previous studies revealed that the lesion diameter and smoking (or male gender) were predictors for the growth of GGNs as described above (13,17). However, the genetic differences among GGNs with or without growth remain unclear.

Thus, we conducted genetic analyses of surgically resected GGNs (18). Genetic alterations in the *EGFR*, *KRAS*, *ALK*, and *HER2* genes were evaluated in 104 GGNs, and all lesions were categorized as EGFR-, KRAS-, ALK-, or HER2-positive or quadruple-negative because of mutually exclusive relationships among driver gene mutations. The frequencies of *EGFR*, *KRAS*, *ALK*, and *HER2* mutations were 64%, 4%, 3%, and 4%, respectively. To the best of our knowledge, this study is the only study to analyze the association between genetic alterations of GGNs and their growth. Our study demonstrated that *EGFR* mutation positivity (EGFR$^+$) was significantly associated with growth, whereas a quadruple-negative status was associated with no-growth (*Figure 4*). This finding is also supported by the result that a quadruple-negative status is associated with pathological noninvasiveness.

Clinical characteristics of patients with *EGFR* mutation and those with GGNs seem to be similar because EGFR+ GGNs account for the majority of all GGNs. As we summarized in *Table 1*, GGNs are found more in non-smokers and female. Considering that pathological features of GGNs are adenocarcinoma or its preinvasive lesions, GGNs and *EGFR* mutation share the same features: non-smoker, female, and adenocarcinoma. Regarding ethical differences, it could be suspected that GGNs, especially *EGFR*-mutant GGNs, may be found more in East Asian than in others although there are no data.

KRAS mutation

Although the general incidence of *KRAS* mutations of lung adenocarcinomas in Caucasians is approximately 26% (670/2,529), KRAS mutations tend to occur more frequently in smokers (34%) than in never-smokers (6%) (21). In Asians *KRAS* mutations were detected in only 8%

(429/5,125) in all cases (22).

When Sakamoto *et al*. examined *KRAS* mutations in various stages of preinvasive lesions and invasive adenocarcinoma, most *KRAS*-mutated tumors were categorized into AAH: the incidences of *KRAS* mutations were 33%, 12%, and 8% in AAH, AIS, and MIA, respectively (23). A similar trend was observed in another study, with KRAS detection rates of 27%, 17%, and 10% in each of the above stages of adenocarcinoma (24). Considering that the overall frequency of *KRAS* mutations in lung adenocarcinoma is limited to 13% (25), these findings cannot be explained without assuming that some tumors and preneoplastic lesions with *KRAS* mutations undergo spontaneous regression. This hypothesis was originally suggested by Yatabe *et al*. (26). One possible mechanism may be associated with the dual role of *KRAS*. Oncogenic Ras has been shown to cause senescence through the activation of the p53-p21 WAF and p16INK4A-Retinoblastoma tumor-suppressor pathways (27,28). Another potential explanation is that not all *KRAS* mutant AAHs are same and the differences are derived from the cells of origin. In analyses using genetically engineered mouse models, not all *KRAS*-mutant lung cells are equally permissive to transformation: only surfactant protein C+ alveolar type II cells are able to sustain *KRAS*-driven formation of AAH, whereas some of which progress to adenomas and malignant adenocarcinomas regardless of surrounding microenvironment or inflammatory stimulation (29,30). Additionally, the transcriptional analysis of KRAS-expressing AAH *in vivo* reveals that only a fraction retains the signature of advanced lung adenocarcinoma, whereas the others show a transcriptional profiling comparable to normal alveolar cells (31). In clinical and radiological aspects, *KRAS*-mutant GGNs on CT image seem to be very similar or identical. However, the origins of these nodules may not be identical, and this difference could cause different biological behavior: some gradually grow and others remain unchanged or disappear.

This seemingly paradoxical observation that *KRAS* mutation is more common in AAH than in invasive adenocarcinoma is in accordance with recent reports by Sivakumar *et al.* and Sato *et al.* (32). Sivakumar *et al.* analyzed normal tissue, AAH, and invasive adenocarcinoma from the same patients to assess progression of lung adenocarcinoma. Undeniably, these comparisons did not directly reflect the progression of lung cancer because the discordance rate of driver mutations between invasive adenocarcinoma and paired synchronous GGNs in the same patient was 80% (24/30) (33). Yet, *KRAS* mutations were detected in as many as 24% (4/17) of AAHs. Sato *et al.* also reported a relatively high frequency of *KRAS* mutations in Japanese patients with GGNs. *KRAS* mutations in codon 12 were detected in 17% (5/30) of resected GGNs (15). These data suggest that not all *KRAS* mutation-positive AAHs progress to more advanced adenocarcinomas (*Figure 4*).

BRAF mutation

BRAF mutations are detected in approximately 3% (18/687) of lung adenocarcinomas in Caucasians, and the V600E mutation accounts for approximately 50% of these tumors (34). *BRAF* mutations are categorized into 3 classes (35). Class 1 *BRAF* mutants (*BRAF* V600 mutations) are RAS-independent and activated as monomers. Class 2 mutants are RAS-independent and activated as dimers. Class 3 mutants are RAS-dependent and have impaired kinase activity, in other words, they are kinase-dead. Similar to the low frequency of *KRAS* mutations in Asians, *BRAF* mutations were detected in only 0.5% (26/5,125) of Asians (22).

In the above-mentioned study by Sivakumar *et al.*, the frequencies of *EGFR*, *KRAS*, and *BRAF* mutations in invasive adenocarcinoma were 47% (8/17), 6% (1/17), and 0%, respectively. However, the $BRAF^+$ rate in AAHs was as high as 29% (5/17) (32). Four of the five AAHs exhibited *BRAF* K601E mutation, and the other AAH harbored *BRAF* N581S mutation. These mutations belong to class 2 and class 3, respectively. These non-V600E mutations have been previously noted in lung cancer (36,37) and demonstrated to be oncogenic drivers (38). Sivakumar *et al.* hypothesized that progression to invasive adenocarcinoma is induced by an initial stimulation by the *BRAF* or *KRAS* mutations and the subsequent secondary mutations (32). Although this hypothesis is interesting, there must be an advantage to lose the mutated allele during progression in these cases. In other words, *KRAS* or *BRAF* are not acting as driver oncogenes. Confirmation of this hypothesis through analyses of sequential biopsied samples is essential.

Similar to AAHs with *KRAS* mutations, not all *BRAF*-mutated AAHs develop into invasive adenocarcinomas. The similar roles of *KRAS* and *BRAF* in the mitogen-activated protein kinase (MAPK) pathway might be associated with this phenomenon.

Timing of surgery for GGN

The criteria of surgery for GGNs vary depending on the guideline. According to the guidelines of the American College of Chest Physicians, surgical resection is

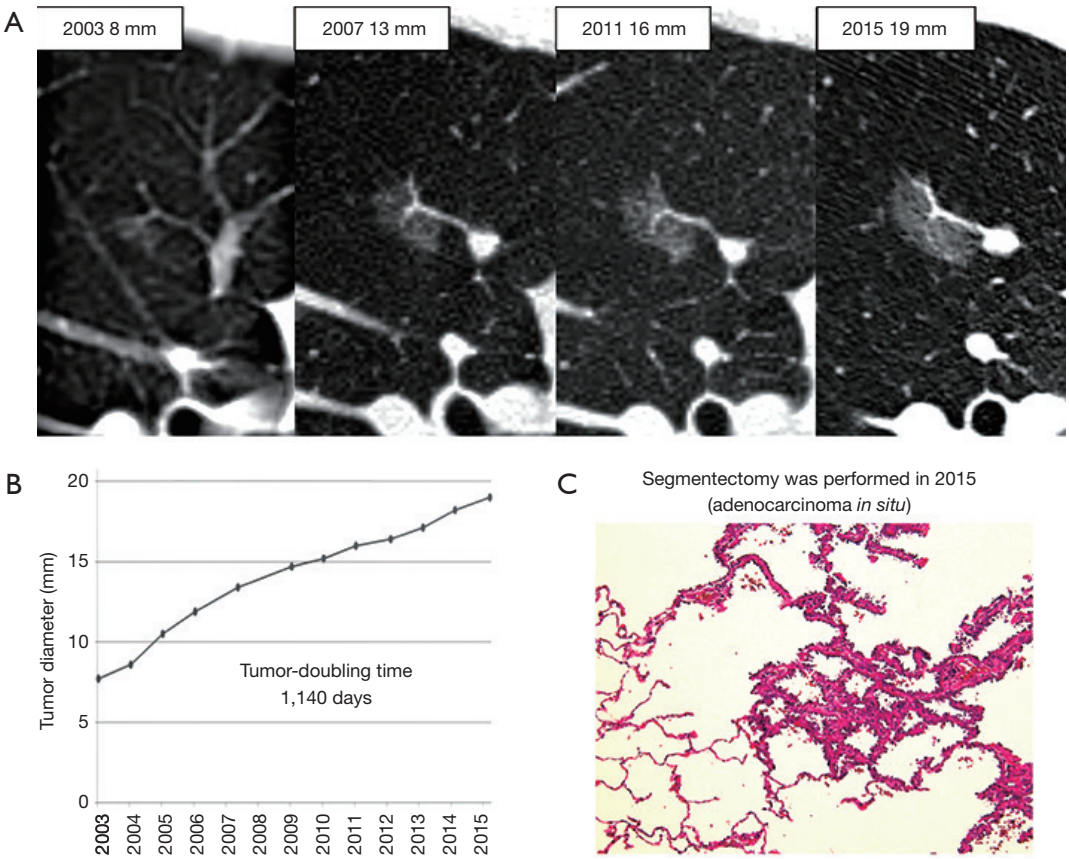

Figure 5 Computed tomography images and pathological features of representative pure GGN. (A) Pure GGN was detected in a 49-year-old male with previous smoking history of 4 pack years; This GGN slowly increased in diameter without appearance of solid components; (B) tumor-doubling time was 1,140 days; (C) segmentectomy was performed in 2015 after 12-years of follow-up. This tumor was diagnosed as adenocarcinoma *in situ* (hematoxylin-eosin staining, ×40). GGN, ground-glass nodule.

recommended for GGNs that meet any of the following conditions: any GGN with growth or the development of solid components, pure GGNs >10 mm with confirmed persistence, part-solid GGNs >8 mm with confirmed persistence, or part-solid GGNs >15 mm without follow-up (39). The Fleischner Society recommends that pure GGNs with the development of solid components or grow and persistent part-solid nodules with solid components ≥6 mm should be resected (16).

However, it is doubtful whether immediate surgery is necessary for all GGNs showing growth. In our case with pure GGN, segmentectomy was performed after 12 years' follow-up. Although the GGN had continued to grow for 12 years, tumor-doubling time was as long as 1,140 days and pathological diagnosis revealed that it was still AIS without invasive lesions (*Figure 5*). It is unclear when this type of tumor begins to invade surrounding structures and threaten patient's life and whether surgery is really necessary. Therefore, the balance between the benefits of surgery and life expectancy should be considered particularly in elderly patients.

Extent of surgery for GGN

A Clinical trial on radiological criteria

A prospective multi-institutional study was conducted by the Japan Clinical Oncology Group (JCOG) to identify radiological criteria that predict the pathologic noninvasiveness of clinical IA lung cancer arising in the periphery of the lung (JCOG 0201) (40). The consolidation/tumor ratio (C/T ratio) was used to evaluate the proportion of the ground-glass component. This study revealed that the specificities for the diagnosis of pathological non-invasiveness were 96.4% and 98.7% for lesions ≤3 cm with

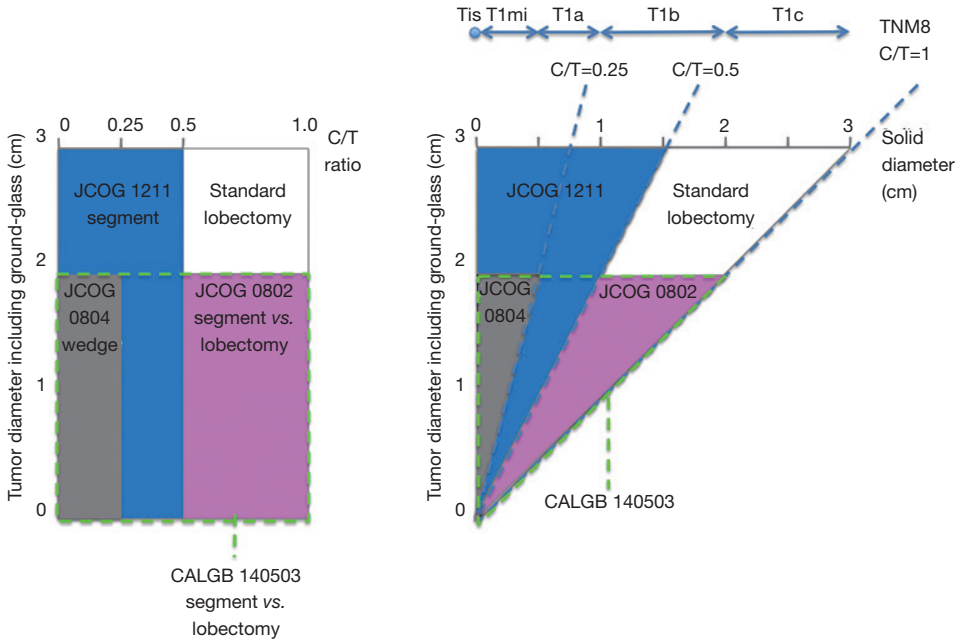

Figure 6 Summary of Japanese clinical trials evaluating the efficacy of limited surgery for GGNs. The inclusion criteria of each trial are summarized on the left side. The 8th TNM classifications using the solid diameter were combined with the abovementioned inclusion criteria using the consolidation/tumor ratio (C/T ratio). GGN, ground-glass nodule.

a C/T ratio ≤0.5 (>50% ground-glass component) and lesions ≤2 cm with a C/T ratio ≤0.25 (>75% ground-glass component), respectively (40).

The long-term survival rate of patients in the JCOG 0201 trial who underwent lobectomy and lymph node dissection was reported. The overall and relapse-free 5-year survival rates of all the patients were 90.6% and 84.7%, respectively. When a lesion size ≤3 cm with a C/T ratio ≤0.5 was used as a cutoff, the 5-year overall survival rates of radiological noninvasive and invasive adenocarcinomas were 96.7% and 88.9%, respectively (P<0.001). With the use of lesions ≤2 cm with C/T ratios ≤0.25, the 5-year overall survival rates of radiological noninvasive and invasive adenocarcinomas were 97.1% and 92.4%, respectively (P=0.259) (41).

Clinical trials on limited surgery for GGNs

Although the standard treatment for operable non-small cell lung cancer is lobectomy with dissection of ipsilateral hilar and mediastinal lymph nodes (42), retrospective data support the efficacy and less invasive nature of limited surgery such as segmentectomy or wedge resection for GGNs. Based on the results of the JCOG 0201 study, three clinical trials evaluating the efficacy of limited surgery were conducted (*Figure 6*). JCOG 0802 is a phase III trial comparing lobectomy and segmentectomy for lung cancer ≤2 cm with C/T ratio >0.5 (43), which is similar to the Cancer and Leukemia Group B (CALGB) 140503 trial in the United States (44). JCOG 0804 is a phase III non-randomized confirmatory study of wedge resection for lung cancer ≤2 cm with a C/T ratio ≤0.25 (45). JCOG 1211 is a confirmatory Phase III trial of segmentectomy for lung cancer ≤3 cm with a C/T ratio ≤0.5 (46).

The results of JCOG 0804 were presented in ASCO 2017 (47). The surgical procedure is basically set as wedge resection, but segmentectomy is allowed when the surgical margin is insufficient (<5 mm) or when the tumor is histologically invasive. The 5-year recurrence-free survival was 99.7%, which met the primary endpoint, and no local relapse was noted.

The TNM classification was revised in 2017. Regarding the measurement of a GGN, the diameter of the solid component within the part-solid nodule on CT instead of the whole tumor size should be measured for staging (48). The application of the results of the JCOG trials to the 8th TNM classification is somewhat complicated because the JCOG trials measure the C/T ratio while the TNM classification addresses the direct measurement of the solid

component (*Figure 6*).

Conclusions

Recent clinical and genetic data mark the beginning of elucidating biological aspects of GGNs. GGNs are often found in never-smokers, but smoking is a predictor of growth. In terms of genetic alterations, *EGFR* mutation, which is associated with never-smokers, is also a predictor of growth, whereas a subset of GGNs with smoke-related *KRAS* or *BRAF* mutations may undergo spontaneous regression. Additionally, driver mutation-negative GGNs tend to remain unchanged. Although these data superficially appear paradoxical, further genetic analyses and clinical trials could contribute to deeper understanding of preinvasive adenocarcinoma and the development of less invasive management strategies for GGNs.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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