ORIGINAL ARTICLE

Natural History of Pulmonary Subsolid Nodules: A Prospective Multicenter Study

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ABSTRACT

Introduction: The purpose of this study was to evaluate the natural course of the progression of pulmonary subsolid nodules (SSNs).

Materials and Methods: Eight facilities participated in this study. A total of 795 patients with 1229 SSNs were assessed for the frequency of invasive adenocarcinomas. SSNs were classified into three categories: pure ground-glass nodules (PGGNs), heterogeneous GGNs (HGGNs) (solid component detected only in lung windows), and part-solid nodules.

Results: The mean prospective follow-up period was 4.3 ± 2.5 years. SSNs were classified at baseline as follows: 1046 PGGNs, 81 HGGNs, and 102 part-solid nodules. Among the 1046 PGGNs, 13 (1.2%) developed into HGGNs and 56 (5.4%) developed into part-solid nodules. Among the 81 HGGNs, 16 (19.8%) developed into part-solid nodules. Thus, the SSNs at the final follow-up were classified as follows:

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977 PGGNs, 78 HGGNs, and 174 part-solid nodules. Of the 977 PGGNs, 35 were resected (nine minimally invasive adenocarcinomas [MIAs], 21 adenocarcinomas in situ [AIS], and five atypical adenomatous hyperplasias). Of the 78 HGGNs, seven were resected (five MIAs and two AIS). Of the 174 part-solid nodules, 49 were resected (12 invasive adenocarcinomas, 26 MIAs, 10 AIS, and one adenomatous hyperplasia). For the PGGNs, the mean period until their development into part-solid nodules was 3.8 ± 2.0 years, whereas the mean period for the HGGNs was 2.1 ± 2.3 years ($p = 0.0004$).

Conclusion: This study revealed the frequencies and periods of development from PGGNs and HGGNs into part-solid nodules. Invasive adenocarcinomas were diagnosed only among the part-solid nodules, corresponding to 1% of all 1229 SSNs.

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Keywords: Subsolid nodule; Ground-glass nodule; Natural history; Computed tomography; Lung adenocarcinoma

Introduction

With the introduction of computed tomography (CT) screening for lung cancer,[1–4] pulmonary subsolid nodules (SSNs) have emerged as a possible indicator of lung cancer.[5–9] SSNs are classified into pure ground-glass nodules (PGGNs) and part-solid GGNs. PGGNs are focal nodular areas of increased lung attenuation, including both well and poorly defined lesions through which normal parenchymal structures, including airways and vessels, can be visualized; part-solid GGNs include a combination of ground-glass and solid components, the latter obscuring the underlying lung architecture.[10] Although some SSNs are transient,[11,12] persistent SSNs have a high likelihood of being malignant.[7,13] However, the natural history of SSNs has not yet been clarified thoroughly.[10,14] Regarding the causes of SSNs, transient SSNs have been mainly caused by inflammation,[11,15,16] whereas most of the persistent SSNs have been preinvasive or invasive adenocarcinomas.[17] Although various algorithms have been developed to address these lesions,[10,18–22] to our knowledge, these algorithms have not been based on prospective follow-up results for SSNs.

Thus, the purpose of this prospective multicenter study was to evaluate the natural course of the progression of pulmonary SSNs.

Materials and Methods

Ethics Statement

This study was conducted with the approval of the institutional review boards of each of the eight participating institutions. Informed consent was obtained from the patients.

Participating Institutions

The eight institutions that participated in this study were as follows: Kanagawa Cancer Center, National Cancer Center Hospital East, National Cancer Center Research Center for Cancer Prevention and Screening, Niigata Cancer Center, Osaka Medical Center for Cancer and Cardiovascular Diseases, Shiga University of Medical Science, Shikoku Cancer Center, and Tochigi Cancer Center.

Nodule-Related Entry Criteria

The inclusion criteria for SSNs were as follows. First, the persistence of the SSNs for 3 months was confirmed after the initial CT examination. Second, the included GGNs had a long axial diameter of 3 cm or less.[23] Third, the included part-solid nodules had a long axial diameter of 3 cm or less and a solid component with a long axial diameter of 5 mm or less when viewed using a mediastinal window. Finally, each SSN had been evaluated using thin-section CT images with a section thickness of 1.25 mm or less.

Numbers of Patients and SSNs

A total of 845 patients with 1325 SSNs agreed to participate in this study between April 2009 and December 28, 2011. However, 57 SSNs in 50 patients were excluded because of the following reasons: availability of thick-section CT images only (31 nodules in 26 patients [21 with one nodule and five with two nodules]), resection within 2 months after the first CT scan (seven nodules in five patients [three with one nodule and two with two nodules]), a decrease in maximal diameter of 2 mm or more (six nodules in six patients), a maximal diameter of the solid component larger than 5 mm (five nodules in five patients), fluctuation in maximal diameter (three nodules in three patients, with *fluctuating* defined as an increase in diameter after a decrease in diameter or vice versa, as a result of which an increase in maximal diameter of 2 mm or more from the baseline CT could not be determined), a diameter of an SSN larger than 3 cm (two nodules in two patients), disappearance after persistence for at least 3 months (two nodules in two patients), and hospital transfer (one nodule in one patient). In addition, 30 other SSNs in patients with multiple SSNs were excluded because of the following reasons: availability of thick-section CT images only (20 nodules in 20 patients), diameter of solid component larger than 5 mm (five nodules in four patients [three with one nodule and one with two nodules), and diagnosis of inflammation on the basis of the conclusions of a radiology panel (five nodules in one

patient). Thus, 795 patients with 1238 SSNs were eligible for an assessment of the frequency of growth.

After the exclusion of nine resected nodules (two non–lung cancer nodules reviewed by the pathology panel and seven nodules not reviewed by the pathology panel because those pathological specimens were not sent to the study secretariat by the last review session), the frequency of invasive adenocarcinomas was assessed in 795 patients with 1229 SSNs.

The final evaluation of the presence or absence of progression of SSNs was performed as of December 27, 2013. Information regarding patient sex, age, smoking status, past history of lung cancer, reasons for SSN detection, and number of SSNs per patient was collected.

The flow diagram is shown in a figure (see Fig., Supplementary Data 1).

Protocol for CT scanning

The section thickness was prescribed as 1.25 mm or less. Other parameters (i.e., tube voltage, tube current, pitch factor, field of view, and reconstruction kernel) were based on the protocols of each institution (see Table, Supplementary Data 2). The interval for the CT scans was, in principle, 1 year, although the intervals varied for some follow-up CT examinations depending on the situation at each institution or the patient's availability.

Classification of SSNs

In this study, the SSNs were classified into three groups on the basis of their texture (Fig. 1): pure GGNs (PGGNs), heterogeneous GGNs (HGGNs), and part-solid nodules.

Surgery

The criteria for surgery were not prescribed by the study protocol. Decisions regarding resection were made according to the protocols of each institution.

Follow-up Report

Follow-up reports on the patients treated at each institution were submitted to the study secretariat. The follow-up reports contained anonymized patient identification numbers, dates of the CT examinations, slice thickness, slice interval, maximal diameter and perpendicular diameters of each SSN, presence or absence of a solid component in lung windows (if present, the maximal diameter and perpendicular diameter of the solid component were included), and presence or absence of a solid component in mediastinal windows (if present, the maximal diameter and perpendicular diameter of the solid component were included) for each CT examination. A single doctor at each institution who had more than 10 years of experience reading chest CT images measured the diameters of the SSNs and solid components. Growth of an SSN or solid component was defined as an increase in the maximal diameter of 2 mm or more. The appearance of a solid component in a PGGN or a HGGN when viewed using a mediastinal window was also defined as growth. For patients who underwent resection, the date of surgery, surgical procedure, pathological diagnosis, and pathological stage were also included in the report.

Central Review by Radiology Panel

The radiology panel consisted of three board-certified radiologists (K. A., 25 years of experience in reading chest CT scans as of March 2012; K. K., 27 years of experience in reading chest CT scans; and S. M., 31 years of experience in reading chest CT scans). The radiology panel reviewed the CT images of patients in which an increase in the size of an SSN, a change from PGGN to HGGN, a change from PGGN to part-solid nodule, a change from HGGN to part-solid nodule, or an increase in the size of a solid component had been noted by the participating institution where the images had originated. The CT images had been anonymized at each facility and sent to the study secretariat. The three radiologists gathered together at the Research Center for Cancer Prevention and Screening and reviewed these CT images simultaneously on the monitor of an Apple iMac using the OsiriX MD (Pixmeo SARL, Bernex, Switzerland). The lung windows were set at a window width of 1500 Hounsfield units (HU) and a window level −500 HU. Mediastinal windows for the measurement of solid components were set at a window width of 350 HU and a window level of 40 HU. Assessments of the consistency of the SSNs were based on the consensus of the three radiologists. The measurement of the diameter of an SSN in a lung window or the measurement of the diameter of a solid component in a mediastinal window was performed by a single radiologist during all the review sessions and confirmed by the consensus of the three radiologists. For measurements of solid components, the CT image was magnified by an appropriate power to enable the measurement of the solid component in a mediastinal window. The radiologists were not informed whether the patient had undergone a resection or whether a pathological diagnosis was present or absent.

Central Review by Pathology Panel

The pathology panel consisted of three board-certified pathologists (A.M.M., 17 years of experience as of March 2012; Y.M., 29 years of experience; and M.N, 33 years of experience). Pathological specimens (stained using hematoxylin-eosin stain and elastica van Gieson stain) were sent to the study secretariat. The three pathologists

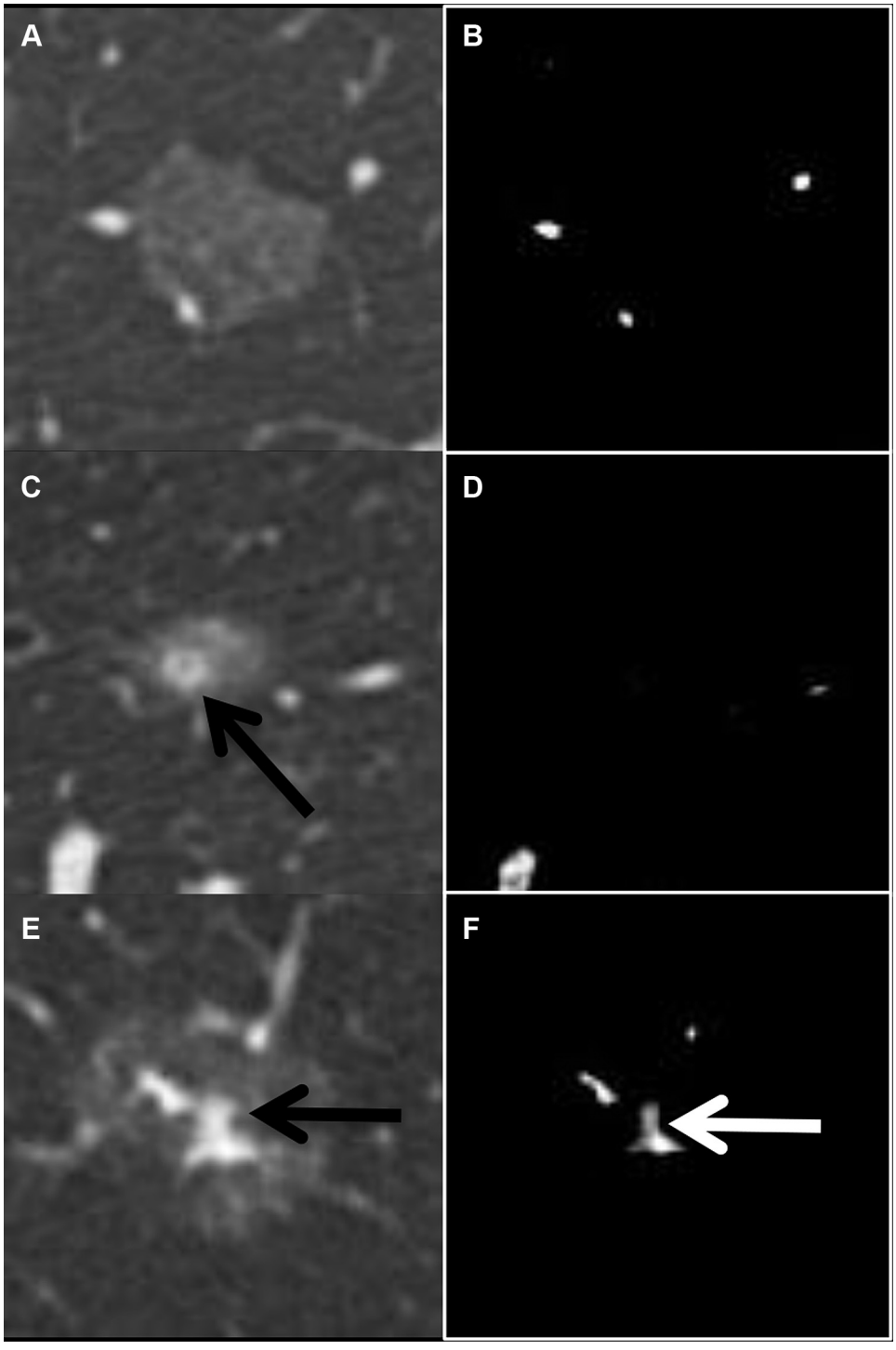

Figure 1. Classification of subsolid nodules. (*A*) The first group of pure ground-glass nodules (GGNs), referred to here as pure GGNs, consisted of homogeneous opacities when viewed using the lung window. (*B*) A solid component in the mediastinal window was not observed. (*C* and *D*) The second group consisted of heterogeneous GGNs, or GGNs with a solid component (*black arrow*) in only the lung window but not in the mediastinal window. (*E* and *F*) The third group of part-solid nodules consisted of GGNs with a solid component both in the lung window (*black arrow*) and in the mediastinal window (*white arrow*).

gathered together at the National Cancer Center Hospital and reviewed these specimens using a multi-headed microscope simultaneously without information regarding the CT findings. Lung adenocarcinomas were classified on the basis of the 2015 World Health Organization (WHO) classification of tumors of the lung, pleura, thymus, and heart[24]; that is, they were classified as preinvasive lesions (atypical adenomatous hyperplasia

[AAH] or adenocarcinoma in situ [AIS]), minimally invasive adenocarcinoma (MIA), invasive adenocarcinoma, or variants of invasive adenocarcinoma. If an invasive focus was detected in a pathological specimen, the maximal diameter of the invasive focus was measured by a single pathologist during all the review sessions and confirmed by the consensus of the three pathologists.

CT-Pathological Correlation of Solid Components on CT Images in MIAs among Part-Solid Nodules

The maximal diameters of the solid components in mediastinal windows on CT images of MIAs were correlated with the maximal diameters of invasive foci in pathological specimens of the MIAs.

VDT of Resected SSNs

The volume-doubling times (VDTs) of the resected SSNs that showed growth, i.e., an increase of 2 mm or more in the maximal diameter of the SSN or an increase of 2 mm or more in the maximal diameter of the solid components, were calculated using a modified Schwartz equation[25]: $VDT = (t \times \log 2)/[\log (Vt/V0)]$, where Vt and V0 are respectively the volumes of an SSN or a solid component at last thin-section CT scan and baseline thin-section CT scan, t is the interval between the two CT scans, and $V = \pi/6 \times ab^2$ (where a is the maximal diameter of an SSN or a solid component and b is perpendicular dimension of an SSN or a solid component).

Statistical Analyses

The mean and median age, maximum diameter of the SSN, maximum diameter of the solid component, maximum diameter of the invasive foci, follow-up period, and VDT were calculated. Multiple comparisons of the mean diameters of the solid components of the AIS, MIAs, and invasive adenocarcinomas (three groups), and of the mean follow-up periods of the SSNs (three or four groups) were evaluated using the Kruskal-Wallis test followed by the Wilcoxon signed rank test with Bonferroni correction. Other comparisons were evaluated using the Mann-Whitney U test. Univariate analyses for factors affecting the time until SSN growth of 2 mm or more in maximal diameter, the appearance of a solid component in a PGGN or HGGN, and solid component growth of 2 mm or more in maximal diameter were analyzed using the Kaplan-Meier method. Differences between curves were determined using the log-rank test. A multivariate analysis of several variables was performed using the Cox proportional hazards regression model. An evaluation of the cutoff value for the maximal diameter of a solid component in the mediastinal window for differentiating AIS and MIA from invasive adenocarcinoma was performed using a receiver operating characteristic analysis. All the statistical evaluations were performed using JMP version 11 (SAS Institute Inc., Cary, NC). A p value less than 0.05 was considered statistically significant for the Mann-Whitney U test. When the Bonferroni correction was used, a p value less than 0.0167 was considered statistically significant for comparisons of three groups and a p value less than 0.0083 was considered statistically significant for comparisons of four groups.

Results

Characteristics of the Patients

Table 1 shows the characteristics of the patients. The 795 patients consisted of 454 women and 341 men (mean age 62 ± 9.4 years, median age 62 years, and interquartile range [IQR] 56–69 years). Among the 795 patients, 588 patients with SSNs were detected using CT screening for lung cancer, and the other 207 patients with SSNs were detected using nonscreening CT

Table 1. Characteristics of the Patients (N = 795)

Characteristic	n	%
Sex		
Female	454	57.1
Male	341	42.9
Reason for detection		
CT screening	588	74.0
Incidental	133	16.7
Chest radiograph screening	45	5.7
Symptomatic	29	3.6
Smoking status		
Never smoked	474	59.6
Ex-smoker	259	32.6
Smoker	58	7.3
Unknown	4	0.5
History of lung cancer		
Absent	729	91.7
Present	64	8.1
Unknown	2	0.3
No. SSNs		
Solitary	549	69.1
Multiple	246	30.9
Eligible for assessment of frequency of growth (No. nodules = 1238)		
Consistency		
PGGN	1053	85.1
HGGN	81	6.5
Part-solid	104	8.4
Assessment of invasive adenocarcinoma frequency (No. nodules = 1229)		
Initial consistency		
PGGN	1046	85.1
HGGN	81	6.6
Part-solid	102	8.3

CT, computed tomography; SSN, subsolid nodule; PGGN, pure ground-glass nodule; HGGN, heterogeneous ground-glass nodule.

examinations. The reasons for the nonscreening CT examinations were as follows: chest radiograph abnormality was detected incidentally during a follow-up for another disease (meaning that the SSN was not visible on the chest radiograph, but another abnormal shadow was pointed out on the chest radiograph) (n = 133 patients); workup after chest radiography screening for lung cancer (meaning that the SSN was not visible on the chest radiograph, but another abnormal shadow was pointed out on the chest radiograph) (n = 45 patients); and symptoms leading to a suspicion of pulmonary disease (n = 29 patients). A total of 1238 SSNs that were eligible for an assessment of the frequency of growth were classified into three subgroups: 1053 PGGNs, 81 HGGNs, and 104 part-solid nodules; the mean diameter of the SSNs was 7.8 ± 3.4 mm (median 7.0 mm, IQR 5.5–9.0 mm). The median number of SSNs per patient was 1 (IQR 1–2). No new SSNs developed in any of the patients in this study cohort during the observation period of this study.

SSN Growth

The time until SSN growth of 2 mm or more in maximal diameter, the time until the appearance of a solid component, and the time until solid component growth of 2 mm or more in maximal diameter are shown according to the SSN consistency in Figure 2. For the PGGNs and HGGNs, the curves for a solid component growth of 2 mm or more did not show any growth during the first 2 years of the follow-up period (Fig. 2*C*) whereas the curve for a solid component growth of 2 mm or more for part-solid nodules showed growth at 6 months after the start of the follow-up period.

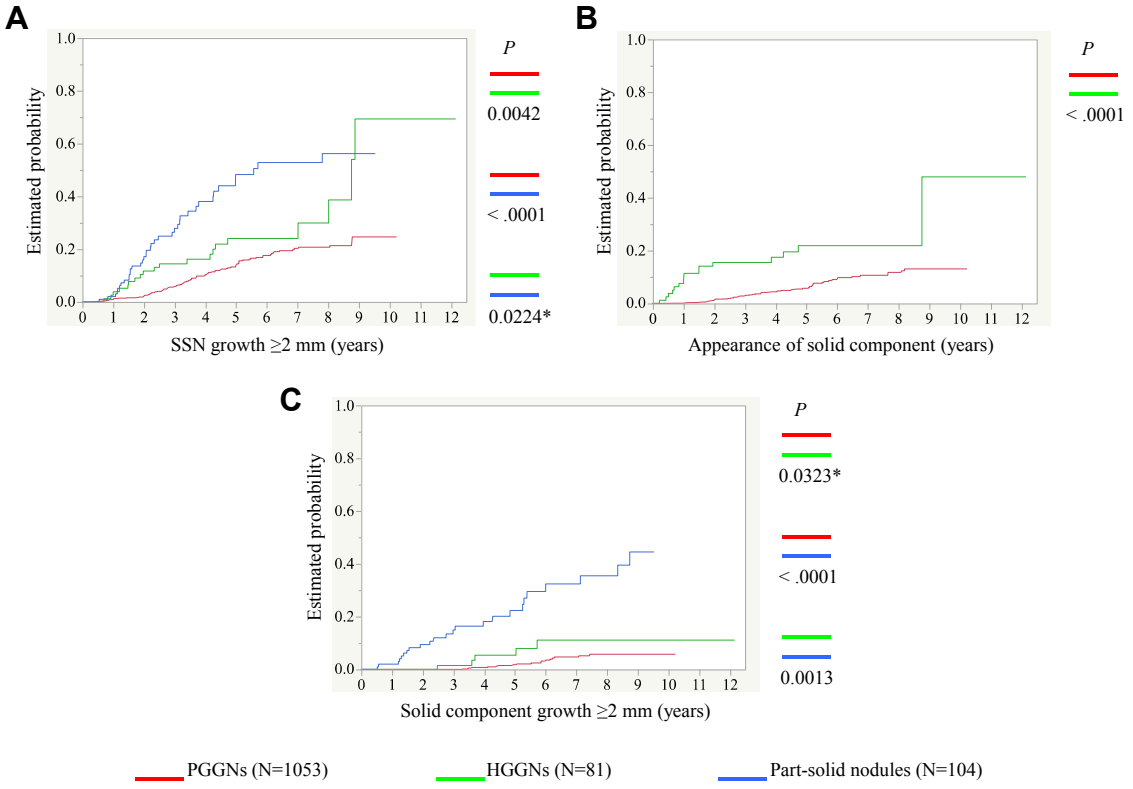

Figure 2. Growth curves of subsolid nodules (SSNs). The red, green, and blue curves indicate the accumulated percentages of growth of pure ground-glass nodules (PGGNs), heterogeneous ground-glass nodules (HGGNs), and part-solid nodules, respectively. Each pair of colored lines on the right side of each graph shows the results of a log-rank test (i.e., the red and green lines indicate PGGNs versus HGGNs, whereas the red and blue lines indicate PGGNs versus part-solid nodules and the green and blue lines indicate HGGNs versus part-solid nodules, respectively). (*A*) Time until SSN growth of 2 mm or more according to SSN consistency. The 2-year and 5-year estimated probabilities of nodule growth were 2% and 14% for PGGNs, 12% and 24% for HGGNs, and 17% and 48% for part-solid nodules, respectively. Each pair of growth curves except for that for HGGNs and part-solid nodules showed a statistically significant difference after Bonferroni correction (*). (*B*) Time until the appearance of a solid component according to SSN consistency. The 2-year and 5-year estimated probabilities of the appearance of a solid component were 1% and 6% for PGGNs and 16% and 22% for HGGNs; the pair of growth curves showed a statistically significant difference. (*C*) Time until solid component growth of 2 mm or more according to SSN consistency. The 2-year and 5-year estimated probabilities of solid component growth were 0% and 2% for PGGNs, 0% and 5% for HGGNs, and 9% and 22% for part-solid nodules, respectively. Each pair of growth curves except for that for PGGNs and HGGNs showed a statistically significant difference after Bonferroni correction (*).

Univariate and multivariate analyses for variables affecting the time until SSN growth are shown in Tables 2 and 3. Multivariate analyses were performed according to each consistency and each type of growth: the main factor for predicting growth was the initial maximal diameter of the SSN. The time until PGGN growth according to the initial maximal diameter and sex is shown in Figure 3 (see Fig., Supplementary Data 3). Univariate analyses indicated that SSN growth events detected using nonscreening CT scans occurred more often than SSN growth events detected using screening CT scans (Table 2); however, the multivariate analysis did not show any significant difference between screening CT–detected SSNs and nonscreening CT–detected SSNs (Table 3).

Frequency and Period of Progression into Part-Solid Nodules from PGGNs and HGGNs

After the exclusion of nine resected nodules (two non–lung cancer nodules [an alveolar collapse and a nodular lymphoid hyperplasia] and seven lesions that were not reviewed by the pathology panel), the remaining 1229 pulmonary SSNs among which the frequency of invasive adenocarcinoma had been assessed were classified at baseline as follows: 1046 PGGNs, 81 HGGNs, and 102 part-solid nodules (Table 1). The mean prospective follow-up period was 4.3 ± 2.5 years (median 3.5 years, IQR 2.4–6.0 years). Among the 1046 PGGNs, 13 developed into HGGNs and 56 (5.4% [56 of 1046]) developed into part-solid nodules. Among the 81 HGGNs, 16 (19.8% [16 of 81]) developed into part-solid nodules. Thus, the 1229 SSNs were classified at the time of the final follow-up as follows: 977 PGGNs (79.5% [977 of 1229]), 78 HGGNs (6.3% [78 of 1229]), and 174 part-solid nodules (14.2% [174 of 1229]). For the 56 PGGNs, the mean period until development into a part-solid nodule was 3.8 ± 2.0 years (median 3.4 years, IQR 2.0–5.2); for the 16 HGGNs, the mean period until development into a part-solid nodule was 2.1 ± 2.3 years (median 1.0 year, IQR 0.7–3.4 years) ($p = 0.0004$).

Histopathological Features of the Resected SSNs and Frequency of Invasive Adenocarcinomas

Of the 977 PGGNs, the 35 resected PGGNs consisted of nine MIAs, 21 AIS, and five AAHs; of the 78 HGGNs, the seven resected HGGNs consisted of five MIAs and two AIS; and of the 174 part-solid nodules, the 49 part-solid nodules consisted of 12 invasive adenocarcinomas (nine lepidic, two acinar, and one solid), 26 MIAs, 10 AIS, and one AAH. In total, among the 1229 SSNs, 12 invasive adenocarcinomas (1.0%), 40 MIAs (3.3%), 33 AIS (2.7%), and six AAHs (0.5%) were resected as of December 27, 2013, after a mean prospective follow-up period of 4.3 years.

Surgical Procedures for Resected Lung Cancer Cases and Outcomes

The total number of patients with resected SSNs was 80; 71 patients had single resected SSNs and nine patients had multiple resected SSNs (two with three SSNs and seven with two SSNs). The surgical procedures were as follows: segmentectomy in 22 patients, wedge resection in 33 patients, and lobectomy in 25 patients. All the tumor resections were confirmed pathologically to be complete. All the patients were stage I (78 stage IA and two stage IB). The mean follow-up period after resection was 3.0 ± 1.1 years (median 3.0 years, IQR 2.0–3.9 years). As of March 31, 2015, no recurrences had occurred in any of the patients who had undergone resection.

Solid Components in Part-Solid Nodules

The relationship between the diameters of the solid components on thin-section CT images in mediastinal windows and the pathological diagnoses was analyzed (see Table, Supplementary Data 4). The mean diameters of the solid components in the 10 AIS, 26 MIAs, and 12 invasive adenocarcinomas were 2.5 ± 1.3 mm (median 2.8 mm, IQR 1.2–3.7 mm), 3.3 ± 2.0 mm (median 3.0 mm, IQR 1.9–4.7 mm), and 5.5 ± 2.7 mm (median 4.8 mm, IQR 3.7–7.2 mm), respectively; each comparison between groups except for the comparison of AIS and MIA was statistically significant (AIS versus invasive adenocarcinomas, $p = 0.0045$; MIA versus invasive adenocarcinomas, $p = 0.0087$; AIS versus MIA, $p = 0.48$). The mean follow-up periods for the 10 AIS, 26 MIAs, and 12 invasive adenocarcinomas from baseline CT examination until surgery were 4.2 ± 2.5 years (median 5.2 years, IQR 1.7–6.2 years), 3.3 ± 2.6 years (median 2.6 year, IQR 1.0–4.9 years), and 3.3 ± 1.6 years (median 3.3 years, IQR 2.0–4.4 years), respectively; none of the comparisons between groups were statistically significant (see Table, Supplementary Data 5).

The mean diameters of part-solid nodules in 10 AIS, 26 MIAs, and 12 invasive adenocarcinomas were 16.6 ± 7.3 mm (median 16.2 mm, IQR 9.6–24.0 mm), 15.6 ± 4.5 mm (median 15.0 mm, IQR 13.0–18.4 mm), and 14.8 ± 4.5 mm (median 13.9 mm, IQR 12.3–17.7 mm), respectively; none of the comparisons between groups were statistically significant.

Period Until an Increase in the Diameter of the Solid Component in Part-Solid Nodules to 3.3 mm or More on First-Time CT Examinations during Follow-up

On the basis of an receiver operating characteristic analysis for differentiating AIS and MIA from invasive adenocarcinomas, the cutoff value of the maximal

Table 2. Univariate Analyses Based on SSN Consistency and Each Growth Type

			SSN Growth ≥2 mm			Appearance of Solid Component			Solid Component Growth ≥2 mm		
			Estimated Probability			Estimated Probability			Estimated Probability		
Consistency	Variable	N§	2 y	5y	*p* Value	2y	5y	*p* Value	2y	5y	*p* Value
PGGN	Sex				0.0004			0.0834			0.3033
N§ = 635	Male	280	0.06	0.25		0.03	0.13		0.00	0.05	
	Female	355	0.02	0.15		0.02	0.06		0.00	0.02	
	Age				0.0011			0.0815			0.0258
	>60	345	0.04	0.25		0.02	0.11		0.00	0.05	
	≤60	287	0.02	0.14		0.02	0.07		0.00	0.01	
	Initial diameter, mm				<0.0001			<0.0001			<0.0001
	>10	128	0.13	0.54		0.10	0.20		0.00	0.07	
	≤10	507	0.01	0.11		0.00	0.07		0.00	0.02	
	Smoking status				<0.0001			0.0098			0.0664
	Smoker[a]	257	0.06	0.27		0.03	0.15		0.00	0.05	
	Never Smoked	378	0.01	0.14		0.02	0.05		0.00	0.02	
	History of lung cancer				0.0339			0.4289			0.0105
	Present	46	0.02	0.30		0.05	0.13		0.00	0.04	
	Absent	589	0.03	0.19		0.02	0.09		0.00	0.03	
	No. SSNs				0.2194			0.2087			0.6743
	Solitary	432	0.03	0.20		0.02	0.09		0.00	0.04	
	Multiple	203	0.05	0.20		0.03	0.11		0.00	0.01	
	Reason for detection				0.1941			0.0764			0.0848
	CT screening	492	0.03	0.20		0.02	0.08		0.00	0.03	
	Other	143	0.05	0.20		0.03	0.14		0.00	0.03	
HGGN	Sex				0.3702			0.8075			0.3355
N§ = 70	Male	21	0.24	0.36		0.10	0.26		0.00	0.00	
	Female	49	0.07	0.16		0.15	0.19		0.00	0.03	
	Age				0.3239			0.5282			0.2233
	>60	44	0.10	0.25		0.14	0.24		0.00	0.04	
	≤60	26	0.16	0.20		0.12	0.18		0.00	0.00	
	Initial diameter, mm				0.009			0.0769			0.3877
	>10	29	0.23	0.38		0.23	0.40		0.00	0.00	
	≤10	41	0.05	0.12		0.08	0.11		0.00	0.03	
	Smoking status				0.0939			0.2939			0.3951
	Smoker[a]	19	0.26	0.39		0.17	0.33		0.00	0.00	
	Never smoked	51	0.06	0.16		0.12	0.17		0.00	0.03	
	History of lung cancer				0.0127			0.2364			0.8231
	Present	7	0.33	0.50		0.17	1.00		0.00	0.00	
	Absent	63	0.10	0.19		0.13	0.19		0.00	0.03	
	No. SSNs				0.0815			0.0476			0.4186
	Solitary	57	0.13	0.19		0.11	0.15		0.00	0.03	
	Multiple	13	0.08	0.33		0.25	0.42		0.00	0.00	
	Reason for detection				0.2872			0.9921			0.081
	CT screening	37	0.12	0.16		0.11	0.20		0.00	0.00	
	Other	33	0.13	0.32		0.16	0.24		0.00	0.05	
Part-solid nodule	Sex				0.3851			—			0.9823
N§ = 84	Male	38	0.21	0.56		—	—		0.03	0.20	
	Female	46	0.17	0.16		—	—		0.14	0.29	
	Age				0.1382			—			0.013
	>60	56	0.23	0.62		—	—		0.12	0.31	
	≤60	28	0.12	0.32		—	—		0.04	0.13	
	Initial diameter, mm				<0.0001			—			0.0017
	>10	36	0.33	0.87		—	—		0.16	0.38	
	≤10	48	0.10	0.30		—	—		0.04	0.17	

(continued)

Table 2. Continued

			SSN Growth ≥2 mm			Appearance of Solid Component			Solid Component Growth ≥2 mm		
			Estimated Probability			Estimated Probability			Estimated Probability		
Consistency	Variable	N§	2 y	5y	*p* Value	2y	5y	*p* Value	2y	5y	*p* Value
	Smoking status				0.5773			–			0.6425
	Smoker[a]	41	0.19	0.59		–	–		0.03	0.17	
	Never Smoked	43	0.19	0.42		–	–		0.16	0.31	
	History of lung cancer				0.0001			–			0.3645
	Present	11	0.18	1.00		–	–		0.10	0.41	
	Absent	73	0.19	0.40		–	–		0.09	0.23	
	No. SSNs				0.5756			–			0.8226
	Solitary	57	0.23	0.53		–	–		0.06	0.25	
	Multiple	27	0.12	0.44		–	–		0.15	0.25	
	Reason for detection				0.0207			–			0.0126
	CT screening	56	0.18	0.36		–	–		0.08	0.21	
	Other	28	0.21	0.79		–	–		0.12	0.33	

[a]Includes current smokers and ex-smokers.
SSN, subsolid nodule; N§, number of patients; PGGN, pure ground-glass nodule; HGGN, heterogeneous ground-glass nodule; CT, computed tomography.

diameter of a solid component was 3.3 mm, yielding a sensitivity of 61% and a specificity of 91% (see Fig., Supplementary Data 6). During the follow-up of the SSNs, 20 part-solid nodules developed from PGGNs (36% [20 of 56], group A), five part-solid nodules developed from HGGNs (31% [five of 16], group B), and 22 part-solid nodules with solid components 3 mm or less in maximal diameter at the first thin-section CT scan (24% [22 of 93], group C) developed from part-solid nodules with a solid component 3.3 mm or larger in maximal diameter when viewed using a mediastinal window. The minimum periods for the development of part-solid nodules with a solid component 3.3 mm or larger in maximal diameter were 1.8 years for group A, 2.5 years for group B, and 6 months for group C, respectively (Fig. 4).

CT-Pathological Correlation of Solid Components on CT Images in 26 MIAs Resected among the 174 Part-Solid Nodules

Among 18 MIAs (69% [18 of 26]), if the diameter of an invasive focus <1 mm (n = 2) was assumed to be 0.9 mm in diameter, all the diameters of the solid components (mean 4.0 ± 2.0 mm, median 3.5 mm, IQR 2.8–5.0 mm) on CT images viewed using a mediastinal window were larger than the diameters of the invasive foci in the 18 MIAs (mean 1.5 ± 1.0 mm, median 1.0 mm, IQR 1.0–2.0 mm). The difference between the mean diameter of the solid components viewed using a mediastinal window and the mean diameter of the invasive foci in the 18 MIAs was statistically significant ($p < 0.0001$). In three of the 18 MIAs, the maximal diameters of the solid components viewed using a mediastinal window were larger than 5 mm (5.3 mm, 7.2 mm, and 9.1 mm, with corresponding invasive foci of 2 mm, <1 mm, and 3 mm in maximal diameter, respectively). In the remaining eight MIAs (31% [8 of 26]), all the maximal diameters of the invasive foci (mean 3.1 ± 1.3 mm, median 3.5 mm, IQR 2.0–4.4 mm) were larger than the maximal diameters of the solid components viewed using a mediastinal window (mean 2.0 ± 1.3 mm, median 1.9 mm, IQR 0.8–3.0 mm). The difference between the mean diameter of invasive foci and the mean diameter of the solid components in the eight MIAs was not statistically significant ($p = 0.0645$); the difference between the diameter of an invasive focus and the diameter of a solid component in the eight MIAs each ranged from 0.1 mm to 2 mm (mean 1.2 ± 0.6 mm, median 1.2 mm, IQR 0.6–1.7 mm).

VDT of the Resected Adenocarcinomas

Among the resected SSNs, the VDTs of the resected SSNs and the VDTs of the solid components in the resected part-solid nodules were calculated only for lesions showing growth; growth was regarded as an increase of 2 mm or more in the maximal diameter of an SSN or a solid component (Table 4). For the SSNs in nine invasive adenocarcinomas, in 23 MIAs, and in 18 AIS, the mean VDT was longer than 400 days; the mean VDTs of the SSNs for any pair of histological types were not statistically significant. For the solid components in eight invasive adenocarcinomas, in nine MIAs, and in three

Table 3. Multivariate Analyses Based on SSN Consistency and Each Growth Type

Consistency	Type of Growth	Variable	HR	95% CI	*p* Value
PGGN	SSN growth ≥2 mm	Sex	1.71	0.99-2.97	0.0536
		Age	1.52	0.98-2.40	0.0646
		Initial diameter	6.17	3.98-9.57	<0.0001
		Smoking status	1.55	0.91-2.67	0.1084
		History of lung cancer	1.14	0.53-2.35	0.7358
		Number of SSN	1.03	0.67-1.57	0.8832
		Reason for detection	1.03	0.59-1.87	0.9254
		Final model			
		Initial diameter	7.06	4.67-10.72	<0.0001
		Sex	2.39	1.58-3.65	<0.0001
	Appearance of solid component	Sex	1.18	0.57-2.47	0.6592
		Age	1.24	0.65-2.19	0.4750
		Initial diameter	4.14	2.28-7.48	<0.0001
		Smoking status	1.76	0.84-3.66	0.132
		History of lung cancer	0.73	0.23-1.90	0.538
		Number of SSN	1.17	0.65-2.06	0.5893
		Reason for detection	0.70	0.36-1.42	0.3109
		Final model			
		Initial diameter	4.56	2.60-7.94	<0.0001
		Smoking status	1.98	1.14-3.49	0.0151
	Solid component growth ≥2 mm	Sex	0.94	0.27-3.53	0.9205
		Age	2.4	0.81-8.76	0.1159
		Initial diameter	5.69	2.01-16.11	0.0013
		Smoking status	2.24	0.60-8.25	0.2277
		History of lung cancer	1.38	0.28-7.18	0.6888
		Number of SSN	0.71	0.24-1.90	0.5027
		Reason for detection	0.68	0.19-3.11	0.5928
		Final model			
		Initial diameter	7.23	2.84-19.00	<0.0001
HGGN[a]	SSN growth ≥2 mm	Sex	0.88	0.19-3.83	0.8614
		Age	1.99	0.62-7.53	0.2557
		Initial diameter	2.77	0.84-10.44	0.0952
		Smoking status	3.02	0.81-12.38	0.1016
		History of lung cancer	3.2	0.63-13.32	0.1467
		Number of SSN	2.45	0.64-9.44	0.1841
		Reason for detection	0.62	0.18-2.13	0.4439
		Final model			
		Initial diameter	3.52	1.33-10.31	0.0114
	Appearance of solid component	Sex	0.32	0.05-1.79	0.1984
		Age	1.63	0.50-6.50	0.4287
		Initial diameter	2.77	0.76-11.29	0.1220
		Smoking status	3.92	0.75-18.55	0.1024
		History of lung cancer	2.91	0.40-14.26	0.2550
		Number of SSN	2.3	0.60-8.50	0.2138
		Reason for detection	1.27	0.37-4.54	0.7061
Part-solid nodule	SSN growth ≥2 mm	Sex	1.71	0.99-2.97	0.0536
		Age	1.52	0.98-2.40	0.0646
		Initial diameter	6.17	3.98-9.57	<0.0001
		Smoking status	1.55	0.91-2.67	0.1084
		History of lung cancer	1.14	0.53-2.35	0.7358
		Number of SSN	1.03	0.67-1.57	0.8832
		Reason for detection	1.03	0.59-1.87	0.9254
		Final model			
		Initial diameter	7.06	4.67-10.72	<0.0001

(continued)

Table 3. Continued

Consistency	Type of Growth	Variable	HR	95% CI	*p* Value
	Solid component growth ≥2 mm	Sex	0.94	0.27-3.53	0.9205
		Age	2.4	0.81-8.76	0.1159
		Initial diameter	5.69	2.01-16.11	0.0013
		Smoking status	2.24	0.60-8.25	0.2277
		History of lung cancer	1.38	0.28-7.18	0.6888
		Number of SSN	0.71	0.24-1.90	0.5027
		Reason for detection	0.68	0.19-3.11	0.5928
		Final model			
		Initial diameter	7.23	2.84-19.00	<0.0001

[a]*Note:* Solid component growth of 2 mm or more was not analyzed because of number of events was only 2.
HR, hazard ratio; CI, confidence interval; PGGN, pure ground-glass nodule; SSN, subsolid nodule; HGGN, heterogeneous ground-glass nodule.

AIS, the mean VDT was less than 400 days; the mean VDTs of the solid components between any pair of histological types were not statistically significant. However, the mean VDT of the solid components in each histological type was significantly shorter than the mean VDT of the SSNs for each histological type (invasive adenocarcinoma, $p = 0.005$; MIA, $p < 0.0001$; AIS, $p = 0.0067$).

Discussion

This study prospectively evaluated the natural course of the progression of pulmonary SSNs. The mean follow-up period was 4.3 years. As of December 27, 2013, 91 (7.4%) of the 1229 SSNs were resected and 12 (13.2%) of the 91 resected SSNs were invasive adenocarcinomas. The mean maximal diameter of the solid component in the mediastinal window was 3.3 mm for MIAs and 5.5 mm for invasive adenocarcinomas; this difference in the mean diameter of the solid component was statistically significant. If the growth of the solid component has not exceeded 3.3 mm, an option for the management of SSNs on the basis of the results of the present study is as follows: a follow-up examination may be performed every 6 months in cases with a part-solid nodule and every 1 or 2 years in cases with a PGGN or an HGGN.

As of September 30, 2015, two articles based on prospective follow-up studies had reported the natural history of SSNs detected using CT screening for lung cancer. One of these articles was from the NELSON

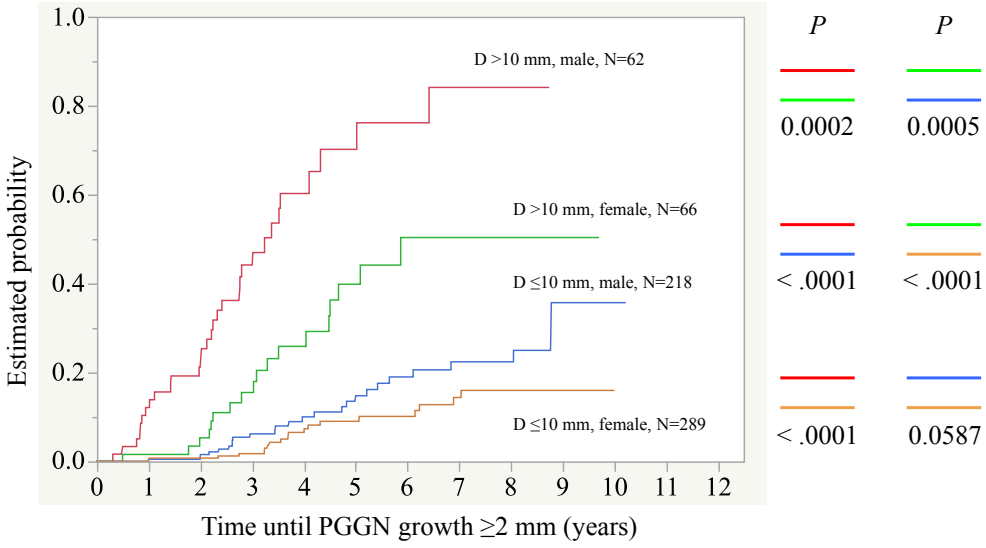

Figure 3. Time until pure ground-glass nodule (PGGN) growth according to the initial maximal diameter and sex. The red, green, blue, and orange curves indicate the accumulated percentages of growth of PGGNs with a maximal diameter larger than 10 mm in male patients, PGGNs with a maximal diameter larger than 10 mm in female patients, PGGNs with a maximal diameter of 10 mm or less in male patients, and PGGNs with a maximal diameter 10 mm or less in female patients, respectively. Each pair of colored lines on the right side of the graph shows the results of a log-rank test. Each pair except for that for PGGNs with a maximal diameter 10 mm or less in male patients and PGGNs with a maximal diameter 10 mm or less in female patients showed a statistically significant difference. However, all curves showed growth within 1 year. D, initial maximal diameter, N, number of patients.

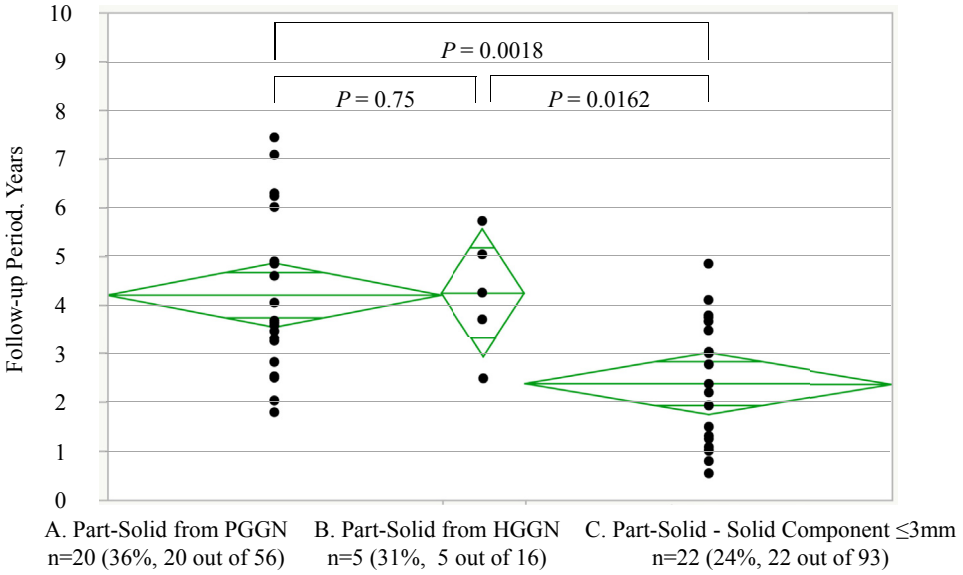

Figure 4. Follow-up periods until an increase in the diameter of the solid component in the part-solid nodules 3.3 mm or larger in maximal diameter. The mean period for the development of part-solid nodules with a solid component 3.3 mm or larger in maximal diameter was 4.2 ± 1.7 years for 20 part-solid nodules developed from pure ground-glass nodules (PGGNs), 4.2 ± 1.2 years for five part-solid nodules developed from heterogeneous ground-glass nodules (HGGNs), and 2.4 ± 1.3 years for 22 part-solid nodules with solid components 3 mm or smaller in maximal diameter at the first thin-section computed tomography scan, respectively.

study,[26] and the other was from the I-ELCAP study.[12] In the NELSON study, the percentage of invasive adenocarcinomas was 18.8% among 101 SSNs, whereas in the I-ELCAP, the percentage was 2.7% among 2392 cases with a nonsolid nodule (a synonym of PGGN) at the baseline screenings and 1.9% among 485 cases with a new nonsolid nodule at the annual repeat screenings. However, neither report differentiated MIAs from invasive adenocarcinomas, although MIA is a newly defined concept with an expected 100% disease-specific survival rate if completely resected.[14] In our study, if we combined the numbers of MIAs (n = 40) and invasive adenocarcinomas (n = 12), the percentage of MIA plus invasive adenocarcinomas was 4.2% among 1229 SSNs. The frequency of the development of a solid component in a PGGN was 29% (20 of 69 cases) in the NELSON study[26] and 1.1% (19 of 1764 cases with persistent nonsolid nodules detected at baseline screenings) and 1.8% (three of 163 cases with persistent nonsolid nodules detected at annual repeat screenings) in the I-ELCAP,[11] whereas the frequency was 5.4% among 1046 PGGNs and 19.8% among 81 HGGNs in our study. In the NELSON study, 65% (46 of 68) of the part-solid nodules were not resected after a median follow-up time of 95 months,[26] whereas in our study, 71.8% (125 of 174) of the part-solid nodules were not resected after a median follow-up period of 3.5 years; moreover, among the 49 resected part-solid nodules, 75.5% (37 of 49) of the part-solid nodules were preinvasive lesions or MIAs; therefore, the appearance of solid components might not always be an appropriate parameter for a "prompt" resection from the standpoint of avoiding overdiagnosis.[10]

SSNs were classified into three categories in this study: PGGNs, HGGNs, and part-solid nodules. From another point of view, an HGGN may be a part-solid nodule with a solid component of 0 mm in the mediastinal window. From the standpoint of the appearance of a solid component, the frequency of the development of a solid component in an HGGN was greater than that of the development of a solid component in a PGGN, and this difference was statistically significant (Fig. 2*B*). In contrast, from the standpoint of solid component growth of 2 mm or more, the difference between HGGNs and PGGNs was not statistically significant (Fig. 2*C*); moreover, solid component growth of 2 mm or more never occurred within 2 years of the start of the follow-up period for either the HGGNs or the PGGNs examined in this study cohort. Further study is warranted to determine whether this intermediate nodule category is appropriate.

Risk factors for SSN growth based on multivariate analyses have been reported by several studies. Regarding SSN (PGGN and part-solid nodule) growth, one study showed that a larger size (more than 10 mm) and a history of lung cancer were risk factors for SSN growth,[27] whereas another study showed that smoking history and the initial lesion diameter were robustly

Table 4. VDTs of the Resected Adenocarcinomas Exhibiting Growth

Characteristic	Histopathological Diagnosis	No. Resected SSNs	With Growth, n (%)[a]	VDT		p Value							
				Mean ± SD	Median	0.2242	0.2688	0.8233	0.1487	0.6082	0.1956	0.0005	<0.0001	0.0067
SSNs	Invasive Ad	12	9 (75)	671 ± 342	631	■	■					■		
	MIA	40	23 (58)	1199 ± 1013	802	■		■					■	
	AIS	33	18 (55)	953 ± 787	811		■	■						■
SCs	Invasive Ad	12	8 (67)	127 ± 59	106				■	■		■		
	MIA	26	9 (35)	209 ± 113	223				■		■		■	
	AIS	10	3 (30)	105 ± 18	100					■	■			■

[a]With growth increase of 2 mm or more in maximal diameter of subsolid nodules or solid components.
Note: Pairwise comparisons performed between the variables indicated by the black squares.
VDT, volume-doubling time; SD, standard deviation; SSN, subsolid nodule; Ad, adenocarcinoma; MIA, minimally invasive carcinoma; AIS, ademocarcinoma in situ; SC, solid component.

associated with SSN growth.[28] Regarding PGGN growth, one study disclosed that a large nodule size (>10 mm) and a history of lung cancer were significant predictors of growth in nonsolid nodules,[29] whereas another study reported that the nodule diameter was the only significant predictor for the interval growth of PGGNs.[30] Regarding part-solid nodules, one study demonstrated that a history of lung cancer and the part-solid GGN diameter were independent predictors of the interval growth of part-solid GGNs,[30] whereas another study did not report any significant predictors of the growth of part-solid nodules.[29] In our study, the main factor for predicting growth was the initial maximal diameter of the SSN; however, a history of lung cancer was not a risk factor for SSN growth.

The CT window that should be used to measure the size of a solid component and the measurement method have been controversial. In 2013, the Fleischner Society proposed that the solid component in a part-solid nodule be evaluated using a narrow and/or mediastinal window and that the size of the solid component be based on the average of the long and short axial dimensions.[10] As of September 30, 2015, however, most of the published articles related to part-solid nodules had used the maximal diameters of the SSN and solid component as viewed using a lung window[30–33] or the maximal diameter of the SSN as viewed using a lung window and the maximal diameter of the solid component as viewed using a mediastinal window.[34] Our study started in 2009, and the parameters for assessing the growth of an SSN and a solid component were defined as the maximal diameter of the SSN as viewed using a lung window and the maximal diameter of the solid component as viewed using a mediastinal window. Although the Fleischner Society recommended that measurements of solid components be based on the average of the long and short dimensions and that 5 mm be used as a threshold for dividing a follow-up group (solid component ≤5 mm) and a workup group (solid component >5 mm), our study showed that the cutoff value for differentiating AIS plus MIAs from invasive adenocarcinoma was a maximal diameter of 3.3 mm as viewed using a mediastinal window. One previous study reported that a maximal diameter of a solid component of 3 mm or less as viewed using a lung window may be a safe and useful radiologic measurement for predicting preinvasive and MIA lesions preoperatively with a high specificity.[34] Another study showed that patients with radiologic AIS (no solid component in lung windows) or MIA (largest axial diameter of a solid component ≤5 mm in lung windows) who underwent sublobar resections had no recurrences and 100% disease-free and overall survival outcomes at 5 years.[32] One study pointed out that an average of the long and short axial dimensions of the solid component

in a mediastinal window may not always be the most appropriate parameter for assessing the progression of a part-solid nodule.[35] Regarding the dimensions of the solid component, further study is warranted to determine how the size of the solid component can best be measured.[14]

The solid components in mediastinal windows are not equal to the invasive foci in pathological specimens.[36] The size of the solid component can be expected to be larger on the CT image than the size of the actual invasive component because the histopathological components of small adenocarcinomas of the lung can include alveolar collapse, inflammatory cells, and miscellaneous changes, as well as invasive adenocarcinoma.[37] In our study, approximately 70% of the MIAs (18 of 26) resected among the part-solid nodules exhibited a mean maximal diameter of the solid components in the mediastinal window that was larger than the mean maximal diameter of invasive foci on pathological specimens, whereas 30% of the MIAs (eight of 26) exhibited the opposite results. In contrast, one study reported that, compared with the invasive component observed pathologically, the size of the solid portion in the mediastinal window as evaluated by one of two observers was significantly smaller.[34] In our study, 12% of the MIAs (three of 26) resected among the part-solid nodules showed that the maximal diameter of the solid components in the mediastinal window was larger than 5 mm despite a maximal diameter of the invasive foci of less than 5 mm. One study also reported that MIAs with solid components larger than 5 mm in the mediastinal window accounted for between 7.7% and 9.6%.[34] Further study is warranted regarding the relationship between the maximal diameter of solid components as viewed using a mediastinal window and the maximal diameter of invasive foci in pathological specimens.

The VDTs of the subtypes of adenocarcinoma based on the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society classification of adenocarcinoma of the lung[14] have been reported in one previous study[38]: for 16 AIS, the median VDT was 1240.3 days; for 3 MIAs, the median VDT was 1328.3 days; and for seven invasive adenocarcinomas, the median VDT was 941.5 days. These median VDTs were longer than the median VDTs in the respective subtypes of adenocarcinoma in our study. Regarding the VDTs of the solid components that exhibited growth in our study, the mean VDTs of the solid components were less than 400 days for each of the adenocarcinoma subtypes, whereas the mean VDTs of the SSNs were more than 400 days. To the best of our knowledge, only one previous study has reported the VDTs of solid components[9]; the VDTs of solid components as viewed using a mediastinal window may enable the differentiation of aggressive part-solid nodules from indolent part-solid nodules.

On the basis of prospective follow-up of CT screening-detected SSNs, one study[26] reported that long-term CT follow-up may be a safe option for monitoring changes in persistent SSNs and recommended that invasive intervention be considered only for SSNs that show 30% or more growth in mass,[39] have a newly appeared solid component, or exhibit the growth of a solid component; another study also reported that non-solid nodules of any size can be safely monitored using CT at 12-month intervals to assess their transition to part-solid lesions.[12] Prospective study of the natural history of PGGNs detected not only by using CT screening but also at follow-up CT after lung cancer resection suggested that some PGGNs will never progress to clinical disease and would be included in the category of PGGNs with an overdiagnosis bias.[40] Retrospective studies of the natural history of SSNs have reported the following findings: more than 2 years of follow-up are necessary to detect the growth of PGGNs[41]; approximately 90% of the screening-detected PGGNs in patients with no history of malignancy did not grow after a median follow-up period of 59 months[42]; the tendency to grow was clear within the first 3 years, and therefore, SSNs should be followed for at least 3 years[43]; and 26% of SSNs had increased in size, with a mean VDT of 1041 days after median follow-up of 45 months.[44]

The interim suggestion for the follow-up of SSNs on the basis of the results of the present study is as follows: every 6 months for a part-solid nodule and every year for a PGGN or HGGN; moreover, to avoid overdiagnosis and overtreatment,[10,45] if the development of a solid component has not exceeded 3.3 mm, a follow-up every 2 years for a PGGN or an HGGN may be possible on the basis of the minimum period for development of the solid component of 3.3 mm or more (as shown in Fig. 4). Regarding part-solid nodules, although a follow-up every 6 months may be initially appropriate, the follow-up period can be subsequently lengthened to, for example, every year; one of the options for deciding on a follow-up strategy may be to make decisions on the basis of the VDTs of the solid components. Although segmentation software for measurement of the volume, mass, and diameter of SSNs has been proposed,[46] this software was not yet available worldwide as of September 30, 2015. Therefore, for the time being, simple parameters, such as the maximal diameter of solid components as viewed using a mediastinal window,[10] should be used for daily clinical practice.

This study had several limitations. First, SSNs that showed a decrease in size ($n = 6$) or a fluctuation in size ($n = 2$) were excluded for the assessment of growth,

although invasive adenocarcinoma exhibiting a decrease in the size of GGNs has been reported.[47] This may have affected the results; however, none of the nodules had shown any changes requiring resection as of December 27, 2013. Second, among the resected cases, the pathology panel did not review seven lesions that were not presented in time for the last pathological review. This may have affected the results for the assessment of the frequency of invasive adenocarcinomas. Third, the protocol for CT scanning was not prescribed in detail, only that the section thickness should be equal to or less than 1.25 mm; consequently, the field of view and kernel for the reconstruction of the CT image were based on the protocols of each institution, which also might have affected the results of this study. Fourth, the radiology panel did not review the CT images for SSNs that did not show growth because of their tight work schedules and the large work burdens involved at each participating institution for anonymizing the personal information in the CT data. However, the definition of growth, (i.e., a 2-mm or greater increase in the maximal diameter of an SSN [ground-glass component] and a 2-mm or more increase in the maximal diameter of a solid component) was thought to be adequate for avoiding interreader variability because the 2-mm criterion exceeded the upper limit of the 95% confidence interval for the limits of agreement.[48,49] Fifth, interreader variability of potential SSNs was not evaluated because of the large volume of CT data. Regarding the evaluation of potential SSNs, moderate interreader variability was reported.[50] This may be a weakness of the present study. Sixth, the correlation between molecular biomarkers and the spectrum of the CT patterns of lung adenocarcinomas[51] was not examined. A molecular-CT correlation was beyond the scope of this study. Future study is warranted. Finally, pathological or cytological diagnoses of SSNs other than the resected lesions were not obtained; this also might have affected the results of this study.

In conclusion, our prospective multicenter study revealed the frequencies and periods of development from PGGNs and HGGNs into part-solid nodules. Invasive adenocarcinomas were diagnosed only among the resected part-solid nodules in this study. The findings of this study could contribute to the development of guidelines for the follow-up of pulmonary SSNs.

Acknowledgments

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at http://dx.doi.org/10.1016/j.jtho.2016.04.006.

References

1. Kaneko M, Eguchi K, Ohmatsu H, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. *Radiology*. 1996;201:798–802.
2. Sone S, Takashima S, Li F, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. *Lancet*. 1998;351:1242–1245.
3. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early lung cancer action project: overall design and findings from baseline screening. *Lancet*. 1999;354:99–105.
4. Nawa T, Nakagawa T, Kusano S, et al. Lung cancer screening using low-dose spiral CT: results of baseline and 1-year follow-up studies. *Chest*. 2002;122:15–20.
5. Hasegawa M, Sone S, Takashima S, et al. Growth rate of small cancers detected on mass screening. *Br J Radiol*. 2000;73:1252–1259.
6. Kodama K, Higashiyama M, Yokouchi H, et al. Prognostic value of ground-glass opacity found in small lung adenocarcinoma on high-resolution CT scanning. *Lung Cancer*. 2001;33:17–25.
7. Nakata M, Saeki H, Takata I, et al. Focal ground-glass opacity detected by low-dose helical CT. *Chest*. 2002;121:1464–1467.
8. Takashima S, Maruyama Y, Hasegawa M, et al. CT findings and progression of small peripheral lung neoplasms having a replacement growth pattern. *AJR*. 2003;180:817–826.
9. Kakinuma R, Ohmatsu H, Kaneko M, et al. Progression of focal pure ground-glass opacity detected by low-dose helical computed tomography screening for lung cancer. *J Comput Assist Tomogr*. 2004;28:17–23.
10. Naidich DP, Bankier AA, MacMahon H, et al. Recommendations for the management of subsolid pulmonary nodules detected at CT: a statement from the Fleischner Society. *Radiology*. 2013;266:304–317.
11. Lee SM, Park CM, Goo JM, et al. Transient part-solid nodules detected at screening thin-section CT for lung cancer: comparison with persistent part-solid nodules. *Radiology*. 2010;255:242–251.

12. Yankelevitz DF, Yip R, Smith JP, et al. CT screening for lung cancer: nonsolid nodules in baseline and annual repeat rounds. *Radiology*. 2015;77:555–564.
13. Henschke CI, Yankelevitz DF, Mirtcheva R, et al. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. *Am J Roentgenol*. 2002;178:1053–1057.
14. Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol*. 2011;6:244–285.
15. Choi WS, Park CM, Song YS, Lee SM, Wi JY, Goo JM. Transient subsolid nodules in patients with extrapulmonary malignancies: their frequency and differential features. *Acta Radiol*. 2015;56:428–437.
16. Oh JY, Kwon SY, Yoon HI, et al. Clinical significance of a solitary ground-glass opacity (GGO) lesion of the lung detected by chest CT. *Lung Cancer*. 2007;55:67–73.
17. Kim HY, Shim YM, Lee KS, et al. Persistent pulmonary nodular ground-glass opacity at thin-section CT: histopathologic comparisons. *Radiology*. 2007;245:267–275.
18. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143:e93S–e120S.
19. National Comprehensive Cancer Network NCCN Clinical Practice Guidelines in Oncology: Lung Cancer Screening, version 1.2016. http://www.nccn.org/professionals/physician_gls/pdf/lung_screening.pdf. Accessed March 7, 2016.
20. American College of Radiology Lung CT Screening Reporting and Data System (Lung-RADS™). http://www.acr.org/Quality-Safety/Resources/LungRADS. Accessed March 7, 2016.
21. Baldwin DR, Callister MEJ, On behalf of the members of the Guideline Development Group. The British Thoracic Society guidelines on the investigation and management of pulmonary nodules. *Thorax*. 2015;70:794–798.
22. The Japanese Society of CT Screening. Guidelines for the management of pulmonary nodules detected by low-dose CT lung cancer screening, version 3. http://www.jscts.org/index.php?page=guideline_index. Accessed March 7, 2016.
23. Hansell DM, Bankier AA, MacMahon H, et al. Fleischner Society: glossary of terms for thoracic imaging. *Radiology*. 2008;246:697–722.
24. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG, eds. *WHO Classification of Tumors of the Lung, Pleura, Thymus and Heart*. 4th ed. Lyon, France: IARC Press; 2015.
25. Hasegawa M, Sone S, Takashima S, et al. Growth rate of small lung cancers detected on mass CT screening. *Br J Radiol*. 2000;73:1252–1259.
26. Scholten ET, de Jong PA, de Hoop B, et al. Towards a close computed tomography monitoring approach for screen detected subsolid pulmonary nodules? *Eur Respir J*. 2015;45:765–773.
27. Hiramatsu M, Inagaki T, Inagaki T, et al. Pulmonary ground-glass opacity (GGO) lesions-large size and a history of lung cancer are risk factors for growth. *J Thorac Oncol*. 2008;3:1245–1250.
28. Kobayashi Y, Sakao Y, Deshpande GA, et al. The association between baseline clinical-radiological characteristics and growth of pulmonary nodules with ground-glass opacity. *Lung Cancer*. 2014;83:61–66.
29. Matsuguma H, Mori K, Nakahara R, et al. Characteristics of subsolid pulmonary nodules showing growth during follow-up with CT scanning. *Chest*. 2013;143:436–443.
30. Lee JH, Park CM, Lee SM, et al. Persistent pulmonary subsolid nodules with solid portions of 5 mm or smaller: their natural course and predictors of interval growth [e-pub ahead of print]. *Eur Radiol*. 2015 Sep 18, accessed March 7, 2016.
31. Zhang Y, Qiang JW, Ye JD, et al. High resolution CT in differentiating minimally invasive component in early lung adenocarcinoma. *Lung Cancer*. 2014;84:236–241.
32. Wilshire CL, Louie BE, Manning KA, et al. Radiologic evaluation of small lepidic adenocarcinomas to guide decision making in surgical resection. *Ann Thorac Surg*. 2015;100:979–988.
33. Lee KH, Goo JM, Park SJ, et al. Correlation between the size of the solid component on thin-section CT and the invasive component on pathology in small lung adenocarcinomas manifesting as groud-glass nodules. *J Thorac Oncol*. 2014;9:74–82.
34. Lee SM, Goo JM, Lee KH, et al. CT findings of minimally invasive adenocarcinoma (MIA) of the lung and comparison of solid portion measurement methods at CT in 52 patients. *Eur Radiol*. 2015;25:2318–2325.
35. Kakinuma R, Muramatsu Y, Kusumoto M, et al. Solitary pure ground-glass nodules 5 mm or smaller: frequency of growth. *Radiology*. 2015;276:873–882.
36. Saito H, Kameda Y, Masui K, et al. Correlations between thin-section CT findings, histopathological and clinical findings of small pulmonary adenocarcinomas. *Lung Cancer*. 2011;71:137–143.
37. Austin JHM, Grag K, Aberle D, et al. Radiologic implications of the 2011 classification of adenocarcinoma of the lung. *Radiology*. 2013;266:62–71.
38. Song YS, Park CM, Park SJ, et al. Volume and mass doubling times of persistent pulmonary subsolid nodules detected in patients without known malignancy. *Radiology*. 2014;273:276–284.
39. de Hoop B, Gietema H, van der Vorst S, et al. Pulmonary ground-glass nodules: increase in mass as an early indicator of growth. *Radiology*. 2010;255:199–206.
40. Kodama K, Higashiyama M, Yokouchi H, et al. Natural history of pure ground-glass opacity after long-term follow-up of more than 2 years. *Ann Thorac Surg*. 2002;73:386–392.
41. Takahashi S, Tanaka N, Okimoto T, et al. Long term follow-up for small pure ground-glass nodules: implications of determining an optimum follow-up period and high-resolution CT findings to predict the growth of nodules. *Jpn J Radiol*. 2012;30:206–217.
42. Chang B, Hwang JH, Choi YH, et al. Natural history of pure ground-glass opacity lung nodules detected by low-dose scan. *Chest*. 2013;143:172–178.
43. Kobayashi Y, Fukui T, Ito S, et al. How long should small lung lesions of ground-glass opacity be followed? *J Thorac Oncol*. 2013;8:309–314.

44. Lee SW, Leem CS, Kim TJ, et al. The long-term course of opacities detected on thin-section computed tomography. *Respir Med*. 2013;107:904–910.
45. Heuvelmans MA, Oudkerk M. Management of subsolid pulmonary nodules in CT lung cancer screening. *J Thorac Dis*. 2015;7:1103–1106.
46. Scholten ET, Jacobs C, van Ginneken B, et al. Detection and quantification of the solid component in pulmonary subsolid nodules by semiautomatic segmentation. *Eur Radiol*. 2015;25:488–496.
47. Kaneda H, Nakano T, Taniguchi Y, et al. A decrease in the size of ground glass nodules may indicate the optimal timing for curative surgery. *Lung Cancer*. 2014;85:213–217.
48. Kakinuma R, Ashizawa K, Kuriyama K, et al. Measurement of focal ground-glass opacity diameters on CT images: interobserver agreement in regard to identifying increase in the size of ground-glass opacities. *Acad Radiol*. 2012;19:389–394.
49. Revel MP, Bissery A, Bienvenu M, et al. Are two-dimensional CT measurements of small noncalcified pulmonary nodules reliable? *Radiology*. 2004;231:453–458.
50. Penn A, Ma M, Chou BB, et al. Inter-reader variability when applying the 2013 Fleischner guidelines for potential solitary subsolid lung nodules. *Acta Radiol*. 2015;56:1180–1186.
51. Aoki T, Hanamiya M, Uramoto H, et al. Adenocarcinomas with predominant ground-glass opacity: correlation of morphology and molecular biomarkers. *Radiology*. 2012;264:590–596.