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ORIGINAL ARTICLE

Natural History of Persistent Pulmonary Subsolid Nodules: Long-Term Observation of Different Interval Growth

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Background The long-term natural course and outcomes of subsolid nodules (SSNs) in terms of true growth, substantial growth, and stage shift need to be clarified.

Methods Between 2002 and 2016, 128 subjects with persistent SSNs of 3 cm or smaller were enrolled. The baseline and interval changes in the series computed tomography (CT) findings during the follow-up period were subsequently reviewed.

Results The mean follow-up period was 3.57 ± 2.93 years. The cumulative percentage of growth nodules of the part-solid nodule (PSN) group was significantly higher than that of the ground-glass nodule (GGN) group by Kaplan-Meier estimation (all $p < 0.0001$). For true SSN growth, GGNs usually take a median follow-up of 7 years to grow; PSNs usually take a median follow-up of 3 years to grow. For substantial SSN growth, GGNs usually take a median follow-up of 9 years to grow; PSNs usually take a median follow-up of 3 years to grow. For stage shift, GGNs usually take a median follow-up of 12 years to grow; PSNs usually take a median follow-up of 9 years to grow.

Conclusions The natural course in terms of true growth, substantial growth, and stage shift differed significantly according to their nodule type, which could contribute to the development of follow-up guidelines and management strategy of pulmonary SSNs.

Introduction

Pulmonary nodules with subsolid nodule (SSN) characteristics have emerged as an important indicator for lung cancer since the introduction of low-dose computed tomography (LDCT) for lung cancer screening in recent years [1,2]. However, lesions with SSNs are also known to be highly associated with adenocarcinoma spectrum, especially in the Asian population [3–7], although several previous studies have reported that SSNs have a high likelihood of malignancy, but are often indolent in growth pattern [8–11].

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Although various studies have been developed to investigate these issues of the natural course of SSNs, to our knowledge, these studies have not focussed on different periods of tumour growth based on significant substantial tumour growth or stage shift [10,12–17]. Previous studies have investigated the natural course of ground-glass nodules (GGNs) mainly based on minimal true SSN growth of 2 mm or more [10,12–16]. The current study provides novel insights into the natural course of SSNs, thereby focussing on substantial SSN growth or stage shift. A more comprehensive understanding of natural course of SSNs can facilitate shared decision-making for future diagnostic, monitoring and treatment choices in the lung cancer screening program. Therefore, the purpose of the present observational study was to clarify the long-term outcomes for SSNs based on minimal true SSN growth, substantial SSN growth and stage shift period. We selected the subjects who have persistent SSNs in diameters 3 cm or smaller in order to investigate the long-term natural history of SSNs and relate them to clinical decision-making.

Material and Methods

Patients

The institutional review board approved this retrospective study, and thus informed consent was waived. A search of our hospital's SSN nodules registry database between January 2002 and August 2016 was conducted. Two radiologists reviewed all chest computed tomography (CT) images on the register, and subjects who met all the following criteria were enrolled in our study cohort: Subjects with (1) persistent SSNs confirmed for more than one year after the initial LDCT scans with/without pathologic proof, (2) SSNs ranging in diameters 3 cm or smaller on the initial CTs, (3) initial and series follow-up chest CT scans using thin-section CT images with slice thickness of 2.5 mm or less, (4) resected SSNs finally showing adenocarcinoma spectrum included, and exclusion of SSNs with non-adenocarcinoma spectrum diagnosed, (5) multiple SSNs, and only one major dominant SSN with largest solid portion or largest diameter was selected.

Finally, a total of 128 subjects with 128 SSNs were included in this study. However, eight SSNs in eight subjects were excluded because of the non-lung adenocarcinoma spectrum reviewed by the pathology panel shown in Figure 1. One-hundred-twenty-eight (128) of 136 (94.1%) subjects were diagnosed with adenocarcinoma spectrum lesion. Among eight subjects with non-lung adenocarcinoma diagnosed, four of eight (50%) had cryptococcus infection, three of eight (37.5%) had focal interstitial fibrosis, and one of eight (12.5%) had mucosa-associated lymphoid tissue of lung. Of 128 subjects, 41 were men and 87 were women. The clinical and radiologic information regarding the subject age, sex, initial nodule size, initial nodule solid component size, nodular type, multiplicity, follow-up duration, Lung Imaging Reporting and Data System (Lung-RADS) categories and pathologic report were collected [18,19]. In subjects with multiple SSNs, we selected the dominant lesion for measurement.

Radiologic Features of SSNs

All scans were performed with a 16-slice multi-detector CT (Somatom Sensation 16, Siemens Healthcare, Erlangen, Germany), a 64-slice multi-detector CT (Aquilion 64, Toshiba Medical Systems Corporation, Tokyo, Japan), and 256-slide multi-detector CT (Revolution CT, GE Healthcare, Milwaukee, WI, USA) from the lung apex to the base without contrast enhancement. Images were reconstructed with a section thickness of 1–2.5 mm and displayed at a lung window width of 1,600 Hounsfield Units (HU), window level of 600 HU, and a mediastinal window width of 350 HU, with a window level of 35 HU.

Other parameters (tube voltage, tube current, patch factor, and reconstruction kernel) were based on the protocols of each vendor recommendation.

Subsolid nodule lesions were classification as GGN or part-solid nodule (PSN) according to the definition of Fleischner guideline. The longest diameters of the whole nodular lesion with solid components (in the maximal diameter when viewing using a lung window setting) were measured on CT on axial images. Persistent SSNs are defined as the persistence of the SSNs for 3 months which were confirmed after the initial CT shown in supplement Figure 1. Follow-up duration with management, and interval period between follow-up CT scans after persistent SSN confirmation were dependent on the referring physician's discretion.

Definition of SSNs Growth

For the enrolled 128 SSNs in 128 subjects, all available chest CT scans were evaluated and SSN growth, interval change in size, nodular characteristics, and Lung-RADS categories were recorded [20]. There are definitions of three types of SSNs growth: true SSN growth, substantial SSN growth, and stage shift. True SSN growth was defined as a minimal required increase of $\geqq$ 2 mm or more in SSNs, solid portion in PSN increased by 2 mm or more, or new developing solid portion $\leqq$ 2 mm within pure GGNs from the initial SSN on initial CT scan to avoid interobserver and intraobserver variability (an example in supplement Figure 2) [10,21]. Substantial SSN growth was defined as an obvious increase of $\geqq$ 5 mm or more in SSNs, solid portion in PSN increased by 5 mm or more from the baseline SSN on initial CT scan to detect obvious interval growth between interval CT scans (an example in supplement Figure 3) [22]. Stage shift was defined as the specific stage shift of lung adenocarcinoma diagnosed to detect obvious different categories/stages shift according to the seventh lung cancer TNM classification and staging system based on their clinical and pathologic information at presentation of follow-up CT scan from the baseline SSN on initial CT scan (an example in supplement Figure 4) [23].

Pathological Examination

During follow-up, indication for surgical resection was dependent on the referring thoracic surgeon's discretion. The pathologic reports on surgical specimens and pathologic

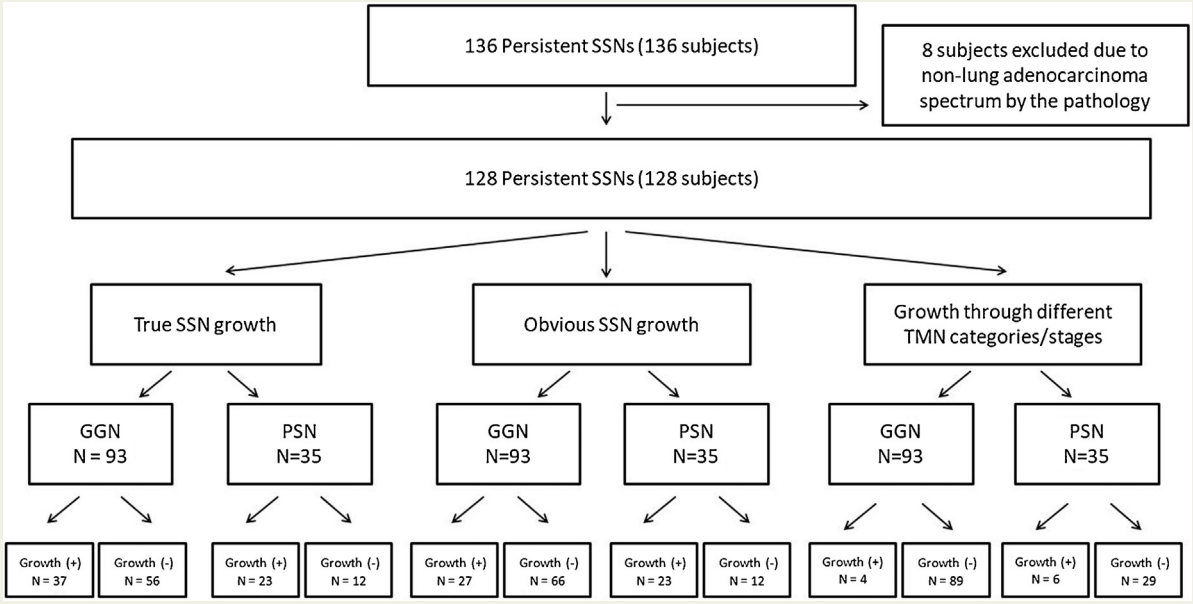

Figure 1 Flow chart showing study population and subject selection.

staging were recorded and classified according to the seventh edition staging system of American Joint Committee on Cancer [24].

Statistical Analysis

All statistical analyses were performed using SPSS 22.0 for Windows (SPSS Inc, Armonk, NY, USA). Because all the continuous variables are normally distributed, differences in continuous variables between the two groups were compared by the independent Student t test. Categorical variables were summarised as frequencies and percentages and compared by using the chi-square test to examine differences in demographic characteristics. The Fisher exact chi-square test was used to analyse when the smallest expected value is less than 5.

The estimating cumulative incidence curves were compared by Kaplan-Maier method with the two groups of GGN and PSN. The statistical significance was evaluated using log-rank test. Correlations between pathologic invasiveness and type of SSN growth were evaluated by Pearson's correlation coefficient test. Multivariate logistic regression was used to determine predictors of true SSN growth adjusted for clinical and radiologic characteristics.

Results

Patient Characteristics

The clinical and radiologic characteristics of 128 SSNs in 128 subjects at the time of the initial detection of the SSNs are summarised in Table 1. Mean age was 60.58 ± 12.01 years (range 27–95 years) and 41 (32.03%) subjects were male. Mean follow-up period after initial CT scan was 3.57 ± 2.93 years. Forty-eight (48) (37.50%) subjects had multiple SSNs in this study cohort.

Of the 128 SSNs, 93 (72.70%) were pure GGN lesions, and 35 (27.30%) were PSN lesions, initially. Initial mean nodule size was 9.98 ± 7.51 mm in the longest diameter at initial CT scan, with initial solid part of 2.72 ± 0.44 mm.

The distribution of baseline Lung-RADS categories of the study subjects were: 97 subjects in category 2 (75.58%), 5 subjects in category 3 (3.90%), and 26 subjects in category 4 (20.31%). Among the 128 SSNs, 62 SSNs were surgically resected for lung cancer. Histological examinations revealed atypical adenomatous hyperplasia (AAH) in one (1.60%) subject, adenocarcinoma in situ (AIS) in four (6.50%) subjects, minimally invasive adenocarcinoma (MIA) in nine (14.50%) subjects, and invasive pulmonary adenocarcinoma in 48 (77.40%) subjects. Among 62 subjects, six were diagnosed with stage IV disease, five diagnosed with stage II disease, and the remaining 51 subjects were diagnosed with having stage I or pre-cancer disease.

In terms of time to SSN classification according to GGN and PSN groups, the clinical characteristics and radiologic findings between two groups are compared and summarised in Table 2. The age, initial nodule size, initial solid part size, the proportion of interval growth in terms of true SSN growth, substantial SSN growth, stage shift, and the proportion of Lung-RADS category 4 lesions were significantly higher in the PSN group than those in the GGN group, except for sex, lesion multiplicity and follow-up duration.

True SSN Growth

Given the time of true SSN growth, the clinical characteristics and radiologic findings between two groups are compared and summarised in Supplementary Table 1. The age, the proportion of PSN lesion, and follow-up duration were

Table 1 Baseline clinical and radiologic characteristics of enrolled 128 subjects.

Characteristics	N = 128
Age	60.58 ± 12.01
Male sex	41 (32.03%)
Initial nodule size (mm)	9.98 ± 7.51
Initial solid part size (mm)	2.72 ± 0.44
SSN classification	
GGN nodule	93 (72.70%)
Part-solid nodule	35 (27.30%)
Lesion multiplicity (%)	48 (37.50%)
Follow-up duration	3.57 ± 2.93
Lung-RADS distribution	
1	0
2	97 (75.58%)
3	5 (3.90%)
4	26 (20.31%)
Histology, IASLC/ATS/ERS classification of 62 resected SSNs	
AAH	1 (1.60%)
AIS	4 (6.50%)
MIA	9 (14.50%)
Invasive adenocarcinoma	48 (77.40%)
Stage distribution	
I (or pre-cancer)	51 (82.20%)
II	5 (8.10%)
III	0 (0%)
IV	6 (9.70%)

Abbreviations: AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; GGN, ground-glass nodule; SSN, subsolid nodule; Lung-RADS, Lung Imaging Reporting and Data System.

significantly higher in the true SSN growth (+) group than those in the true SSN growth (−) group, except for sex, initial nodule size, lesion multiplicity and initial solid part.

The 5-year progression rate of PSN group subjects was 67.3%, which was significantly worse than that of GGN group subjects (35.5%). For true SSN growth, the mean progression time for GGN was 6.947 years and the median progression was 7 years; the PSN group had a mean progression time of 3.960 years and a median of 3 years. There was a significant difference in progression periods between the two groups (log-rank test $p < 0.0001$) shown in Figure 2A.

Of 128 SSNs in 128 subjects, 60 subjects showed true SSN growth during the follow-up period. The time interval from initial CT scan until the detection of true growth was a median follow-up of 4.600 years (mean follow-up period of 5.103 year, 1 ∼ 14 years). The relationships between SSN type and time interval period until the detection of growth are shown in Supplementary Table 4.

Substantial SSN Growth

The 5-year progression rate of PSN group subjects was 67.3%, which was significantly worse than that of GGN group subjects (10.6%). For substantial SSN growth, the mean progression time for GGN was 9.426 years and the median progression was 9 years; the PSN group had a mean progression time of 3.960 years and a median of 3 years. There was a significant difference in progression periods between the two groups (log-rank test $p < 0.0001$) shown in Figure 2B.

Of 128 SSNs in 128 subjects, 40 subjects showed SSN growth during the follow-up period shown in Supplementary Table 2. The time interval from initial CT scan until the detection of substantial growth was a median of 5 years (mean follow-up period of 5.393 year, 1 ∼ 14 years). The relationships between SSN type and time interval period until the detection of substantial growth are shown in Supplementary Table 4. Tumour growth was detected within 2 years in the PSN group. In contrast, a duration of more than 2 years was required in the GGN group.

Stage Shift

The 5-year progression rate of PSN group subjects was 24.2%, which was significantly worse than that of GGN group subjects (0%). For stage shift, the mean progression time for GGN was 12.168 years and the median progression was 12 years; the PSN group had a mean progression time of 7.198 years and a median of 9 years. The log-rank test of the two curves showed them to be significantly different, shown in Figure 2C ($p < 0.0001$).

Of 128 SSNs in 128 subjects, 10 subjects showed stage shift during the follow-up period, shown in Supplementary Table 3. The time interval from initial CT scan until the detection of stage shift was a median of 6.750 years (mean follow-up period of 6.380 year, 1 ∼ 12 years). The relationships between SSN type and time interval period until the detection of stage shift are shown in Supplementary Table 4. Tumour growth was detected within 2 years in the PSN group. In contrast, a duration of more than 6 years was required in the GGN group.

Risk Factors for True SSN Growth

Multivariate analyses for characteristic variables affecting true SSN growth are summarised in Table 3. Older age (OR 1.071, 95% CI 1.018–1.128; $p = 0.009$), PSN nodule type (OR 5.408, 95% CI 1.298–22.526; $p = 0.020$), and longer follow-up time (OR 1.716, 95% CI 1.358–2.169; $p < 0.0001$) were significant predictors for true SSN growth. In addition, the relationships between pathologic invasiveness and SSN growth pattern of resected SSNs are shown in Table 4. Type of SSN growth was classified into true, substantial or stage shift according to the definition in this study. True SSN growth and substantial SSN growth were significantly more positive correlated with pathologic invasiveness ($p < 0$ .05 for true SSN growth; $p = 0.01$ for substantial SSN growth), but not the stage shift. Pathologic invasiveness tended to be more

Table 2 Clinical and radiologic features of 128 dominant SSNs in 128 subjects based on SSN classification.

Characteristics	GGN (N = 93)	PSN (N = 35)	P-value
Age	58.46 ± 11.45	66.23 ± 11.78	0.001
Male sex	31 (33.33%)	10 (28.57%)	0.386
Initial nodule size	7.14 ± 4.52	17.52 ± 8.65	<0.0001
Initial solid part size	0	7.80 ± 6.98	<0.0001
True SSN growth			0.008
Growth	37	23	
No growth	56	12	
Substantial SSN growth			<0.0001
Growth	17	23	
No growth	76	12	
Stage shift			0.025
Growth	4	6	
No growth	89	29	
Lesion multiplicity (%)	34 (36.55%)	14 (40%)	0.436
Follow-up duration (years)			
Mean	3.81 ± 3.16	2.95 ± 2.08	0.137
Median (range)	2.5 (1-12)	4 (1-12)	
The frequency of follow-up visits (mean, range)	3.1 (1-10)	2.8 (1-6)	
Lung-RADS distribution			<0.0001
1	0	0	
2	92	5	
3	1	4	
4	0	26	
Histology, IASLC/ATS/ERS classification of 62 resected SSNs			
AAH	1	0	
AIS	4	0	
MIA	6	3	
Invasive adenocarcinoma	25	23	

Abbreviations: AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; GGN, ground-glass nodule; SSN, subsolid nodule; Lung-RADS, Lung Imaging Reporting and Data System.

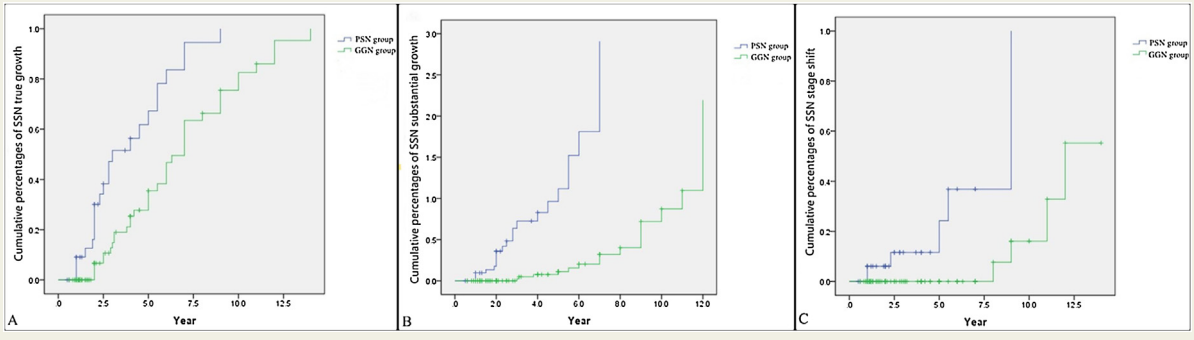

Figure 2 Kaplan-Meier plot for time to SSN growth according to the nodule type classification in the SSNs. (A) In terms of true SSN growth, PSN group shows significantly higher cumulative percentages of growth than GGN group. (B) In terms of substantial SSN growth, PSN group shows significantly higher cumulative percentages of growth than GGN group. (C) In terms of stage shift, PSN group shows significantly higher cumulative percentages of growth than GGN group. Abbreviations: SSN, subsolid nodule; PSN, part-solid nodule; GGN, ground-glass nodule.

Table 3 Multivariate logistic analyses for the risk factors in prediction of true SSN growth in 128 subjects.

Characteristics	OR	CI	P-value
Age	1.071	1.018-1.128	0.009
Male sex	2.413	0.797-7.304	0.119
Initial nodule size	0.915	0.832-1.006	0.066
Initial solid part size	1.071	0.936-1.224	0.318
SSN type			
GGN (Reference)	1		
Part-solid nodule	5.408	1.298-22.526	0.020
Follow-up duration	1.716	1.358-2.169	<0.0001

Abbreviations: GGN, ground-glass nodule; SSN, subsolid nodule; OR, odds ratio; CI, confidence interval.

correlated with substantial SSN growth than with true SSN growth.

Discussion

Several previous studies have investigated the natural course of SSNs and reported its relatively indolent natural clinical course [10,12–17]. In general, GGNs have relatively slow growth and indolent behaviour compared to the PSNs [10,16,17]. Recently, the Fleischner Society guidelines in 2017 recommend that a longer period is recommended before initial follow-up, and the total length of follow-up has been extended to 5 years for subsolid nodules based on the latest evidence from research [25].

Recent studies have reported the natural course of SSN in terms of minimal SSN growth [10,12–16], but limited studies have focussed on the longer-term outcome about substantial SSN growth or stage shift. Nevertheless, the natural history of SSNs remains incompletely defined, with key knowledge gaps including the lack of understanding behind the longer-term outcome about substantial SSN growth, stage shift and the substantial inter-individual variation in disease progression.

In the present study, the purpose was to clarify the natural course of SSNs based on time for growth of stepwise SSN growth from the baseline, minimal required and substantial SSN growth, and finally stage shift. Therefore, it is imperative to understand the natural course of stepwise SSN growth at different stages to gain a better understanding to facilitate appropriate SSNs follow-up and management planning for the optimal timing of surgical resection.

Table 4 The relationships between pathologic invasiveness and SSN growth pattern of resected 62 SSNs.

Growth pattern	Invasive degree	P-value
True SSN growth	0.280	<0.05
Substantial SSN growth	0.387	0.01
Stage shift	0.113	>0.05

Abbreviation: SSN, subsolid nodule.

In this retrospective analysis of natural course of SSNs in terms of stepwise growth, we demonstrated four major findings. The first one is, that for true SSN growth, the mean progression time for GGN was 6.947 years and the median progression was 7 years; the PSN group had a mean progression time of 3.960 years and a median of 3 years. The second finding is that, for substantial SSN growth, the mean progression time for GGN was 9.426 years and the median progression was 9 years; the PSN group had a mean progression time of 3.960 years and a median of 3 years. Third, for stage shift, the mean progression time for GGN was 12.168 years and the median progression was 12 years; the PSN group had a mean progression time of 7.198 years and a median of 9 years. Fourth, pathologic invasiveness degree correlated better with substantial SSN growth than with other parameters.

Recently, the Fleischner Society 2017 guidelines have recommended that a longer period is recommended before initial follow-up, and the total length of follow-up has been extended to 5 years for subsolid nodules based on the latest evidence from research [25]. Our study results also support the consensus. The authors also point out that the recommended 5 years-follow-up is necessarily somewhat arbitrary based on the evidence of PSNs, remained unequivocally stable over that time period of 5 years. Considering the comprehensive stepwise natural course of SSN growth in this study, CT follow-up for at least 7 ~ 9 years was considered to be necessary for the subjects with GGNs because of their incidental nature and invariably indolent biological behaviour; while further follow-up for 3 years may be necessary for the subjects with PSNs because PSNs usually take a median follow-up of 3 years to grow. Given the fact that regarding the 26 PSNs that underwent surgical resection, 88.4% (23/26) PSNs reveal invasive adenocarcnoma. In this study, we demonstrated that most PSNs eventually will usually grow within 3 years, and even some subjects with PSNs will show stage shift within 2 years. Considering these findings, a 3-year follow-up period with 3 ~ 6 month interval is mandatory for PSNs, and prompt tissue proof/surgical resection is indicated while the lesions show interval growth in size.

With respect to GGN growth, GGNs usually take a median follow-up of 7 ~ 9 years to grow. And subjects with GGNs rarely develop stage shift within 6 years.

Persistent GGNs or PSNs are often of the lung adenocarcinoma spectrum, including invasive adenocarcinoma or its precursors [26,27]. These lesions occur more frequently in women, non-smokers, and Asians, suggesting different aetiologies and risk factors compared to non-small cell lung cancer (NSCLC) in general. Previous studies and this study have demonstrated that these GGNs mainly occurred in Asian women and non-smokers, especially those in the middle age [3–6]. Therefore, it is difficult to assume that all GGNs

are less aggressive and would not become clinically significant lung cancer or enter into advanced stages in the remaining lifespan of these subjects.

Considering these findings, a 7–9 year follow-up period with a 12–24-month interval is mandatory for GGNs, and prompt tissue proof/surgical resection is indicated while the lesions show interval obvious growth in size, which were more suggestive of invasive adenocarcinoma.

This study aimed to investigate the stepwise natural course of SSNs from the baseline, interval growth of SSNs, and stage shift into more advanced stage. Our results demonstrated that age, nodule type and follow-up duration were significantly associated with SSN growth. Our findings are consistent with previous results [12,13,16]. In addition, we also demonstrated that pathologic invasiveness degree correlated better with substantial SSN growth than with other parameters.

Therefore, the timing to progression just reaching to the threshold of substantial SSN growth may be the optimal surgical time for SSNs, and this policy has the potential ability to avoid the issue of over-diagnosis and reduce false positives. During the period of the progression time to just reaching substantial SSNs, lesions are also less likely to develop into advanced-stage lung cancer. Thus, this policy can also help to prevent a delay in diagnosis. Among 10 SSNs with stage shift, all 10 have developed into solid nodules or part-solid nodules with solid part >1 cm. Previous studies have demonstrated the importance of the solid part component as a prognostic factor in lung adenocarcinoma [20,28–30]. Our findings also supported this conclusion.

In this study, we also found another possible important prognostic factor in stage shift. We found two SSNs in two subjects have been developed into part-solid nodules with suspicion of pleural invasion by follow-up CT images (an example is in supplement Figure 4). Finally, thoracoscopic exploration was performed for a definitive diagnosis. Thoracoscopy revealed multiple nodules on the visceral and parietal pleura. Finally, the pathologic report also confirmed pathological features of invasive adenocarcinoma of the lung with pleural seeding regardless of the relatively small size of this part-solid nodule. Therefore, we propose the SSN nodule with pleural attachment was the possible important prognosis factor because direct pleural invasion will lead to more rapid disease progression through pleural seeding.

Our study had several limitations. First, this study was retrospectively designed and involved dependence on the physican's professional authority, while follow-up CT interval was not uniform for all subjects. Second, only 62 subjects underwent surgical resection or biopsy tissue proof for confirmation of the adenocarcinoma spectrum. Thus this study was more susceptible to partial verification bias. However, we enrolled all study subjects who met the inclusion criteria of persistent SSN. Persistent SSNs have a high likelihood of a spectrum of pulmonary adenocarcinomas or precursors, with reported malignancy rates ranging from 19.4% to 75% [8,9,27,31]. Third, given the limited number of subjects in this study (especially for events of stage shift), it will be important in the future to study a large-scale cohort population.

In conclusion, our retrospective study demonstrated three major outcomes of the natural course of SSNs. Our study results support the 2017 Fleischner guidelines. In addition, this study could provide new insights into the long-term natural course of SSNs in terms of different interval growth, which could contribute to the development of follow-up guidelines and management strategy of pulmonary SSNs in the Asian lung cancer screening program.

Conflict of Interest

The authors have no conflict of interest.

Grants

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Relationship with Industry

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2018.08.015.

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