Transient Part-Solid Nodules Detected at Screening Thin-Section CT for Lung Cancer: Comparison with Persistent Part-Solid Nodules[1]

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Purpose: To retrospectively investigate clinical and computed tomographic (CT) features of transient part-solid nodules (PSNs) initially detected at screening thin-section CT for lung cancer and to determine predictive factors that may differentiate transient PSNs from persistent PSNs.

Materials and Methods: This study was approved by the institutional review board. From January 2006 to August 2008, 93 individuals with 126 PSNs were identified from among 16777 individuals who underwent chest CT. Clinical features and CT characteristics of PSNs were reviewed, and clinical and thin-section CT features were compared between transient and persistent PSNs. To identify predictive factors of transient PSNs and evaluate predictive performance, logistic regression analysis and *C* statistic analysis were performed.

Results: Eighty-eight (69.8%) of 126 PSNs were transient. Between transient and persistent PSNs, there were significant differences ($P < .05$) in patient age, patient sex, risk of lung cancer, presence of eosinophilia, mode of detection, lesion size, lesion multiplicity, size of solid portion, and lesion border. Multivariate analysis revealed that young patient age, detection of the lesion at follow-up, blood eosinophilia, lesion multiplicity, large solid portion, and ill-defined border were significant ($P < .05$) independent predictors of transient PSNs. The performance in the discrimination of transient PSNs from persistent PSNs of the logistic regression model that incorporated both clinical and thin-section CT features was significantly higher than the performance of the models that incorporated clinical features or thin-section CT features alone.

Conclusion: A substantial proportion of PSNs detected at screening CT were transient. Transient PSNs could be predicted with high accuracy by using the features of young patient age, detection of the PSN at follow-up, blood eosinophilia, lesion multiplicity, large solid portion, and ill-defined lesion border.

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With the widespread use of computed tomography (CT) in clinical practice and the introduction of CT screening for lung cancer, faint or small nodules that had not been detectable at chest radiography have been discovered (1–3). One of these types of nodules is a ground-glass opacity (GGO) nodule (1,4). Although GGO nodules can be seen in a variety of disorders such as inflammatory disease, pulmonary fibrosis, and hemorrhage (5–7), persistent GGO nodules (showing either no change or an increase in size or opacity over a follow-up period of 3 months or longer) suggest the possibility of an early lung cancer such as bronchioloalveolar cell carcinoma or pulmonary adenocarcinoma or a putative precancerous lesion such as atypical adenomatous hyperplasia (4–6,8–10).

Interestingly, the malignancy rate of GGO nodules has been reported to be higher than that of solid nodules. In particular, part-solid nodules (PSNs) have been reported to have a much higher malignancy rate than solid or pure GGO nodules, with the malignancy rate of PSNs ranging from 62.5%–89.6% (4,9). In this context, PSNs of at least 5 mm in diameter are regarded as positive findings, and further work-up is recommended by the New York Early Lung Cancer Action Project (NYELCAP) (11). According to the guidelines of NYELCAP, for nodules 5–14 mm in diameter, further work-up such as follow-up CT performed 3 months later or immediate positron emission tomography (PET) should be performed. For nodules 15 mm or larger in diameter, immediate biopsy is an alternative option to follow-up CT or immediate PET (11).

However, according to a recent report (12), approximately 49% of solitary PSNs detected at baseline chest CT decreased in size or disappeared within 3 months, even though the mean size of these transient PSNs was 14.2 mm. That is, a considerable proportion of PSNs were transient, and a decision based on lesion size may not work well for these lesions. Furthermore, patients with transient PSNs might be subjected to unnecessary radiation exposure, invasive procedures, and unnecessary financial burden, as well as psychiatric stress during further work-up.

Therefore, if we were able to predict whether a PSN detected at screening CT would be transient or persistent, it would help determine the best patient care strategy. Until now, to our knowledge, there has been only one study (12) that has investigated the clinical and CT features of transient and persistent PSNs detected in an asymptomatic population. However, the previous study (12) included only solitary lesions and used thick-section CT scans (5-mm section thickness) for the initial inclusion of the cases in their study. Furthermore, the study lacked meticulous analysis of the CT findings of PSNs.

Thus, the purpose of this study was to retrospectively investigate the clinical and CT features of transient PSNs initially detected at screening thin-section CT and to determine predictive factors that may differentiate transient PSNs from persistent PSNs.

Advances in Knowledge

- A substantial proportion of part-solid nodules (PSNs) detected at lung cancer screening CT were transient.
- Young patient age, PSN detection at follow-up examination, blood eosinophilia, lesion multiplicity, large solid portion, and an ill-defined nodular border at thin-section CT were independent predictors for transient PSNs.
- With the use of both clinical and thin-section CT features, 82.4% of PSNs can be correctly classified as transient without missing persistent PSNs.

Implication for Patient Care

- PSNs with characteristic findings of transience can be safely followed up in a short-term period without immediate intervention, even in cases of PSNs larger than 1 cm.

Materials and Methods

This study was approved by the institutional review board of Seoul National University Hospital, which waived the requirement of patient informed consent for this retrospective study.

Study Population

From January 2006 to August 2008, 16777 individuals underwent 21005 low-dose thin-section chest CT examinations for lung cancer screening in the Health Care System Gangnam Center, a clinic for comprehensive cancer screening affiliated with Seoul National University Hospital. Participation in the cancer screening program was voluntary and at each individual's own expense. Individuals who were asymptomatic persons either 40 years old or older or at risk for lung cancer because of a first-degree family history of lung cancer or occupational exposure to asbestos, beryllium, uranium, or radon were included in our screening program (13). With regard to smoking, never-smokers were not excluded from our cancer screening program (13)

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Abbreviations:
AUC = area under the curve
CI = confidence interval
CRP = C-reactive protein
ESR = erythrocyte sedimentation rate
GGO = ground-glass opacity
NYELCAP = New York Early Lung Cancer Action Project
PSN = part-solid nodule
WBC = white blood cell

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See also the editorial by Naidich and the article by de Hoop et al in this issue.

because pulmonary adenocarcinoma, one subtype of the most common lung cancer, frequently occurs in women and never-smokers (14,15), particularly in an Asian population. From this population, one radiologist (S.M.L.) retrospectively searched for individuals with pulmonary PSNs identified at low-dose thin-section CT, using electronic medical records and the radiology information system of our hospital. First, all CT studies for which the reports included the words "GGO," "GGOs" "ground-glass opacity," "ground-glass opacities," "subsolid nodule," "subsolid nodules," "part-solid nodule," and/or "part-solid nodules" were selected. A total of 612 individuals were identified. Second, two radiologists (C.H.L. and S.M.L., with 10 and 4 years of experience in chest CT, respectively) reviewed all CT studies in the 612 individuals who were included in the first step and then selected the cases in which GGO lesions showed rounded or irregular nodular shapes with well- or poorly defined borders and measured up to 3 cm in diameter. Diffuse GGOs were excluded in this step. From among these selected cases, we included cases that met the following criteria: *(a)* nodules containing internal solid portions, *(b)* PSNs larger than 5 mm and smaller than 3 cm, *(c)* PSNs initially detected at baseline CT or newly detected at follow-up CT, *(d)* and individuals with at least one or more follow-up thin-section CT studies available (so that we could determine the temporality of the PSNs). With respect to the lowest threshold of nodule size, we used a nodule diameter of 5 mm in this study because, according to the guidelines of NYELCAP (11), which we adopted, PSNs at least 5 mm in diameter were regarded as positive findings, and, in our experience, it was not practical or easy for us to evaluate PSNs smaller than 5 mm with respect to CT features, including lesion border, lesion margin, lesion size, size of solid portion, proportion of solid portion, air bronchogram, or bubble lucency.

Finally, 126 PSNs in 93 individuals (age range, 26–79 years; mean age, 53.8 years ± 9.7) were included in this study. There were 59 men (age range, 26–79 years; mean age, 51.6 years ± 9.3) and 34 women (age range, 41–76 years; mean age, 57.6 years ± 9.3). In terms of the 126 PSNs, solitary PSNs were found in 67 individuals, two PSNs were found in 22 individuals, three PSNs were found in two individuals, five PSNs were found in one individual, and more than 10 PSNs were found in one individual. In the case of the individual with more than 10 PSNs, only four of the nodules were included in this study because the other PSNs were smaller than 5 mm. Among 126 nodules, six were confirmed at pathologic examination (one bronchioloalveolar cell carcinoma and five adenocarcinomas).

We defined a PSN as transient when a nodule decreased in size or disappeared at follow-up CT within 3 months, and we designated a PSN as persistent when a nodule remained stable or increased in size over a follow-up period of 3 months or longer. We decided whether a nodule was transient or persistent through the consensus of two observers (C.H.L. and S.M.L.), who considered the anatomic relationship between the PSN and the vascular and bronchial structure around the nodule, as well as size measurements. We considered a nodule to be decreased in size when a nodule on a subsequent CT image had decreased in size by at least 20% compared with the same nodule on previous CT images.

Analysis of Clinical Features

Clinical and laboratory data for individuals with PSNs were recorded by one radiologist (M.J.K.) and one clinician. The following clinical data were detailed: *(a)* patient age and sex, *(b)* smoking history (never-smoker, ex-smoker, current smoker), *(c)* smoking amount, and *(d)* detection mode of the lesion (ie, baseline detection, follow-up detection). According to smoking amount (10 pack-years), first-degree family history, and other risk factors, the study group was divided into high and low risk groups. With respect to the detection mode of the lesion, when PSNs were detected at baseline screening CT, we designated them as having been detected at baseline. When a detected nodule was absent on previously available chest CT studies, the nodule was considered as having been detected at follow-up. In our study, 19 of 93 individuals had data from previous chest CT examinations, all of which were performed during lung cancer screening in our institution. In three of the 19 individuals, there were solid pulmonary nodules smaller than 5 mm in size, and in the remaining 16 individuals, there were no clinically important abnormalities at previous CT.

Laboratory findings such as *(a)* white blood cell (WBC) count, *(b)* blood eosinophil count, *(c)* presence of blood eosinophilia, *(d)* erythrocyte sedimentation rate (ESR), and *(e)* C-reactive protein (CRP) level were also recorded. These laboratory tests were performed on the same day as the CT examination. Among the 93 individuals, the WBC count was available in 90; the eosinophil count, in 90; the ESR, in 90; and the CRP level, in 78. Blood eosinophilia was defined as an eosinophil count exceeding 500 per microliter.

CT Examinations

All 93 individuals underwent at least two thin-section CT examinations (section thickness, ≤1.25 mm). The mean number of CT examinations was 2.82 ± 1.05 (range, two to seven), and the mean CT follow-up period was 331.1 days ± 256.4 (range, 34–965 days). Most CT examinations (176 of 183) were performed by using a 16–detector row CT scanner (Sensation 16; Siemens Medical Systems, Erlangen, Germany). For the remaining seven examinations, a 64–detector row CT scanner (Brilliance 64; Phillips Medical Systems, Best, the Netherlands; $n = 4$) and an eight–detector row CT scanner (LightSpeed Ultra; GE Medical Systems, Milwaukee, Wis; $n = 3$) were used. All CT studies were performed without contrast material. Scanning parameters for low-dose thin-section CT were as follows: detector collimation, 1.0–1.25 mm; beam pitch, 0.75–1.0; reconstruction thickness, 1.0–1.25 mm; reconstruction interval, 1.0–1.25 mm; rotation time, 0.4–0.5 seconds; tube voltage, 120 kVp; tube current, 40 mAs; and reconstruction kernel, medium-sharp algorithm (B50F).

Analysis of Thin-Section CT Features

All thin-section CT images were reviewed by two radiologists (C.M.P. and J.M.G., with 8 and 16 years of experience in chest CT, respectively) who were blinded to the clinical data and follow-up CT results. Any discrepancy during review was resolved through consensus. The CT findings were analyzed with lung window settings (window level, −700 HU; width, 1500 HU), by using a picture archiving and communication system (Maroview; Marotech, Seoul, Korea) and flat-panel monochrome 3-megapixel monitors (ME315; Totoku, Tokyo, Japan).

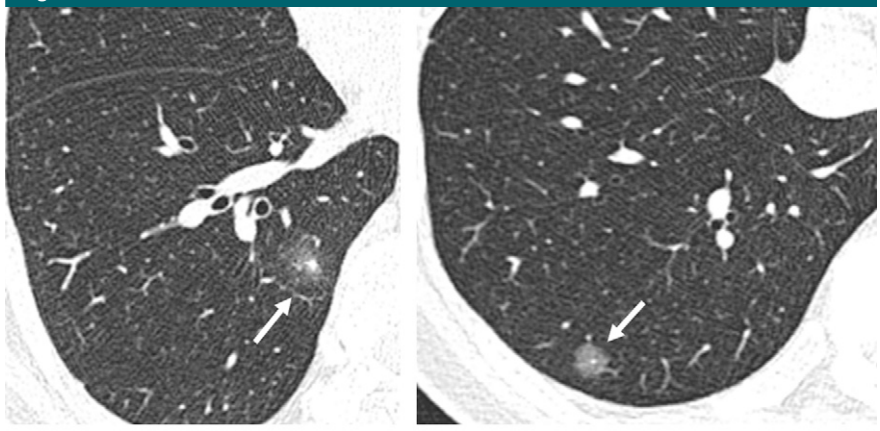
Thin-section CT findings that were analyzed for each lesion included the following: *(a)* lesion location, *(b)* lesion size, *(c)* lesion multiplicity (solitary, multiple), *(d)* margin (spiculated, not spiculated), *(e)* border (well defined, ill defined), *(f)* size of the solid portion, *(g)* border of the solid portion (well defined, ill defined), *(h)* presence of air bronchogram, *(i)* presence of bubble lucency, and *(j)* presence of pleural retraction. We did not assess the shape of the nodule because a substantial proportion of the nodules in our study showed an indistinct border and could not be clearly categorized. An ill-defined border was considered to be present when the peripheral parts of the PSN faded out into the adjacent normal lung parenchyma and the junction between the nodule and surrounding lung parenchyma could not be clearly defined (Fig 1). To determine lesion size, one chest radiologist (C.M.P.) recorded the average product of the height and width of the lesion.

Statistical Analysis

Statistical differences between transient and persistent PSNs were analyzed by using the independent sample *t* test for patient age, smoking amount, WBC count, blood eosinophil count, ESR, and CRP level. Statistical differences in patient sex, smoking history, risk of lung cancer, blood eosinophilia, and mode of detection were analyzed by using the Pearson x^2 test and the Fisher exact test. Thin-section CT findings were evaluated by using univariate analysis with generalized estimating equations to consider the clustering effects of multiple nodules per individual.

To identify variables that could be used in differentiating transient from persistent PSNs and to adjust the effect of the correlation from multiple PSNs per individual, logistic regression analysis with generalized estimating equations was performed. Characteristics with a *P* value of less than .10 at univariate analysis were used as the independent variables for simple and multiple logistic regression analyses. In multiple logistic regression analysis, a backward stepwise selection mode was used, with iterative entry of variables on the basis of test results (*P* values of less than .05). The removal of variables was based on likelihood ratio statistics with a probability of .10. The *C* statistic was also performed to evaluate performance of this multiple logistic regression model in discriminating transient from persistent PSNs. The *C* statistic equals the area under a receiver operating characteristic curve when the response is binary (16). This measured how well the models discriminated between transient and persistent nodules. A *C* statistic of 0.5 indicated no ability to discriminate, while a value of 1.0 indicated perfect discrimination (17). Statistical analyses were performed by using software (SAS, version 9.1.3 for Windows; SAS Institute, Cary, NC). A *P* value of less than .05 was considered to indicate a statistically significant difference.

Figure 1



a. b.

Figure 1: Transverse thin-section CT scans show PSN borders. **(a)** Scan in 51-year-old man shows a 12-mm PSN (arrow) with an ill-defined border in the right lower lung lobe. The border of the nodule fades out into the adjacent normal lung parenchyma without distinct differentiation. **(b)** Another PSN (arrow) is seen in the right lower lobe in a 43-year-old man. This nodule has a well-defined border. The PSN in **a** was transient and the PSN in **b** was persistent.

Results

Clinical Features

Among 126 PSNs in 93 individuals, 88 nodules (69.8%) in 58 individuals were transient. Among the 88 nodules, 81 showed complete resolution, and seven decreased in size. Transient PSNs were more frequently seen in younger patients and in male patients ($P < .05$ for both).

There were 15 current smokers, 44 never-smokers, and 34 ex-smokers in our study. Forty-one individuals were included in the high-risk group: 36 individuals with more than 10 pack-years of smoking history and seven with a first-degree family history of lung cancer. Two individuals had both a 10–pack-year smoking history and a first-degree family history of lung cancer. There were no individuals with occupational exposure to asbestos, beryllium, uranium, or radon. Transient PSNs were

associated with a larger smoking amount and presence in the high-risk group ($P < .05$ for both).

Ninety-six PSNs in 74 individuals were detected at baseline CT, and the remaining 30 nodules in 19 individuals were newly detected at follow-up CT. Twenty-eight (93%) of the 30 nodules newly detected at follow-up CT were transient. In these cases, the mean interval between the previous CT examination and the follow-up CT examination that newly showed the PSNs was 495.8 days ± 220.5 (range, 85–877 days). PSNs that were detected at follow-up CT were significantly ($P < .05$) more likely to prove transient. Blood eosinophil count and the presence of eosinophilia were higher with transient PSNs than with persistent PSNs ($P < .05$). The sensitivity and specificity of blood eosinophilia for transient PSNs were 37.6% and 97.4%, respectively. Table 1 summarizes the clinical features of transient and persistent PSNs.

Table 1

Clinical Features in 93 Individuals with Transient and Persistent PSNs

Characteristic	Individuals with Transient PSNs ($n = 58$)	Individuals with Persistent PSNs ($n = 35$)	*P* Value
Age (y)*	51.1 ± 8.7	58.2 ± 9.7	<.001†
Male-to-female ratio	44:14	15:20	.001‡
Smoking history			<.001§
Never-smoker	23	21	
Ex-smoker	20	14	
Current smoker	15	0	
Smoking amount (pack-years)*	15.3 ± 18.2	7.0 ± 11.4	.008†
Risk level			.006§
Low	26	26	
High	32	9	
Mode of detection			.007§
Baseline	41	33	
Follow-up	17	2	
WBC count (per microliter)*	6023 ± 1962	5544 ± 1409	.182†
Blood eosinophil count (per microliter)*	411.2 ± 330.1	150.4 ± 131.9	<.001†
Blood eosinophilia			.002§
≤500 per microliter	39	34	
>500 per microliter	16	1	
ESR*	9.9 ± 10.8	10.5 ± 8.8	.805†
CRP level*	0.15 ± 0.27	0.13 ± 0.19	.757†

Note—Except where indicated, data are numbers of individuals.

* Data are means ± standard deviations.

† Calculated with the independent sample *t* test.

‡ Calculated with the Pearson χ^2 test.

§ Calculated with the Fisher exact test.

Thin-Section CT Findings

Twenty-five transient PSNs were located in the right upper lobe (RUL), six in the right middle lobe (RML), 30 in the right lower lobe (RLL), 16 in the left upper lobe (LUL), and 11 in the left lower lobe (LLL). Eighteen persistent PSNs were located in the RUL, two in the RML, nine in the RLL, five in the LUL, and four in the LLL. Regarding lesion location, there was no significant difference between transient and persistent PSNs ($P > .05$).

Table 2 summarizes the thin-section CT features of transient and persistent PSNs. There was a significant difference between transient PSNs and persistent PSNs in mean lesion size (11.9 mm ± 4.7 vs 9.9 mm ± 4.8, $P < .05$). With respect to lesion multiplicity and lesion border, transient PSNs were significantly more likely to be multiple lesions ($P < .05$) and to have ill-defined borders ($P < .05$) compared with persistent PSNs (Figs 2, 3). The solid portion of transient PSNs was significantly larger than that of persistent PSNs ($P < .05$) and was more likely to be well-defined compared with that of persistent PSNs ($P < .05$). However, all PSNs with spiculated margins, air bronchograms, or pleural retraction (Fig 4) were persistent.

Results of Logistic Regression Analysis in Discriminating Transient PSNs from Persistent PSNs

Logistic regression analysis with generalized estimating equations was performed to find the independent variables that differentiated transient PSNs from persistent PSNs (Table 3). Among the clinical data, patient age, risk of lung cancer, mode of detection, and blood eosinophilia were used as input variables for logistic regression analysis. Patient smoking amount and sex were not included in logistic regression analysis because they showed strong correlation with the risk of lung cancer, which was a more important factor from a clinical aspect.

Among thin-section CT findings, lesion size, lesion multiplicity, lesion border, size of solid portion, border of solid portion, and bubble lucency were used for logistic regression analysis. Smoking history, margin, air bronchogram, and pleural retraction were not included as input variables for logistic regression analysis because persistent PSNs were not present in current smokers and transient PSNs did not show spiculated borders, air bronchograms, or pleural retractions.

At simple logistic regression analysis, risk of lung cancer, lesion size, border of solid portion, and bubble lucency were not statistically significant (P = .153, .244, .204, and .202, respectively).

At multiple logistic regression analysis, clinical features of young patient age, detection at follow-up, and blood eosinophilia, as well as the thin-section CT features of multiple PSNs, large solid portion, and ill-defined nodular border proved to be significantly associated with transient PSNs. The adjusted odds

Table 2

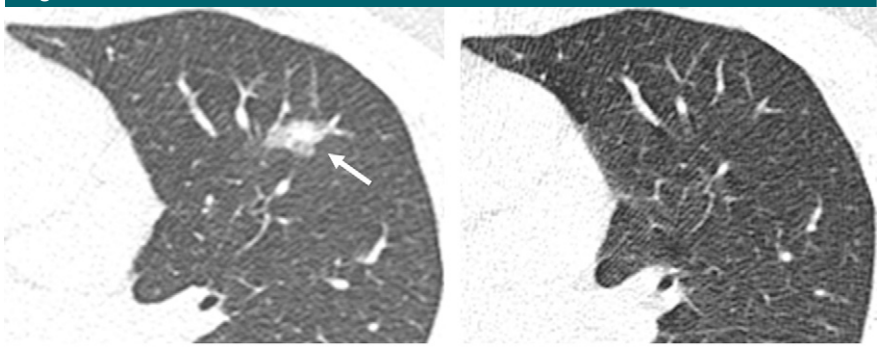
Thin-Section CT Findings of Transient and Persistent PSNs

Characteristic	Transient PSNs (n = 88)	Persistent PSNs (n = 38)	P Value
Lesion size (mm)*	11.9 ± 4.7	9.9 ± 4.8	.021
Lesion multiplicity			.001
Solitary	34	33	
Multiple	54	5	
Lesion margin			Complete separation
Spiculated	0	5	
Nonspiculated	88	33	
Lesion border			<.001
Well defined	11	27	
Ill defined	77	11	
Solid portion size (%)*	48.2 ± 20.9	39.6 ± 16.7	.021
Solid portion border			.024
Well defined	65	21	
Ill defined	23	17	
Air bronchogram	0	5	Complete separation
Bubble lucency	2	5	.077
Pleural retraction	0	10	Complete separation

Note— Except where indicated, data are numbers of nodules.

* Data are means ± standard deviations.

Figure 2



a. b.

Figure 2: Transverse thin-section CT scans show transient PSN with multiplicity in a 43-year-old man. **(a)** Scan shows a 16-mm PSN (arrow) in the left upper lobe. Another 8-mm PSN (not shown) was in the right middle lobe. This patient had eosinophilia (eosinophil count, 574 per microliter). **(b)** Follow-up scan obtained 1 month later shows disappearance of the PSN.

ratios for blood eosinophilia, detection at follow-up, multiple PSNs, and ill-defined nodular border were 248.614, 18.899, 10.614, and 61.277, respectively.

C Statistics of the Predictive Factors

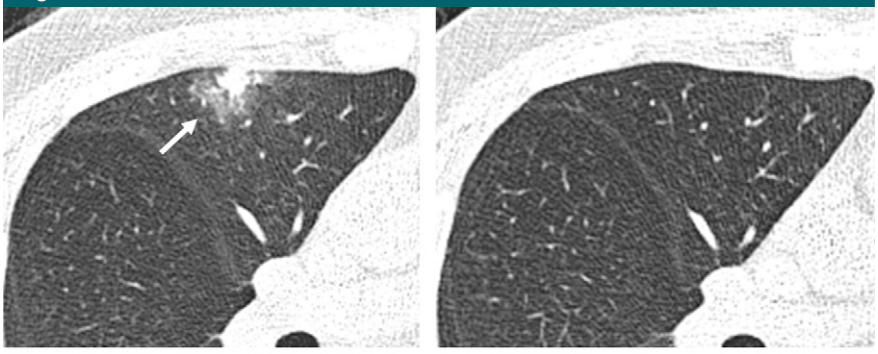
C statistic analysis was performed to evaluate the performance of the multiple logistic regression models in discriminating transient PSNs from persistent PSNs by using significant clinical and thin-section CT features (Fig 5). When clinical independent predictors, including patient age, mode of detection, and eosinophilia were used as input data, the area under the curve (AUC) was 0.889 (95% CI: 828, 950). When only the presence of eosinophilia was used as input data, the AUC was 0.675 (95% CI: 0.581, 0.769). When independent predictors at thin-section CT, including lesion multiplicity, size of solid portion, and lesion border, were used as input data, the AUC was 0.897 (95% CI: 0.840, 0.954). When both the clinical and thin-section CT features were used as input data, the AUC was 0.973 (95% CI: 0.948, 0.998), and sensitivity and specificity were 94.1% and 94.7%, respectively. We could correctly classify 82.4% of PSNs as transient without missing persistent PSNs (sensitivity of 82.4% at 100% specificity). There was no significant difference between the AUCs of the logistic regression model incorporating only the clinical data and that incorporating only the thin-section CT features (0.889 vs 0.897, P = .871). However, the performance of the logistic regression model incorporating both clinical and thin-section CT features was significantly higher than that of those incorporating only the clinical features (0.973 vs 0.889, P = .004) or the thin-section CT features (0.973 vs 0.897, P < .001) independently in discriminating transient PSNs from persistent PSNs.

Discussion

PSNs have been reported to indicate a high probability of early lung cancer in many previous studies (4,9,18–20); thus, when these lesions are encountered in screening or clinical situations, immediate work-up of PSNs is often recommended by radiologists or clinicians (11).

However, it is well known that a substantial proportion of nodules detected at screening CT could be transient because of inflammation or hemorrhage (21). In the present study, we found that 69.8% of PSNs detected at lung cancer screening CT were transient. Similar numbers were also reported by Oh et al (12), who reported that 48.7% of PSNs detected on chest CT decreased in size or disappeared within 3 months. The higher proportion of transient PSNs in our present study compared with that in the previous report (12) could be explained by

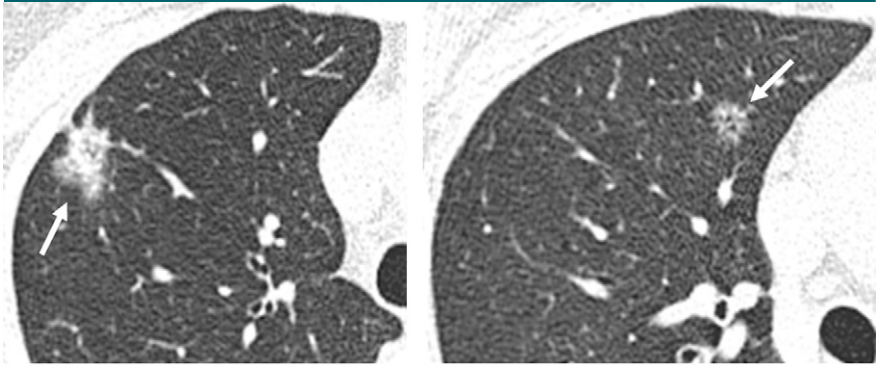
Figure 3



a. b.

Figure 3: Transverse thin-section CT scans show transient PSN with ill-defined border in 37-year-old man. **(a)** Scan shows a 27-mm PSN (arrow) with an ill-defined border in the right upper lobe. This patient had blood eosinophilia (eosinophil count, 1577 per microliter). **(b)** At follow-up CT performed 3 weeks later, the PSN has disappeared.

Figure 4



a. b.

Figure 4: Transverse thin-section CT scans show persistent PSNs with spiculated margins or air bronchograms. **(a)** Scan in 56-year-old woman shows a 17-mm PSN (arrow) with a spiculated margin in the right upper lobe. **(b)** Scan in 46-year-old woman shows a 10-mm PSN (arrow) with air bronchogram in the right upper lobe. These two nodules were confirmed to be adenocarcinomas at lobectomy.

Table 3

Results of Logistic Regression Analysis with Generalized Estimating Equations for Clinical and Thin-Section CT Determination of Transient and Persistent PSNs

Variable	Odds Ratio	95% CI*	*P* Value
Age	0.793	0.689, 0.912	.0012
Detection at follow-up	18.899	1.946, 183.57	.0113
Blood eosinophilia	248.614	8.869, 6969.509	.0012
Multiple lesions	10.614	1.625, 69.325	.0136
Ill-defined lesion border	61.277	6.863, 547.192	.0002
Solid portion size	1.055	1.008, 1.104	.0206

* CI = confidence interval.

the fact that we used thin-section CT scans, not thick-section CT scans, and we included not only solitary PSNs but also multiple PSNs, which were found to have a tendency to be transient in our study. From the results of the present study, follow-up CT for PSNs can be an appropriate strategy with respect to both discrimination of persistent from transient PSNs and the reduction of unnecessary further work-up in patients with transient PSNs (21).

However, with a simple follow-up strategy that does not include further evaluation of the clinical and CT features, there is a risk of diagnostic delay and the possibility of loss to follow-up in patients with persistent PSNs that have a high probability of malignancy, and in patients with transient PSNs, there is a risk of additional radiation exposure, financial cost, and psychiatric stress during unnecessary further work-up. Therefore, early discrimination between transient and persistent PSNs by using clinical data and lesion characterization at thin-section CT is essential as we can decrease the risk of diagnostic delay and loss to follow-up in patients with persistent PSNs and we can confidently and safely follow up PSNs with the characteristics of transience in a short-term period without immediate intervention. Our study results showed that early discrimination between transient and persistent PSNs with use of clinical data and lesion characterization at thin-section CT was indeed possible with high accuracy.

With respect to the clinical features of PSNs, transient PSNs were more frequently found in patients of younger age, which is consistent with results of previous studies (12,22). Transient PSNs were also associated with male sex and current smoking. It has been shown that smoking could be a cause of respiratory bronchiolitis, desquamative interstitial pneumonitis, or inflammatory lesions and that these diseases can manifest as GGOs and are likely to be transient (23). In addition, considering that pulmonary eosinophilia was more frequently shown in men and current smokers (22), the relationship between transient PSNs and smoking and male sex could be linked to the high proportion of blood eosinophilia in individuals with transient PSNs.

In the present study, there were no persistent PSNs in all 15 current smokers in our study population. With

Figure 5

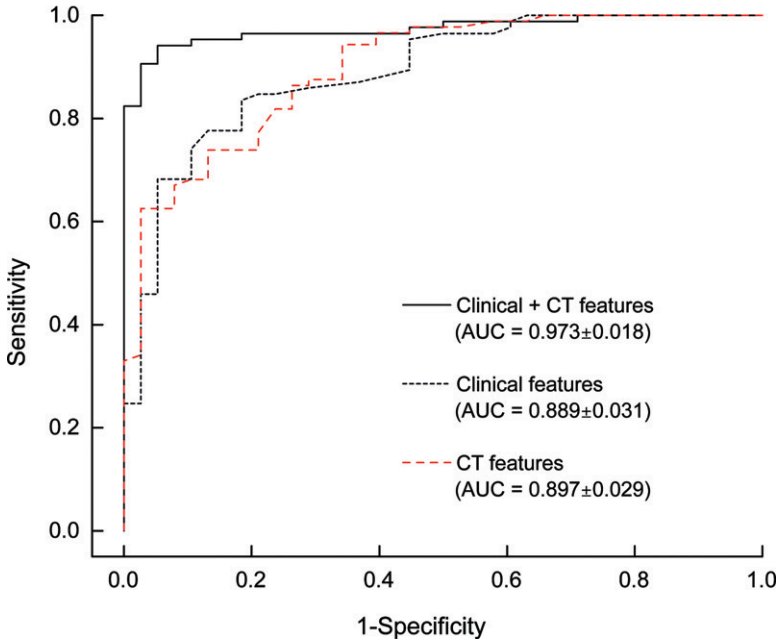


Figure 5: Graph shows results of *C* statistic analysis of multiple logistic regression models in discriminating transient PSNs from persistent PSNs. There were three combinations of independent predictors in the differentiation between transient and persistent PSNs. The highest area under the curve (AUC) was achieved for the combination of both clinical and CT predictors (AUC = 0.973). The AUC of clinical predictors alone (AUC = 0.889) was not significantly different from the AUC of thin-section CT predictors alone (AUC = 0.897) ($P = .871$). However, the AUC of the combination of both clinical and CT predictors was significantly higher than that of either the clinical or the CT predictors alone ($P < .05$). AUCs are shown as means ± standard deviations.

this finding, along with the previous transient tendency shown for PSNs associated with smoking, it may be suggested that smoking may cause transient and inflammatory lesions far more frequently than persistent PSNs. However, at this point in time, it would be a reach to state that every PSN found in asymptomatic current smokers would be transient. We believe that these observations deserve further prospective evaluation in a larger population.

As for the detection mode of PSNs, 93.3% of PSNs detected at follow-up were transient. The mean follow-up interval was 495.8 days, and the mean size of transient nodules detected at follow-up CT was 11.3 mm. According to Hasegawa et al (24), the mean volume doubling time of persistent PSNs was 457 days. A recent study (25) also showed that the mean volume doubling time of persistent PSNs was 568 days. Therefore, it could be reasonable for us to think that PSNs detected at follow-up CT are likely not to be malignant but rather transient.

Blood eosinophilia is also one of the well-known causes of transient inflammation in the lung, as in the case of simple pulmonary eosinophilia. According to a recent report (22), simple pulmonary eosinophilia most often manifested as solid nodules with ground-glass halos showing an ill-defined border, which are the exact CT imaging features of PSNs. In our study, even though blood eosinophilia showed the highest odds ratio among the independent factors for transient PSNs, the sensitivity and specificity of blood eosinophilia for transient PSNs were 37.6% and 97.4%, respectively. Blood eosinophilia showed very high specificity but low sensitivity; thus, this finding should be supplemented by lesion characterization with thin-section CT findings in the discrimination of transient from persistent PSNs.

In regards to thin-section CT features, transient PSNs were significantly larger than persistent PSNs, and the mean size of transient nodules was larger than 10 mm. Thus, immediate further work-up of PSNs using only size criteria could be quite ineffective. It may also cause unnecessary anxiety to the individual with transient PSNs, and furthermore, there may be a risk of unnecessary invasive procedures such as biopsy.

Among other thin-section CT findings, lesion multiplicity and ill-defined border also proved to be independent predictors for transient PSNs. These findings could be objective and reproducible. So, we hope that clinicians as well as radiologists could use these findings to determine whether a PSN would be transient or persistent, confidently and reproducibly. Spiculated margin, air bronchogram, and pleural retraction could also be very useful in differentiating persistent from transient PSNs because none of the transient PSNs in our study showed those CT findings, although we did not include them in the logistic regression analysis because of statistical reasons. These three CT findings could be associated with persistent or malignant nodules (6,26). Furthermore, these findings could be independent predictors and help to determine the persistency or malignancy of a nodule.

With logistic regression analysis and the *C* statistic, we found several independent predictors for transient PSNs—that is, the clinical features of young patient age, detection at follow-up, and blood eosinophilia, as well as the thin-section CT features of multiple PSNs, large solid portion, and ill-defined nodular border. And compared with clinical or thin-section CT findings alone, we found that a combination of clinical and CT findings showed a significant increase in performance in differentiating between

transient and persistent PSNs. In our study, we were able to predict transient PSNs with very high accuracy when we used both the clinical and CT findings. Even though follow-up CT might not be able to be skipped for definite confirmation of a lesion's persistency, unnecessary procedures, including antibiotics or biopsy, might be obviated. Tentative diagnosis of transient inflammation could reduce the anxiety of an individual with PSNs that have the features of transient PSNs.

Our study had several limitations. First, our study had a retrospective design, and our inclusion criteria for our lung cancer screening program was different from that of other screening programs that include only a typical high-risk population for lung cancer such as smokers aged 50 or 60 years or older; thus, our results might have limited application to those populations. Further prospective studies with a larger population are likely necessary to prove our results in those populations. Second, we did not evaluate the reproducibility of CT features of PSNs with various observers as we had resolved any discrepancies between the observers through consensus. Third, we retrospectively searched for individuals with pulmonary PSNs identified at low dose thin-section CT, using electronic medical records and the radiology information system of our hospital. Thus, there is a possibility that nodules might have been unreported and therefore missed by this search method. Fourth, with respect to the transiency of PSNs detected at follow-up, the present study had a limitation in that the time interval between previous CT and follow-up CT studies showing newly detected PSNs was not uniform and varied widely. Further prospective studies with regular and longer follow-up intervals would be necessary in a larger population to confirm this observation.

In conclusion, a substantial proportion of PSNs detected at screening CT for lung cancer were transient. Young age, detection of PSNs at follow-up, blood eosinophilia, lesion multiplicity, large solid portion, and an ill-defined border were found to be independent predictors of transient PSNs. Furthermore, using these clinical and thin-section CT features, transient PSNs could be predicted with high accuracy.

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