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Persistent pulmonary subsolid nodules with solid portions of 5 mm or smaller: Natural course and management

5mm 이하의 고형 성분을 가지는 지속적인 폐 아고형 결절: 자연경과와 관리

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임상의과학과

이 종 혁

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Abstract

Persistent pulmonary subsolid nodules with solid portions of 5 mm or smaller: Natural course and management

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Objective: To investigate the natural course of persistent pulmonary subsolid nodules (SSNs) with solid portions ≤5mm and whether "follow-up and surgical resection after interval growth" can have negative influence on recurrence or overall death in patients with persistent PSNs with solid component ≤ 5mm.

Methods: From 2005 to 2013, the natural courses of 213 persistent SSNs in 213 patients were evaluated. To identify significant predictors of the interval growth, Kaplan-Meier analysis and Cox proportional hazard regression analysis were performed. Meanwhile, 125 part-solid nodules (PSNs) were evaluated for disadvantage of delay in surgical resection only after the sole evidence of interval growth on patient outcomes, using Cox-regression analysis.

Results: Among the 213 nodules, 136 were pure ground-glass nodules (GGNs) (growth, 18; stable, 118) and 77 were part-solid GGNs with solid portions ≤5mm (growth, 24; stable, 53). For all SSNs, lung cancer history ($p=0.001$), part-solid GGNs ($p<0.001$), and nodule diameter ($p<0.001$) were significant predictors for the interval growth. On subgroup analysis, nodule diameter was an independent predictor for the interval growth of both pure GGNs ($p<0.001$), and part-solid GGNs ($p=0.037$). For part-solid GGNs, lung cancer history ($p=0.002$) was another significant predictor of the interval growth. Interval growth of pure GGNs ≥10mm and part-solid GGNs ≥8mm were significantly more frequent than in pure GGNs <10mm ($p<0.001$) and part-solid GGNs <8mm ($p=0.003$), respectively. With respect to prognosis in PSNs, There were five equivocal cases of recurrences. However, even if these 5 equivocal cases were actually recurrences, there were no significant differences between these two groups in terms of recurrence-free survival ($p=0.485$) and overall survival ($p=0.185$).

Conclusion: Natural course of SSNs with solid portions ≤5mm differed significantly according to their nodule type and nodule diameters, with which their managements can be subdivided. And "follow-up and surgical resection after interval growth" did not show negative influence on prognosis of patients with persistent PSNs with solid components ≤ 5mm.

Keywords: Ground-glass nodule; Lung adenocarcinoma; Adenocarcinoma in Situ; Computed tomography; Follow-Up Studies; Operation; Recurrence; Mortality

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CONTENTS

Introduction

Persistent pulmonary subsolid nodules (SSNs) that persist or grow over follow-up examinations of 3 months or longer can be categorized into pure ground-glass nodules (GGNs) and part-solid GGNs (1). Barring a few exceptions, they pathologically represent invasive pulmonary adenocarcinoma or their preinvasive lesions such as atypical adenomatous hyperplasia (AAH), or adenocarcinoma-in-situ (AIS) (1-3), and along with the increased utilization of CT in lung cancer screening and in daily clinical practice, the detection of these SSNs is expected to increase (2).

According to recent Fleischner Society guidelines, persistent subsolid nodules are categorized into three groups, pure ground-glass nodules (GGNs), part-solid nodules (PSNs) with solid component ≤ 5mm, and PSNs with solid component > 5mm (1). They recommend yearly surveillance follow-up CT for persistent pure GGNs larger than 5 mm, and suggest that part-solid GGNs with solid portions ≤ 5 mm may also be followed-up with yearly surveillance CT, as these nodules show a markedly indolent clinical course and a substantial proportion of these nodules may not be clinically relevant malignancies (1). However, such conservative management on these nodules with high malignancy potential can take a risk of stage shift and worse prognosis due to the resultant treatment delay. Indeed, one retrospective study reported that a delay in surgical resection only after the sole evidence of interval growth had no adverse effect on patient outcomes (4).

Several previous studies have also investigated the natural course of SSNs and reported its indolent clinical course as well as various clinico-radiological factors that can be utilized to predict the interval growth of these nodules (2, 5-15). However, although pure and part-solid GGNs can show very distinct clinical behaviors with different malignant probabilities (1, 16), these studies analyzed pure GGNs and part-solid GGNs altogether without separate sub-classification, or arbitrarily decided the cut-off values for the evaluation of SSNs without elaborate categorization. In addition, there have been no studies that have evaluated the natural course of persistent SSNs with solid portions ≤ 5 mm, classified in the new Fleischner Society's guidelines, and investigated the predictors for interval growth of these nodules over follow-ups. Moreover, there has been no study dealing with whether there would be any difference regarding disease recurrence or patients' survival between "follow-up and surgical resection only after interval growth" and "immediate surgical resection" in patients with persistent PSNs with solid component ≤ 5mm. Therefore, our study aimed to investigate the natural course of persistent pulmonary SSNs with solid portions ≤ 5 mm and whether "follow-up and surgical resection after interval growth" can have negative influence on recurrence or overall death in patients with persistent PSNs with solid component ≤ 5mm.

MATERIALS AND METHODS

This retrospective study was approved by the institutional review board of Seoul National University Hospital with a waiver of the requirement for patients' informed consent.

Natural course of persistent pulmonary SSNs with solid portions ≤ 5 mm

A search of our hospital's Ground-Glass Nodule registry (17-20) between May 2005 and February 2013 was conducted. Two radiologists (J.H.L. and C.M.P., with 4 and 17 years of experience in thoracic radiology) reviewed all chest CT images of this registry and patients who met all of the following criteria comprised our study population: Patients with (a) SSNs confirmed as persistent on follow-up CTs with a follow-up interval of 3 months or longer, (b) SSNs ranging in diameter from 5 mm to 3 cm on their initial CTs, (c) solid portions within SSNs, if any, 5 mm or smaller, and (d) initial chest CTs demonstrating SSNs with slice thicknesses ≤ 1.25 mm. Solid portions referred to the part of SSN showing increased attenuation to the degree of obscuring the underlying pulmonary vessels and airway walls within it. In this study, we used the "average diameter" for SSNs' diameter, which is defined as the average between the longest diameter of the SSNs and their perpendicular short-axis diameter on axial CT images based on Fleischner Society recommendations (1). The size of part-solid GGNs'

solid portions was measured in its largest dimension. When patients had multiple SSNs, only one dominant SSN was included according to the following criteria: (a) Part-solid GGNs receive higher priority than pure GGNs, (b) when there are two or more part-solid GGNs, the nodule with the largest solid portion was selected, (c) when size of solid components was similar, a PSN with the largest size was selected, and (d) a pure GGN with the largest diameter was selected, if there were no part-solid GGNs.

Finally, 213 persistent SSNs in 213 patients (mean age, 57.88 ± 10.38 years; range 24 – 87 years) were included in this study (median follow-up duration, 849 days; range, 90 – 2900 days). Of the 213 patients, 72 were men (mean age, 59.10 ± 9.88 years; range 24 – 87 years) and 141 were women (mean age, 57.26 ± 10.6 years; range 24 – 80 years).

One author (S.M.L., with 10 years of experience in thoracic radiology) searched the electronic medical records and the radiology information systems of our hospital for the clinical and demographical features of the study patients including sex, age, smoking history, lung cancer history, as well as a history of other cancers. If the patients had a cancer history, the author investigated whether the SSNs were detected synchronously or metachronously. Pathological diagnoses of the surgically resected SSNs were also recorded. All chest CT images were viewed by two radiologists (J.H.L. and C.M.P.) in consensus. The initial and all follow-up CT images were displayed side-by-side on monitors using the Picture Achieving and Communication Systems, and were compared. All SSNs and their solid portions were evaluated through visual assessment at the lung

window setting (a level of -700 Hounsfield units and a width of 1500 Hounsfield units). The nodule type of SSNs (pure GGNs or part-solid GGNs), multiplicity, location of SSNs and diameters of SSNs on initial CT and follow-up CTs were also recorded. In this study, interval growth of SSNs was designated when one of the following was observed: (a) a size increase of ≥ 2 mm in diameter was identified on follow-up CTs compared with initial CT (21), (b) solid portions in part-solid GGNs increased by 2 mm or greater compared to the initial CT, or (c) solid portions newly occurred within the pure GGNs (1, 5-9).

After that, all 213 SSNs were analyzed using Kaplan-Meier analyses with the log-rank test based on the clinico-radiologic features described above. To determine the independent predictors of interval growth, multivariate Cox proportional hazard regression analysis with backward stepwise selection was performed using input variables with P-values < 0.10 at the log-rank test. Backward stepwise selection was conducted with iterative entry of variables based on the test results (p<0.05), and the removal of variables was based on likelihood ratio statistics with a probability of 0.10. Subsequently, the 213 SSNs were categorized into pure GGNs and part-solid GGNs with solid parts ≤ 5 mm, and subgroup analysis was performed separately for each group in the same statistical manner as described above, as these two groups have been reported to have different malignancy probabilities, and assumingly different natural courses (1, 16). In the part-solid GGN group, the cut-off value of the solid portion was determined using ROC curve analysis. Among the significant variables on the Cox proportional hazards

model, nodule diameter was selected for further categorization. For each type of SSN, we divided the patients into three groups according to their diameter on initial CT (<8mm; 8-10mm; ≥10mm) and post hoc power analysis was performed for the results of Kaplan-Meier analyses with the log-rank test to confirm the most significant cut-off diameter for growth. Finally, the annual cumulative percentages of growing nodules were analyzed with respect to the determined cut-off diameters in pure GGN and part-solid GGN groups.

Prognosis comparison between "follow-up and surgical resection only after interval growth" and "immediate surgical resection" in patients with persistent PSNs with solid portions ≤ 5mm

One author (J.H.L.) searched the lung parenchymal operation records of our hospital between April 2006 and February 2015 and selected all pathologic information with the descriptive terms "pulmonary adenocarcinoma", "minimally invasive adenocarcinoma", or preinvasive lesion such as "atypical adenomatous hyperplasia", "adenocarcinoma in-situ" or "bronchioloalveolar carcinoma". A total of 2959 pathologies were identified and two radiologists (J.H.L. and C.M.P.) reviewed all pre-operation chest CT images of these 2959 pathologies. Lesions which met all of the following criteria comprised our study population: Lesions with (a) appearance of PSNs ranging in size from 5mm to 30mm on initial chest CT and persistent over short-term follow-up 3months or shorter, (b) solid components within PSNs,

5mm or smaller on initial CT, (c) initial chest CTs demonstrating PSNs with slice thicknesses ≤ 1.25 mm, (d) available post-operative CT scans to evaluate patients' postoperative disease status. When one patient had multiple PSNs with solid component ≤ 5mm, only one dominant nodule was included in the same manner as described above. A total of 144 patients with 144 PSNs with solid parts 5mm or smaller were selected. Among this population, 19 patients with 19 PSNs (median follow-up period, 255 days; range 123 - 1150 days) which were followed-up and surgically resected later without evidence of interval growth on follow-up CTs, were excluded in this study since this study aimed to investigate whether there would be any difference regarding disease recurrence or patients' survival between "follow-up and surgery only after interval growth" and "immediate surgery" in patients with persistent PSNs with solid component ≤ 5mm.

Thus, 125 individuals (men:women=41:84; mean age, 59.9 ± 9.1 years; range 38 - 80 years) with 125 PSNs (mean diameter, 13.16 ± 5.32mm; range, 5 - 29.7mm) were finally included in this study (figure 1) and they were categorized into two groups (interval growth group vs. immediate surgery group). The interval growth group is defined as PSNs which are designated when one of the growth indications as described above. The immediate surgery group is referred to group of the nodules with just short-term follow-up CT demonstrating persistency of the nodules. Among the 125 patients, 54 patients were classified into "interval growth group" (median follow-up period before surgery, 554 days; range, 90 - 3222 days) and the remaining 71 were categorized into "immediate surgery

group" (median follow-up period before surgery, 49 days; range, 25 - 91 days).

One author (J.H.L.) searched the electronic medical records and the radiology information systems of our hospital for the clinical and demographical features of this study population including age, sex, smoking history, and history of malignancy. Pathological diagnoses and stages of the surgically resected PSNs were also recorded. In addition, the individuals' survivals were investigated. Two radiologists (J.H.L. and C.M.P.) reviewed all pre- and post-operation chest CT images in consensus. All PSNs and their solid components were evaluated through visual assessment at the lung window setting (a level of -700 Hounsfield units and a width of 1500 Hounsfield units). Multiplicity, location of PSNs and sizes of the nodules and their solid components on initial CT and pre-operation follow-up CTs were recorded. As for interval growth group, clinical tumor stage shift was evaluated both based on whole nodule size and solid component' size. For evaluation of recurrence, all follow-up chest CTs after surgery were evaluated at both lung and mediastinal window setting (a level of 30 Hounsfield units and a width of 400 Hounsfield units).

Independent t-test, Wilcoxon rank sum test, Chi-square test, and Fisher's exact test were performed to analyze mean and proportions of baseline clinical and radiological findings of the two groups, as appropriate. To evaluate the influence of follow-up till interval growth on recurrence and survival, Cox proportional hazard model was performed (22). To control the potentially different baseline characteristics between these two groups, rigorous adjustment for the variables was conducted. For the continuous variables including age,

size of the nodules, and solid components, restricted cubic spline regression was performed for linearity assumption and proportional hazard assumption (23-25). Sex, history of malignancy, smoking history, location and position of the nodules, and multiplicity were modeled as categorical variables, and log-log survival plot was used for proportional hazard assumption. A P value < 0.05 was considered to indicate a statistical significance, with all statistical analyses performed using SPSS ver. 20.0 (SPSS Inc., Chicago, IL, USA) and MedCalc ver. 12.0 (MedCalc Software, Mariakerke, Belgium).

Seven different CT scanners were used in this study (Sensation 16, SOMATOM Definition, Siemens Medical Solutions, Forchheim, Germany; Brilliance-64, Ingenuity, Phillips Medical Systems, Best, Netherlands; Aquilion One, Toshiba, Japan; Discovery CT750 HD, LightSpeed Ultra, GE Medical Systems, Waukesha, Wis). All CT examinations were performed with the following parameters: 120 kVp; 60-90 mAs; pitch of 0.75 - 1.5; and collimation of 0.625 - 1.25mm. All image data were reconstructed using the medium-sharp reconstruction algorithm with a thickness of 1.25mm or less. CT scans were performed in the supine position at full inspiration. In the case of contrast-enhanced CT, 100 mL of contrast medium was injected at a rate 2 mL/sec. Intervals between follow-up CTs after confirmation of SSNs' persistency were decided upon at the referring physicians' discretion (mean interval, 12.4 months; range, 6 months - 2 years).

RESULTS

Natural course of persistent pulmonary SSNs with solid portions ≤ 5 mm

Clinical and initial radiological characteristics of the 213 patients and 213 persistent SSNs are summarized in Table 1. Among the 213 SSNs, 136 were pure GGNs, and 77 were part-solid GGNs with solid portions ≤ 5 mm on initial chest CT scans. With respect to nodule growth, 42 nodules were classified to have shown growth and 171 were determined to have remained stable. Among the 42 SSNs classified as having shown growth, nodule size increased in 22, new solid portions occurred within the SSNs in 4, internal solid portions increased in 4, and the remaining 12 showed a combination of these patterns. For follow-up duration, there were 165, 112, 63, 40, and 24 nodules at 1, 2, 3, 4, 5 year's follow-up, respectively, and 24 nodules had been followed-up for more than 5 years.

Among the 213 nodules, 58 nodules were surgically resected (median follow-up period before surgical resection, 557 days; range, 94 - 2903 days). Fourteen were invasive adenocarcinomas (pure GGN in 3, part-solid GGN in 11), 5 were minimally invasive adenocarcinomas (MIA) (pure GGN in 4, part-solid GGN in 1), 30 were AIS (pure GGN in 19, part-solid GGN in 11), and 9 were AAH (pure GGN in 7, part-solid GGN in 2). Twenty-seven of the 58 nodules were judged to have shown growth prior to surgical resection and were confirmed as invasive adenocarcinomas (n=5), MIA (n=3), AIS (n=17), and AAH

(n=2), pathologically. The remaining 31 of the 58 nodules consisting of 19 pure GGNs and 12 part-solid GGNs were resected without evidence of growth. The mean diameter of these 19 pure GGNs and 12 part-solid GGNs were 8.88 mm (range, 5.0 - 14.4 mm) and 9.3 mm (range, 5.1 - 15.3 mm), respectively. Pathologically, 19 pure GGNs turned out to be AAH (n=5), AIS (n=9), MIA (n=2), and invasive adenocarcinomas (n=3). As for the 12 part-solid GGNs, there were 2 AAH, 4 AIS, and 6 invasive adenocarcinomas. Meanwhile, the 15 SSNs showing interval growth on follow-ups (median, 19 months; range, 3 - 63 months) were not resected owing to several reasons such as patient's refusal of surgery (n=10) or loss of follow-up (n=5). These 15 nodules consisted of 4 pure GGNs (mean diameter, 9.08 mm; range, 7.4 - 12.3 mm) and 11 part-solid GGNs (mean diameter, 11.45 mm; range, 5.7 - 17.8 mm).

On Kaplan-Meier analysis with the log-rank test, lung cancer history ($p=0.002$), nodule type of SSNs ($p<0.001$) (Figure 2a), and the diameter of SSNs ($p<0.001$) were shown to be significant variables for SSN growth. Subsequent Cox proportional hazard regression analysis revealed that lung cancer history (Hazard ratio (HR), 3.884; $p=0.001$), part-solid GGNs (HR, 3.570; $p<0.001$), and the diameter of SSNs (HR, 3.576; $p<0.001$) were independent predictors for interval growth of SSNs.

Table 2 demonstrates the results of univariate and multivariate analyses on the growth of pure GGNs. The diameter of pure GGNs ($p<0.001$) was a single significant variable associated with interval growth on Kaplan-Meier analysis with the log-rank test. Subsequent Cox regression analysis also revealed that their diameter (HR, 6.620;

p<0.001) was the only significant predictor for the interval growth of pure GGNs. According to the analysis of the three subgroups based on SSN diameters (<8mm; 8-10mm; ≥10mm), a cut-off value of 10 mm was determined to be the most significant cut-off diameter in terms of nodule growth (*p<0.001, p=0.013*). The annual cumulative percentages of growing pure GGNs with a cut-off value of 10 mm is demonstrated in Table 3. Pure GGNs ≥ 10 mm on initial CT showed significantly more frequent interval growth than pure GGNs < 10 mm (12.9% vs. 1.9%, 30.4% vs. 4.0%, 42.0% vs. 10.9%, 42.0% vs. 13.5%, 71.0% vs. 13.5%, at 1, 2, 3, 4 and 5 year's follow-up, respectively; *p<0.001*) (Figures 2b).

Univariate and multivariate analyses on the growth of part-solid GGNs with solid portions ≤ 5 mm are summarized in Table 4. The log rank test revealed that patient's age (*p=0.043*), lung cancer history (*p<0.001*), diameter of part-solid GGNs (*p=0.003*), and solid portion size (*p<0.001*) were significant variables associated with interval growth. Subsequent Cox regression analysis demonstrated that lung cancer history (HR, 5.917; *p=0.002*) and diameter of part-solid GGNs (HR, 2.749; *p=0.037*) were independent predictors for interval growth of part-solid GGNs, while the size of the solid portion (HR, 2.394; *p=0.094*) did not show statistical significance. According to the analyses of the three groups based on their diameters (<8mm; 8-10mm; ≥10mm), the most significant cut-off diameter in terms of nodule growth was 8 mm (*p=0.014, p=0.011*). The annual cumulative percentages of part-solid GGNs showing growth with a cut-off value of 8 mm is presented in Table 3. Part-solid GGNs ≥ 8 mm had a significantly higher frequency of interval growth than those < 8 mm

(11.5% vs. 11.5%, 38.0% vs. 21.5%, 43.6% vs. 21.5%, 78.9% vs. 21.5%, 78.9% vs. 21.5%, at 1, 2, 3, 4 and 5 year's follow-up, respectively; *p=0.003*) (Figures 2c).

Prognosis comparison between "follow-up and surgical resection only after interval growth" and "immediate surgical resection" in patients with persistent PSNs with solid portions ≤ 5mm

The baseline clinical and CT characteristics for 125 PSNs of 125 individuals and the comparison between the two groups were summarized in the table 5. Among the 54 PSNs of interval growth group, nodule size increased in 30 (mean increase of size, 3.96 ± 1.54mm; range, 2.1 – 7.0mm), internal solid parts increased in 10 (mean increase of solid parts, 3.8 ± 3.75mm; range, 2.0 – 14.4mm) and the remaining 14 showed a combination of the two patterns (mean increase of nodule size, 4.5 ± 1.78mm; range, 2.3 – 8.5mm; mean increase of solid component, 3.84 ± 2.44mm; range, 2.1 – 9.2mm). In the interval growth group, median time interval between initial CT and occurrence of interval growth / surgical resection were 527 days (range, 90 – 1281 days) and 579.5 days (range, 91 – 3255 days), respectively. For reference, median time interval between last pre-operative CT and surgery was 8 days (range, 1 – 73 days) for interval growth group. And the median time interval between last pre-operative CT scans and surgical resections was 17 days (range, 0 – 76 days) in the immediate surgery group. On the last CT before surgery, size of solid component of interval growth group (4.44 ±

2.76mm; range, 1.5 – 16.9mm) was significantly larger than that of immediate surgery group (3.49 ± 1.01mm; range, 1.6 – 5.6mm; *p=0.02*) though size of PSNs did not show difference (interval growth group, 14.76 ± 5.06mm; immediate surgery group, 14.54 ± 5.50mm; *p = 0.*823). Surgical and pathological results for these 125 nodules were summarized in the table 6. There were five PSNs with invasion of visceral pleura and no PSN with lymphatic or vascular invasion.

The median follow-up periods after surgical resection were 957.5 days (range, 158 – 2365 days) and 1277 days (range, 179 – 2543 days) in the interval growth group and immediate surgery group, respectively. In the interval growth group, five PSNs showed clinical stage shift based on the size of whole nodule during preoperative follow-up period (initial size, 16.68 ± 3.01mm; range 13 – 20mm; size after interval growth, 22.92 ± 2.57mm; range, 20.3 – 27mm), in which tumor stage did not change based on their solid components' size (initial solid size, 2.68 ± 0.83mm; range 1.4 – 3.5mm; solid size after interval growth, 4.12 ± 1.42mm; range, 3.2 – 6.6mm). These five PSNs were clinical stage T1a on initial chest CT, which progressed as clinical stage T1b after interval growth, which were pathologically confirmed as adenocarcinoma (n=2), MIA (n=2), and AIS (n=1).

There were five equivocal cases (4.0%) in which recurrences occurred or not among 125 individuals. The profile of theses five cases is summarized in table 7. Otherwise, there was no recurrence on their post-operative follow-ups. Even if these 5 equivocal cases were actually recurrences, there was no significant recurrence difference between interval growth group and immediate surgery

group (adjusted hazard ratio (HR) = 0.455; 95% confidence interval (CI), 0.050 – 4.156; *p=0.485*). For survival analysis, four individuals died (interval growth group, n=1; immediate surgery group, n=3). There was no significant difference in the respect of survival (HR = 0.068; 95% CI, 0.001 – 3.616; *p=0.185*) (figure 3). For reference, five individuals with above-mentioned PSNs of clinical stage shifts had not equivocalness of recurrence or death.

DISCUSSION

In our study, we found that lung cancer history, part-solid GGNs, and the diameter of SSNs were significant predictors for the growth of SSNs with solid portions ≤ 5 mm. On subgroup analysis, nodule diameter was observed to be a significant predictor of growth for both pure GGNs and part-solid GGNs, with lung cancer history shown to be another significant factor of growth for part-solid GGNs. Pure GGNs ≥ 10 mm and part-solid GGNs ≥ 8 mm were also shown to have a significantly higher cumulative percentages of growth than pure GGNs < 10 mm ($p<0.001$) and part-solid GGNs < 8 mm ($p=0.003$), respectively. In addition, we proved that conservative follow-up until confirmation of interval growth did not result in disadvantage of recurrence or survival in the PSNs with solid component ≤ 5mm.

Previous studies (2, 9) have also reported that the size of SSNs was a significant predictor of nodule growth. Interestingly, Matsuguma et al. (8) had reported that lung cancer history and nodule size were significantly associated with nodule growth in pure GGNs, however they were unable to find any significant predictors for nodule growth in part-solid GGNs. In our study, nodule diameter was shown to be a significant predictor of interval growth for both pure GGNs and part-solid GGNs with solid portions ≤ 5 mm. This discrepancy may be due to the differences in SSN measurement methods between ours and the previous study (8). In the previous study (8), the diameter of SSNs was determined using only the maximal diameter, while we

recorded the average diameter between the longest diameter and that of the perpendicular short-axis diameter according to Fleischner Society recommendations (1). Since the shape of SSNs could frequently vary and appear as round, oval, or even spiculated rather than spherical, determination of the diameter using both the largest and their perpendicular short-axis diameters may better reflect the actual size of the SSNs than only the maximal diameter. Although it still remains debatable whether SSNs in patients with a lung cancer history are second primary lung cancers or metastasis from previous lung cancers, two previous studies (8, 9) suggested that they may in fact be second primary lung cancers rather than metastasis. Hiramatsu et al. reported that none of their patients with lung cancer history had extrathoracic metastasis or bilateral multiple metastasis and Matsuguma et al. also reported no recurrence on their patients' follow-up periods except for only one patient (8, 9). In fact, all five patients in our study who had a previous history of lung cancer also showed interval growth of part-solid GGNs without any local recurrence or other distant metastasis. Nevertheless, it remains difficult to know confirmatively the exact relationship between lung cancer history and growing SSNs owing to the lack of a pathological diagnosis of growing SSNs and the small number of these patients with both SSNs and previous lung cancer history. Further large scaled studies would be necessary to address this issue.

In this study, pure GGNs < 10 mm showed a significantly lower frequency of interval growth than those in the ≥ 10 mm group, with cumulative percentages of 1.9%, 4.0%, 10.9%, 13.5%, 13.5% at 1, 2, 3, 4, and 5 year follow-ups, respectively. Therefore, considering their

very slow growth rate (17) and the low incidence of interval growth, pure GGNs < 10 mm may be best followed-up biennially after one-year follow-up. Through the one-year follow-up, rapidly growing pure GGNs, which may be biologically more aggressive and thus clinically relevant malignancies, could be avoided from being missed, while subsequent biennial follow-ups can reduce the cumulative radiation dose as well as the monetary burden of the patients without missing the growth of relatively indolent pure GGNs. Although there may be nodules that show interval growth at second-year follow-up CTs without detectable growth on first year follow-up, we believe that as their growth rate may be low, the chance of a significant delay in the diagnosis of clinically relevant malignancies would not be substantially high.

The annual cumulative percentages of growing pure GGNs ≥ 10 mm in our study was 12.9%, 30.4%, 42.0%, 42.0%, 71.0% at 1, 2, 3, 4, 5 year follow-ups, and this frequency is thought to be substantial. Previous studies have reported that the growth of SSNs was typically observed within the first 3 years in large pure GGNs (6, 8), and revealed that pure GGNs ≥ 10 mm may frequently be invasive adenocarcinomas pathologically (16, 19). In this context, for pure GGN ≥ 10 mm, annual follow-up CT may be reasonable, as recommended by the management guidelines of the Fleischner Society (1). For part-solid GGNs with solid portions ≤ 5 mm, interval growth can occur frequently regardless of their diameter. Therefore, we believe that annual surveillance should not be skipped for these persistent part-solid GGNs. Particularly, in the case of part-solid GGNs ≥ 8 mm, their interval growth was observed to occur consistently and

frequently (11.5%, 38.0%, 43.6%, 78.9%, 78.9% at 1, 2, 3, 4, and 5 year follow-ups, respectively) and approximately 80% of these nodules grew in 4 year follow-ups. Thus, immediate surgical resection of theses nodules may not be unreasonable after confirmation of their persistency.

With respect to prognosis comparison study, five PSNs with solid component ≤ 5mm showed clinical stage shift during the follow-up period before confirmation of interval growth. These 5 nodules were demonstrated as clinical stage T1a on initial chest CT, which shifted to clinical stage T1b after interval growth and turned out as adenocarcinoma (n=2), MIA (n=2), and AIS (n=1), pathologically. In spite of stage shift during follow-up, however, five individuals who had these five nodules did not show disease recurrence after surgery or die. It could be because surgical resection for theses nodules were performed too early state to change patients' prognosis, considering three of these five PSNs consisted of MIA or AIS. It is widely accepted that size of tumor is important for the prognosis prediction of the patient with lung cancer (26). And according to previous study, size of solid part is better prognostic factor than nodule size in part-solid GGN (27). As suggested by previous study (27), if clinical stages for these five PSNs are applied with solid part instead of nodule size, they are all T1a without stage shift even after interval growth. Considering this result, the fact that recurrence or death did not occur in these five nodules can be explainable.

Meanwhile, when sizes of PSNs and solid components within them were adjusted to minimize different baseline characteristics between the two groups in the present study, recurrence and survival were

comparable between the two. In addition, sizes of PSNs on the last preoperative CT and pathologic sizes of the lesions reflecting actual pathologic tumor sizes were not significantly different between the two groups. In this context, nodules' size itself can be better than the presence of interval growth in terms of prognosis of patients with PSN with solid component ≤ 5mm. However, although sizes of solid components were different on the last preoperative CT between the two groups with increased size of solid components in the interval growth group, the patient's prognosis was not significantly influenced by it, unlike previous study (27). It may be because a little increases in solid component' size may not actually have significant effect on patient's prognosis to a certain degree. Actually, sizes of solid components in the two groups are less than 10mm even on the last pre-operative CT. Further large scaled studies would be necessary to address this issue clearly.

Several limitations of our study should be mentioned. First, this study was of retrospective design, and CT examinations or patients' management were not uniformly performed. Second, in spite of our relatively large study population, the number of growing nodules was relatively small. Third, follow-up of SSNs was not uniform or quite long. Fourth, we selected dominant nodules in one patient who had multiple SSNs as dominant nodules are generally regarded to determine a patient's outcome and further management (1). However, there may have been the possibility that non-dominant nodules would show a different gwth rate or tendency than dominant lesions. Fifth, study population of prognosis comparison study was limited to surgically resected PSNs with solid component ≤ 5mm. There must

be PSNs with solid component ≤ 5mm which were not resected though they showed interval growth. Sixth, all SSNs showing interval growth in our study were not resected nor were they diagnosed pathologically, owing to patient's refusal of surgery or loss of follow-up. Lastly, there were five equivocal cases which had recurrence or not in prognosis comparison study.

In conclusion, natural course of SSNs with solid portions ≤ 5 mm significantly differed according to nodule type and nodule diameters, with which their managements can be subdivided. And "follow-up and surgical resection after interval growth" did not show negative influence on prognosis of patients with persistent PSNs with solid components ≤ 5mm.

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TABLES AND FIGURES

Table 1. Baseline clinical and radiological characteristics of 213 patients and their 213 persistent pulmonary SSNs

Clinical Features of Patients		Radiological Characteristics	
Follow-up period, days	849 (90 - 2900)	Multiplicity (multiple, single)	99, 114 (46.5%, 53.5%)
Sex (Male, Female)	72, 141 (33.8%. 66.2%)	Location of SSNs (RUL, RML, RLL, LUL, LLL)	69, 18, 36, 64, 26 (32.4%, 8.5%, 16.9%, 30.0%, 12.2%)
Age (years)	57.88 ± 10.38 (24 - 87)	Location of SSNs (central, peripheral)	92, 121 (43.2%, 56.8%)
Smoking history (never-smoker, ever-smoker, unknown)	143, 59, 11 (67.1%, 27.7%, 5.2%)	Position (subpleural, perifissural, parenchymal)	105, 33, 75 (49.3%, 15.5%, 35.2%)
Time of occurrence		Type of SSNs	
Synchronous	53 / 77 (68.8%)	Pure GGN	136 (63.8%)
Metachronous	24 / 77 (31.2%)	Part-solid GGN (solid portion ≤ 5 mm)	77 (36.2%)
Cancer history	77 (36.2%)	Diameter of SSNs (mm)	8.23 ± 2.88
Lung cancer history*	16 (7.5%)	Size of solid portion (in part-solid GGN) (mm)	2.42 ± 1.15

Note - Data are median (range) or mean ± standard deviation (range) or numbers (percentage).

*All 16 patients had history of surgically resection of lung cancer or their preinvasive lesion (Invasive adenocarcinoma in 14, adenocarcinoma-in-situ in 2).

SSN, Subsolid nodule; GGN, Ground-glass nodule RUL, Right upper lobe; RML, Right middle lobe; RLL, Right lower lobe; LUL, Left upper lobe; LLL, Left lower lobe.

Table 2. Univariate and multivariate analyses on the growth of persistent pure GGNs

Variables		Univariate analysis		Multivariate analysis		
		No. of patients (n=136)	P-value	HR	95% CI	P-value
Sex	Male	45	0.674			
	Female	91				
Age	>52	95	0.399			
	≤52	41				
Cancer history	Yes	50	0.051			
	No	86				
Lung cancer history	Yes	11	0.232			
	No	125				
Time of occurrence (n=50)	Synchronous	37	0.695			
	Metachronous	13				
Smoking history (n=131)	Never-smoker	94	0.219			
	Ever-smoker	37				
Multiplicity	Single	68	0.781			
	Multiple	68				
Nodule diameter (mm)	≥10	21	<0.001	6.620	2.582, 16.969	<0.001
	<10	115				

GGN, Ground-glass nodule; No, Number; HR, Hazard ratio; CI, Confidence interval

Table 3. Annual cumulative number and percentages of growing nodules according to nodule diameter for pure GGNs and part-solid GGNs with solid portions ≤ 5 mm

Type of SSNs	Nodule size (mm)	Cumulative number of growing nodules (cumulative percentages of growing nodules)					P-value
		1 year	2 year	3 year	4 year	5 year	
Pure GGN (n=136)	<10 (n=115)	2 (1.9%)	5 (4.0%)	9 (10.9 %)	10 (13.5 %)	10 (13.5 %)	<0.001
	≥10 (n=21)	2 (12.9 %)	4 (30.4 %)	5 (42.0 %)	5 (42.0 %)	7 (71.0 %)	
Part-solid GGN with solid portion ≤5mm (n=77)	<8 (n=41)	3 (11.5 %)	7 (21.5 %)	7 (21.5 %)	7 (21.5 %)	7 (21.5 %)	0.003
	≥8 (n=36)	4 (11.5 %)	10 (38.0 %)	11 (43.6 %)	16 (78.9 %)	16 (78.9 %)	

SSN, Subsolid nodule; GGN, Ground-glass nodule

Table 4. Univariate and multivariate analyses on the growth of persistent part-solid GGNs with solid portions ≤ 5 mm

Variables		Univariate analysis		Multivariate analysis		
		No. of patients (n=77)	P-value	HR	95% CI	P-value
Sex	Male	27	0.517			
	Female	50				
Age	>52	53	0.043			
	≤52	24				
Cancer history	Yes	27	0.602			
	No	50				
Lung cancer history	Yes	5	<0.001	5.917	1.928, 18.164	0.002
	No	72				
Time of occurrence (n=27)	Synchronous	16	0.530			
	Metachronous	11				
Smoking history (n=71)	Never-smoker	49	0.474			
	Ever-smoker	22				
Multiplicity	Single	46	0.509			
	Multiple	31				
Nodule diameter (mm)	≥8	36	0.003	2.749	1.064, 7.104	0.037
	<8	41				
Size of solid portion (mm)	≥3	29	<0.001	2.394	0.862, 6.648	0.094
	<3	48				

GGN, Ground-glass nodule; No, Number; HR, Hazard ratio; CI, Confidence interval

Table 5. Baseline clinical characteristics of 125 individuals and initial CT features of their part-solid nodules with solid component ≤ 5 mm

Variable		Interval growth group (n=54)	Immediate surgery group (n=71)	P-value
Age (years)		60.46 ± 8.08	59.48 ± 9.84	0.551
Sex	Female, Male	31, 23 (57.4%, 42.6%)	53, 18 (74.6%, 25.4%)	0.042
History of malignancy	No Yes	34 (63.0%) 20 (37.0%)	53 (74.6%) 18 (25.4%)	0.159
Smoking history	Never Ever	40 (74.1%) 14 (25.9%)	61 (85.9%) 10 (14.1%)	0.096
Location (lobe)	RUL, RML, RLL, LUL, LLL	17, 4, 13, 14, 6 (31.5%, 7.4%, 24.1%, 25.9%, 11.1%)	31, 2, 20, 13, 5 (43.7%, 2.8%, 28.2%, 18.3%, 7.0%)	0.389
Location	Central, Peripheral	26, 28 (48.1%, 51.9%)	24, 47 (33.8%, 66.2%)	0.105
Position	Subpleural, Perifissural, Parenchymal	23, 13, 18 (42.6%, 24.1%, 33.3%)	42, 7, 22 (59.2%, 9.9%, 31.0%)	0.063
Multiplicity	Multiple, Single	11, 43 (20.4%, 79.6%)	19, 52 (26.8%, 73.2%)	0.407
Diameter (mm)		11.48 ± 4.78	14.44 ± 5.4	0.002
Size of solid component (mm)		2.53 ± 0.91	3.19 ± 0.95	<0.001

RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe

Table 6. Surgical and pathological results of 125 part-solid nodules with solid component ≤ 5 mm

Variable		Interval growth group (n=54)	Immediate surgery group (n=71)	P-value
Operation name	Wedge resection	22 (40.7%)	18 (25.4%)	0.112
	Segmentectomy	7 (13.0%)	7 (9.9%)	
	Lobectomy	25 (46.3%)	46 (64.8%)	
Pathological size (mm)		11.8 ± 3.7	11.8 ± 5.1	0.930
Lymph nodes metastasis	No	45 (83.3%)	64 (90.1%)	0.259
	Not evaluate	9 (16.7%)	7 (9.9%)	
Pathologic stage (n=119)	Tis	20 (37.0%)	25 (38.5%)	0.285
	T1a	32 (59.3%)	33 (50.8%)	
	T1b	0 (0%)	4 (6.2%)	
	T2a	2 (3.7%)	3 (4.6%)	
Pathology	Pre-invasive lesion	20 (37.0%)	31 (43.7%)	0.232
	MIA	9 (16.7%)	5 (7.0%)	
	Invasive adenocarcinoma	25 (46.3%)	35 (49.3%)	

Pre-invasive lesion including atypical adenomatous hyperplasia and adenocarcinoma in-situ

MIA: minimally invasive adenocarcinoma

Table 7. Profile of five cases which were equivocal in aspect of recurrence among 125 part-solid nodules with solid component ≤ 5 mm

	Sizes of part-solid nodule and solid portion on initial CT	Equivocal lesion	Comment
case 1	17.4 mm (3.7 mm)	Lung nodule	Patient had second primary cancer (cholangiocarcinoma)
case 2	28.6 mm (4.5 mm)	Pleural lesion	Patient had adjuvant chemotreatment
case 3	7.5 mm (2.0 mm)	Lung nodule	1. Patient had previous cancer history (lung adenocarcinoma) 2. Equivocal lesion: recurrence versus another primary cancer
case 4	18.5 mm (4.6 mm)	Lung nodule	Equivocal lesion: recurrence versus another primary cancer
case 5	17.1 mm (1.7 mm)	Lung nodule	Equivocal lesion: Second primary cancer (Adenocarcinoma) versus local recurrences

Figure 1. Flowchart showing how study population was selected and its retrospective manner. Numbers in parentheses are the numbers of the part-solid nodules with solid component ≤ 5 mm.

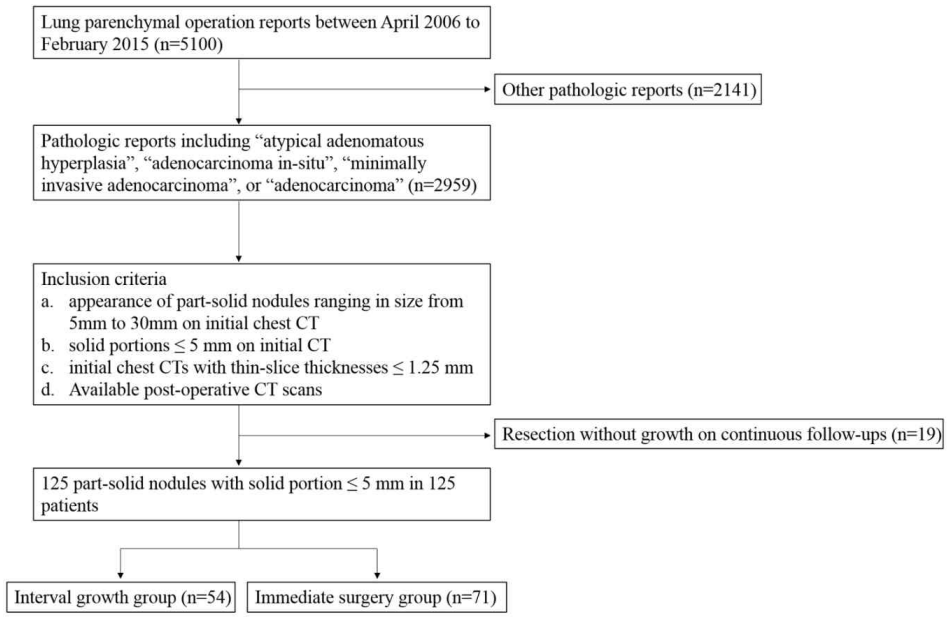
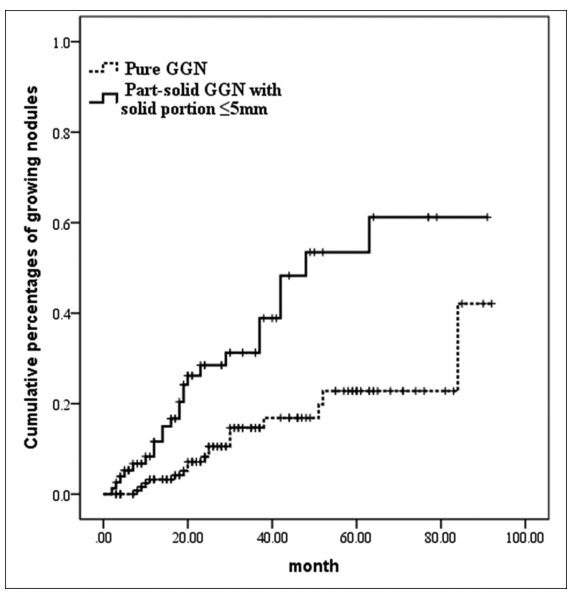
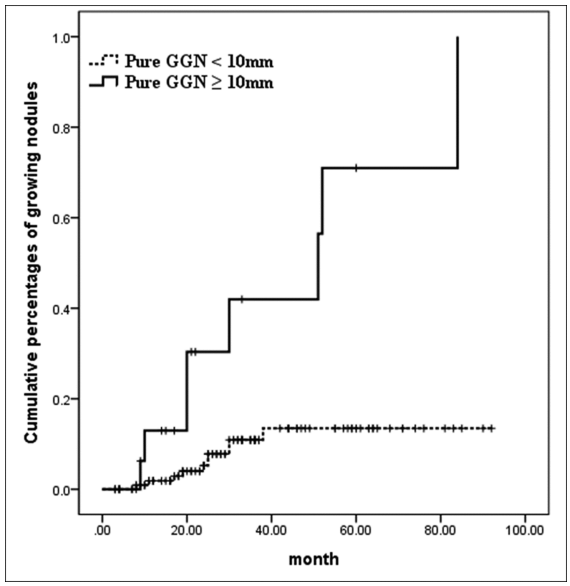


Figure 2. Kaplan-Meier plot for time to nodule growth according to nodule type in the SSNs (a), nodule diameter in pure GGN group (b) and nodule diameter of part-solid GGN group (c). (a) Part-solid GGNs show significantly higher cumulative percentages of growth than pure GGNs. (b) In subgroup analysis, pure GGNs ≥ 10 mm show significantly higher cumulative percentages of growth than pure GGNs < 10 mm. (c) Part-solid GGNs with solid portions ≤ 5 mm were best subcategorized with the cut-off diameter value of 8 mm in terms of cumulative percentages of growing nodules, and those ≥ 8 mm show significantly more frequent growth over follow-ups than those < 8mm.

(a)



(b)


Pure GGN < 10mm
Pure GGN ≥ 10mm
Cumulative percentages of growing nodules
1.0
0.8
0.6
0.4
0.2
0.0
.00
20.00
40.00
60.00
80.00
100.00
month

(c)

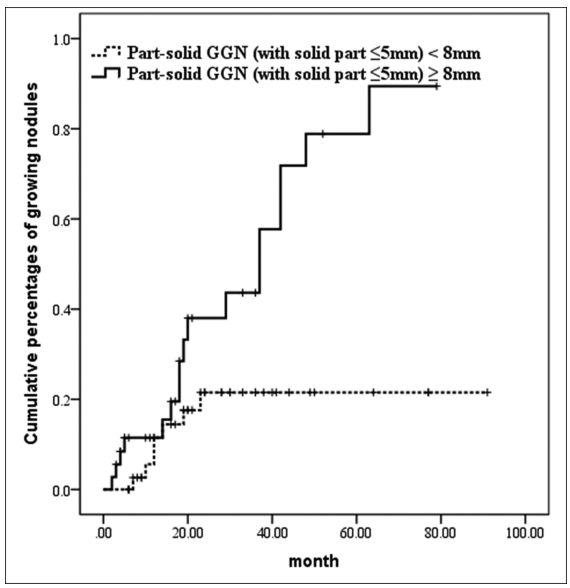
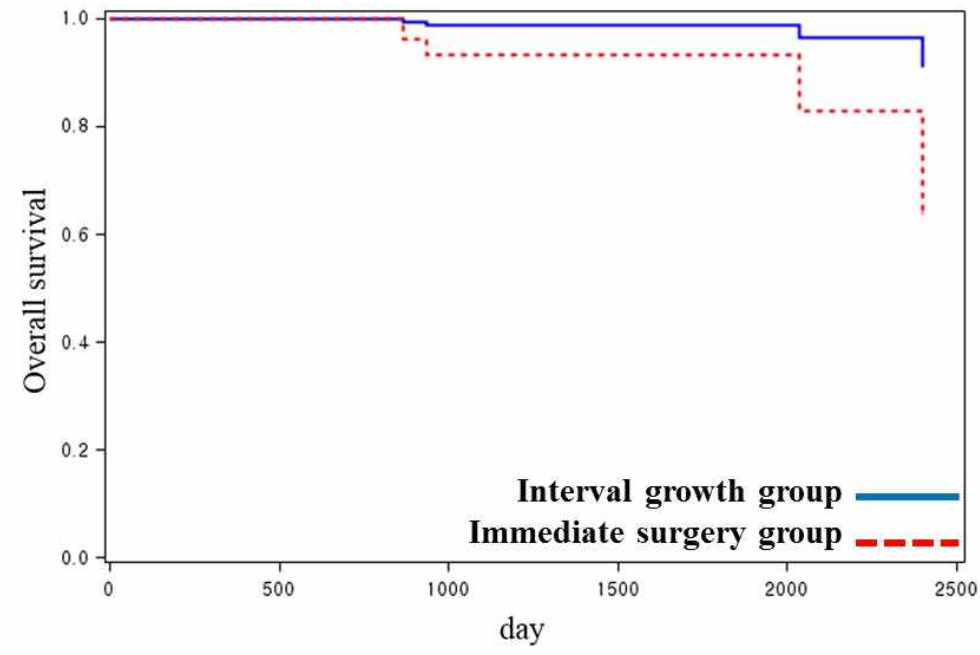

Part-solid GGN (with solid part ≤5mm) < 8mm
Part-solid GGN (with solid part ≤5mm) ≥ 8mm
Cumulative percentages of growing nodules
1.0
0.8
0.6
0.4
0.2
0.0
.00
20.00
40.00
60.00
80.00
100.00
month

Figure 3. Plots for time to overall survival after surgical resection of persistent part-solid nodule with solid component ≤ 5 mm. No significant difference is noted in the respect overall survival (*p=0.185*) between interval growth group and immediate surgery group.



요약 (국문초록)

5mm 이하의 고형 성분을 가지는 지속적인 폐 아고형 결절: 자연경과와 관리

이종혁

임상의과학과

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목적 : 이 연구의 목적은 고형 성분이 5mm 이하인 폐 아고형 결절의 자연경과 확인과, 5mm 이하의 고형 성분을 지니는 부분 고형 결절에 대하여 성장을 보일 때까지 기다린 후 수술적 치료를 하는 것이 환자의 예후에 나쁜 영향을 미치는지 확인하는 것이다.

방법 : 2005년부터 2013년까지 213명의 환자에게서 얻은 5mm 이하의 고형 성분을 지니는 아고형 결절들을 대상으로 그 자연경과를 확인하고자 하며, 이와는 별개로, 125명의 환자에게서 얻은 125개의 부분 고형 결절을 대상으로 성장을 보일 때까지 기다린 후 수술하는 것이 예후에 어떤 영향을 미치는지 알아보고자 한다. 이는 Kaplan-Meier, Cox proportional hazard regression, 그리고 Cox-regression analysis를 이용하여 증명하고자 한다.

결과 : 213개의 폐 아고형 결절 중, 136개는 간유리음영 결절 (성장:

18개; 비성장: 118개)이었고, 77개는 5mm이하의 고형 성분을 가지는 부분 고형 결절 (성장: 24개; 비성장: 53개)이었다. 전체 환자군에서는 폐암의 병력 ($p=0.001$), 고형 성분의 여부 ($p<0.001$), 결절 크기 ($p<0.001$)가 성장을 예측하는 유의한 인자로 밝혀졌다. 결절의 크기는 간유리음영 결절 ($p<0.001$)과 부분 고형 결절 ($p=0.037$)들을 나눈 추가 연구에서도 유의한 성장인자로 판명되었고, 폐암의 병력은 부분 고형 결절에서만 또 다른 유의한 인자로 판명되었다 ($p=0.002$). 10mm 이상의 간유리음영 결절들과 8mm 이상의 부분 고형 결절들은 10mm 미만의 간유리음영 결절들과 8mm 미만의 부분 고형 결절에 비해 유의하게 높은 성장 빈도를 보였다.

예후 관련 연구에 있어서 5mm 미만의 고형 성분을 가지는 125개의 부분 고형 결절 중에 5개의 재발이 의심되는 증례가 있었으나, 이를 실제 재발이라고 하더라도 부분 고형 결절이 성장을 보인 후 수술적 절제를 하는 것이 바로 절제를 하는 것에 비해 무재발 생존 ($p=0.485$)과 최종 생존율 ($p=0.185$)에 있어서 의미 있는 차이를 보이지 않았다.

결론 : 5mm 이하의 고형 성분을 가지는 폐 아고형 결절의 자연경과는 고형 성분의 여부, 결절의 크기에 따라 의미 있게 달랐으며, 이를 이용하여 추적검사의 방향을 나눌 수 있을 것으로 기대한다. 또한 5mm 이하의 고형 성분을 가지는 부분 고형 결절의 경우, 성장을 보인 후 수술적 절제를 하더라도 환자의 예후에는 나쁜 영향을 끼치지 않는 것을 확인하였다.

주요어: 간유리음영 결절, 폐선암, 최소침습 폐선암, 전산화 단층촬영, 추적관찰, 재발, 사망

학번: 2015-22255