Low-dose CT screening of persistent subsolid lung nodules: first-order features in radiomics

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Abstract:
Background: Non-disappearing subsolid nodules requiring follow-up are often detected during lung cancer screening, but changes in their invasiveness can be overlooked owing to slow growth. We aimed to develop a method for automatic identification of invasive tumors among subsolid nodules during multiple health check-ups using radiomics technology based on low-dose computed tomography (LD-CT) and examine its effectiveness.

Methods: We examined patients who underwent LD-CT screening from 2014 to 2019 and had lung adenocarcinomas resected after 5-year follow-ups. They were categorized into the invasive or less-invasive group; the annual growth/change rate (Δ) of the nodule voxel histogram using three-dimensional computed tomography (e.g., tumor volume, solid volume percentage, mean computed tomography value, variance, kurtosis, skewness, and entropy) was assessed. A discriminant model was designed through multivariate regression analysis with internal validation to compare its efficacy with that of a volume doubling time of <400 days.

Results: The study included 47 tumors (23 invasive, 24 less invasive), with no significant difference in the initial tumor volumes. Δskewness was identified as an independent predictor of invasiveness (adjusted odds ratio, 0.021; p=0.043), and when combined with Δvariance, it yielded high accuracy in detecting invasive lesions (88% true-positive, 80% false-positive). The detection model indicated surgery 2 years earlier than the volume doubling time, maintaining accuracy (median 3 years vs. 1 year before actual surgery, p=0.011).

Conclusion: LD-CT radiomics showed promising potential in ensuring timely detection and monitoring of subsolid nodules that warrant follow-up over time.

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Contributors’ Statement: Data collection: N. Yoshiyasu, D. Yamada; design of the study: N. Yoshiyasu, F. Kojima, T. Bando; statistical analysis: N. Yoshiyasu, K. Hayashi; analysis and interpretation of the data: N. Yoshiyasu, K. Hayashi, D. Yamada, F. Kojima, T. Bando; drafting the manuscript: N. Yoshiyasu, K. Hayashi, F. Kojima, T. Bando; critical revision of the manuscript: N. Yoshiyasu, D. Yamada, K. Hayashi, F. Kojima, T. Bando.

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ABSTRACT

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**Keywords:** Lung cancer treatment (surgery, medical); Lung cancer, diagnosis (includes staging, imaging, fiducials); Minimally invasive surgery (includes port access, minithoracotomy)

**INTRODUCTION**

Early-stage lung cancer is commonly detected during lung cancer screening using low-dose computed tomography (LD-CT). Nevertheless, lung cancer remains the leading cause of death due to cancer worldwide [1]. Regarding lung cancer screening in the USA, the Lung Imaging Reporting and Data System (Lung-RADS) categories of tumor size and volume and the size of the solid component are widely implemented for management decisions [2]. Furthermore, LD-CT is commonly used in Europe for assessing tumor volume [3]. Despite standardizations for management decisions based on tumor size and volume [2,3], slow-growing tumors, which tend to be overlooked during screening, become more invasive than expected. For patients with a positive result on screening with LD-CT, high-resolution CT and/or transbronchial lung biopsies are generally performed. Additionally, close investigation by surgery is performed in cases with small-sized subsolid nodules in the periphery of the lungs. However, non-specialists may struggle in providing referral to a thoracic surgeon with the recommended screening methods for slow-growing tumors [2,4]. In contrast, our
previously reported radiologic technology possesses the potential to screen for changes in the invasiveness of lung adenocarcinomas and automatically notify in cases of increased need for surgery [5]. Thus, in this exploratory study, we focused on slow-growing tumors. Additionally, unlike previous studies, we thought that our method could be applied to LD-CT, which is used in screening, rather than to thin-slice CT [5, 6, 7]. Using radiomics based on the voxel histogram of serial LD-CT, we aimed to develop a novel method that identifies tumors with increasing invasiveness that require surgery among subsolid nodules during health check-ups. Additionally, we examined the effectiveness of this technique, compared with that of the volume doubling time (VDT) < 400 days, which is commonly used for predicting the presence of a malignant tumor.

PATIENTS AND METHODS

Patients’ medical records were retrospectively reviewed under a waiver of authorization and consent. This single-center observational study was approved by the Institutional Review Board (approval no. 19-R026; issued April 9, 2020) and conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Patient inclusion

A total of 201,275 patients underwent periodic health examinations between January 2014 and 2019. After 51,136 patients were examined using chest CT, 309 were suspected of having malignancies and were referred to the outpatient clinic for close surgical investigation; 115 surgeries were performed for nodules suspected to be
malignant. We excluded patients with (i) no available data on annual LD-CT in the last 5 years (n=53) to minimize measurement bias and (ii) a pathological diagnosis, except for lung adenocarcinoma (n=15). Finally, 47 patients (47 × 6 = 282 subsolid nodules) were enrolled (Figure 1). Only one subsolid nodule was detected in each patient.

LD-CT image acquisition

LD-CT was performed using a 64-detector row scanner (Aquilion ONE, Toshiba Medical Systems, Tokyo, Japan; Revolution and Optima 660, GE Healthcare Japan, Tokyo, Japan) using the following standard parameters: 120 kV, automatically set for amplification, and bone reconstruction algorithm. A 2.5-mm slice thickness was acquired for all the images using standard reconstruction kernels with lung window settings (window level, −500 Hounsfield units [HU]; window width, 1500 HU). The acquired images were evaluated by expert radiologists (DY with 5 years of experience, MM and YK with >20 years of experience each).

Assessment of the followed-up nodules at multiple medical checks

The data of 282 pulmonary lesions (47 nodules per year) detected on LD-CT were extracted semi-automatically. The volume of interest (VOI) was estimated using a three-dimensional image analysis software (SYNAPSE VINCENT; Fujifilm Medical, Tokyo, Japan). This was equivalent to the overall tumor volume determined using voxels (mm³) and CT values (HU). We set the ratio of the solid component (within −300 HU) expressed as the volume percentage (% solid), and the area of ground-glass opacity (ranging from −1000 HU to −300 HU) had a border of −300 HU (Figure 2). Subsequently, a voxel-based histogram analysis (VHA) was conducted for the VOI by
calculating the following five parameters, as previously described [5]: mean CT value, variance, skewness, kurtosis, and entropy. Variance, skewness, and kurtosis represent the deviation of each data point from the mean CT value in the second, third, and fourth orders, respectively. In contrast, entropy indicates irregularity or impurity. We focused on the changes in the tumor from initial detection until the most recent check-up after 5 years.

Therefore, the growth or change rate ($\Delta$) of seven radiological parameters ($X$) based on VHA was calculated and evaluated using the following formula:

$$\Delta X \text{ per year} = \frac{\text{value at the time of surgery}}{- \text{mean value for four years from the initial detection to one year prior to surgery (mean of five times)}}$$

$X =$ tumor volume ($\text{cm}^3$), solid volume percentage (% solid, %), mean CT value (HU), variance ($\times 10^4$), kurtosis, skewness, or entropy.

**Clinicopathological findings**

The 8th edition of the Tumor, Node, Metastasis staging system was applied in this study [6]. According to the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society classification of lung adenocarcinoma, 47 resected specimens were classified into the following two groups: the less-invasive (adenocarcinoma in situ [AIS] and minimally invasive adenocarcinoma [MIA]) and invasive (invasive adenocarcinoma [IA]) groups [8]. The measurements of the tumor dimensions (maximum and solid sizes in diameter) for all the 282 lesions performed by expert radiologists were applied as references for assessing the clinical T factors. The consolidation-to-tumor ratio was also determined based on the findings.
VDT

VDT calculation was performed using the equation based on the modified Schwartz formula [7]:

\[ VDT = \left(\frac{\ln 2 \times \Delta T}{\ln (V2/V1)}\right) \]

where,

- \( V1 \) and \( V2 \) are the initial and subsequent nodule volumes, respectively, detected annually during the follow-ups,
- \( \Delta T \) represents the time (in days) between two scans, and \( \ln \) is the natural logarithm. We defined lung nodules with \( VDT < 400 \) days as IAs in this study.

Statistical analyses

We calculated descriptive statistics for patient characteristics and continuous data in terms of \( \Delta \) of the seven radiological parameters. Categorical variables are summarized as numbers and proportions and continuous variables as medians and interquartile ranges (IQR). To compare each continuous variable between the less-invasive and invasive groups, we performed a univariate analysis based on the Mann–Whitney U test. All the data were analyzed using two-sided hypothesis tests. Statistical significance was set at \( p < 0.05 \). To provide a visual analysis of how each parameter changed over time, we plotted all the patient data per year for each parameter and applied locally weighted scatterplot smoothing (LOWESS) to capture the features of the changing trends. We proposed a new approach in terms of the prediction of increasing invasiveness based on \( \Delta \). Therefore, to validate the results derived from our new method, we performed a visualization analysis using LOWESS.
We also performed multiple logistic regression analysis (adjusted) and identified the essential factors needed to detect the invasive group by exploring the differences (Δ) in each of the seven variables between the two groups. We performed stepwise variable selection for the logistic regression model based on the seven variables. Finally, we estimated the most sophisticated logistic regression model after variable selection.

Using the final logistic regression model, we calculated the area under the receiver operating characteristic curve (AUC) to determine the threshold score. A decision tree of the classification and regression tree (CART) model was constructed to predict the IAs and estimate the cut-off values of the critical variables. To conduct the CART analysis, we used the Gini index criterion and set the tuning parameter for the decision-tree complexity to 0.01.

For IAs screened for 5 years until resection among 47 nodules, the model was compared with those of VDT < 400 days in terms of its precision and effectiveness of its timely detection [9]. McNemar’s test was used for the assessment of precision; the Wilcoxon signed rank sum test was used for the evaluation of the terms (year). All statistical analyses were conducted using R software (version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographic characteristics of patients

Forty-seven consecutive patients were reviewed (one pulmonary lesion per patient). Following the medical check-up, the patients were referred for possible malignancy and surgery with diagnostic and curative intent. The possibility of lung cancer was unknown.
5 years before surgery. The median age of the patients was 68 years (IQR: 64–73.5), with a standard body type. The male to female ratio was approximately 1:1 (23 males, 48.9%). A few patients were diagnosed with comorbidities such as chronic obstructive pulmonary disease (n=2, 4.2%) and interstitial pneumonia (n=1, 2.1%). Approximately 43% (n=20/47) of patients were smokers.

**Clinicopathological diagnoses for subsolid nodules**

Table 1 shows the clinicopathological features of resected subsolid nodules. All 47 pulmonary lesions were excised using thoracoscopy, with sufficient margins measuring >2 cm. The subsolid nodules displayed slow growth over the long term; therefore, the majority of patients underwent sublobar resections (n=36/47, 76.6%). During surgery, no significant difference was observed in the maximum tumor size between the less-invasive (12.7 [IQR: 9.0–15.0] mm) and invasive (13.0 mm [IQR: 9.2–16.2] mm; p=0.549) groups. All the lesions corresponded to lung adenocarcinomas at clinical stages 0 and IA. Pathological diagnoses displayed stages N0, M0, 0, and IA in all the cases. Among the 47 resected nodules, 14 (29.8%) were classified as AIS, and 10 (21.3%) were classified as MIA. The remaining 23 (48.9%) resected nodules were classified as IAs.

**Radiological features based on voxel histogram analyses**

A typical histogram transition for a subsolid nodule located in the right lower lobe is shown in Figure 2. The gray scales on the CT images represent tumor conversion to radiological information on voxel histograms based on three-dimensional images. Upon applying the methodology of a previous study [5], 282 lesions were assessed under
seven radiological parameters and followed up for 5 years; these were calculated and are illustrated in Figure 3. The median values of the initial maximum diameter and tumor volume were 5.8 (IQR: 4.0–9.1) mm and 130 (IQR: 81.5–256.8) mm$^3$ in the less-invasive group and 4.2 (IQR: 3.2–8.2) mm and 106 (IQR: 59.1–211.5) mm$^3$ in the invasive group, respectively. No significant differences were observed in the maximum tumor size (p=0.139) and volume (p=0.489) at the initial screening. The growth rate of 45 lung tumors < 523 mm$^3$ (i.e., 10 mm in diameter according to the classification of the Lung-RADS score) at the initial screening is shown in Figure 4. No association was observed between initial volume and growth rate. Furthermore, Table 2 summarizes the variations in the parameters between the less-invasive and invasive groups. All the radiological factors, except tumor volume and mean CT value, showed significant differences between the two groups.

Detection model for IAs that appear as subsolid nodules during long-term follow-up

The factors related to the detection of malignant transformation during multiple screenings using univariate and multivariate analyses are summarized in Table 3. The change in skewness was the most critical independent screening parameter for IAs, following adjustment for confounders. No multicollinearity was observed among the seven factors. In the multivariate analysis, $\Delta$skewness (odds ratio [OR]: 0.096, 95% confidence interval [CI]: 0.020–0.450; p=0.003) and $\Delta$variance (OR: 1.630, 95% CI: 1.030–2.58; p=0.037) remained significant detectable factors in the invasive group. The AUC was 0.84 (95% CI: 0.721–0.960), indicating a sensitivity of 73.9%, a specificity of 87.5%, and an accuracy of 80.9%. Upon utilizing a CART model to construct a decision
tree, the variation in asymmetry was detected to constitute the first step to screen out, followed by variance. The cut-off values for Δskewness and Δvariation per year were −0.21 and 1.09, respectively. If a subsolid nodule measured −0.21 or less for Δskewness and less than 1.09 for Δvariance per year, the tumor was positively associated with increased invasiveness during extended follow-ups.

Comparison of the original detection model with the VDT
To compare with the original model by Δskewness and Δvariance per year, we retrospectively evaluated yearly changes to see whether the 23 IAs had VDT < 400 days in 5 years until resection. Our model yielded an improved result in terms of accuracy, although a significant difference was not seen (VDT; 17/23 among IAs vs. Δskewness and Δvariance; 20/23 among IAs; p=0.238). Regarding the assumed timing for close investigation prior to actual surgery, our model could suggest a significantly earlier time by 2 years compared with VDT < 400 days (median 3 years vs. median 1 year, p=0.011).

DISCUSSION
In this exploratory study on subsolid nodules of early-stage lung adenocarcinomas, we proposed a novel method for detecting invasive lesions that should be closely investigated by surgery during long-term follow-up. VHA was performed for serial LD-CT images of pathological lung adenocarcinomas. Consequently, the variation in skewness over time was more significant for subsolid nodules than for radiological factors such as volume or solid percentage. Thus, our proposed method has the potential
to better clarify changes in invasiveness.

Although the growth process of early-stage lung adenocarcinoma is not fully elucidated, tumor size and solid components are known to increase with growth from atypical adenomatous hyperplasia to IAs [8]. To date, the management of lesions detected by lung cancer screening has been recommended based on tumor size and volume and the size of the solid component, as per the Lung-RADS and National Comprehensive Cancer Network guidelines [2,4]. However, we occasionally observed lesions with uniformly increased internal density suspected of having increased invasiveness without changes in the tumor size or solid components on LD-CT. Therefore, we hypothesized that radiological factors besides tumor size and solid components are necessary to assess invasiveness during the follow-up of subsolid nodules. We decided to focus on subsolid nodules over time to enable a comprehensive analysis of various radiological features.

The study population included 47 patients who were followed-up for 5 years. Despite the limited number of patients, these findings allowed us to understand the growth of lung adenocarcinomas manifesting as subsolid nodules. In our health screening facility, the detection rate of nodules on LD-CT was 0.6% (n=309/51,136). Of the 309 patients/nodules, 115 underwent surgery. Nearly all pathological diagnoses were lung adenocarcinomas (87%; n=100/115), and approximately half (41 subsolid nodules and 12 solid nodules) were resected after 1 year of follow-up. Traditionally, a few slow-growing tumors have required long-term follow-up through radiographic screening. However, slow-growing tumors are frequently detected during health check-ups with LD-CT, and physicians at annual health check-ups find it difficult to determine when to consult surgeons regarding subsolid nodules. Our new method provides the first step
toward resolving this issue.

Recently, there has been growing interest in radiomics studies. Substantial volumes of medical imaging data have been comprehensively analyzed, and the relationship between medical imaging data and clinical information has been investigated [10-12]. In lung cancer research, radiomics has been utilized for diagnosis and the prediction of prognosis and response to treatment [13,14]. Previously, we reported radiomics based on VHA using a single thin-slice CT scan taken before surgery for lung adenocarcinoma, which could accurately assess malignancy [5]. Among the seven radiological factors in this study, those that assessed the level of invasiveness, in ascending order, were tumor volume, % solid, skewness, and entropy. Subtle differences in images invisible to the naked eye were clarified in a previous study [5]. Other investigators have also demonstrated the usefulness of VHA for lung lesions [6,7,15,16]. In this study, we implemented the methodology of our previous study to investigate the differences between less-invasive and invasive lung adenocarcinomas manifesting as subsolid nodules. The seven factors utilized in our previous study were followed up over time to assess subsolid nodules with slow growth. These were detected during annual check-ups by using serial LD-CT. Changes in the tumor volume and solid components (% solid) were not sufficient to evaluate the change in invasiveness among subsolid nodules; however, upon focusing on skewness in the voxel histogram, changes in invasiveness became clearer. Interestingly, Δskewness was found to be an independent factor in the present study. Similarly, in our previous study using thin-slice CT, skewness itself was also one of the independent factors [5]. Thus, skewness (or Δskewness) will be considered a particularly important factor for detecting invasiveness at either one-time or annual checkups. In particular, skewness declined gradually in the
invasive group but increased in the less-invasive group. Such a decrease in skewness may imply a shift to the right in the histogram; that is, the decrease in skewness reflects an increase in internal density, displaying invasiveness in subsolid nodules and a slight change in tumor volume.

VDT has been an established method for predicting malignant lesions in tumors since a long time [9]. A period of 400 days is regarded as the cut-off value; a shorter duration is more likely indicative of malignancy [17,18]. However, VDT was 939 days for less-invasive adenocarcinomas and 678 for IAs [19]. In this study, the derived optimal model based on VHA was compared with the actual VDT < 400 days. Moreover, our model was able to identify invasive lesions requiring surgical examination in a timely and accurate manner. This result demonstrated that VDT only assessed the volume.

Thus, for subsolid nodules with slow growth that do not meet the criteria for changes in tumor size or volume or in the size of the solid component during an annual check-up with LD-CT, the newly proposed evaluation focusing on skewness and VHA would prevent overlooking invasiveness and allow a timely referral for close investigation by surgery. Conversely, watchful waiting without surgery may be recommended for suspected lesions in patients with less-IAs diagnosed using this method.

There are certain limitations in our study. First, this was a retrospective, single-center, exploratory study. To validate the results of this study, a validation set with a different patient cohort would be necessary. Second, a limited number of tumors were included because lesions displaying significant changes within a few years were excluded to minimize the measurement bias. However, owing to the rarity of slow-
Growing adenocarcinomas resected after 5 years of follow-up, the data obtained were of considerable importance. Third, the study object was exclusively pathological lung adenocarcinoma. In lung cancer screening with LD-CT, the utility of the study method in differentiating between benign and malignant lesions needs to be assessed. Efforts should be made to reduce the number of false positives for benign lesions during screening, and our method with serial LD-CT may result in more accurate evaluation; however, this was beyond the scope of this study. Finally, artificial intelligence or deep learning approaches were not adopted because these algorithms are generally considered black boxes that make it difficult to determine the essential radiological factors.

In conclusion, in lung cancer screening with LD-CT, close investigation by surgery can be recommended for subsolid nodules followed up over time with the application of radiomics, particularly focusing on skewness.

Contributions
Data collection: N. Yoshiyasu, D. Yamada; design of the study: N. Yoshiyasu, F. Kojima, T. Bando; statistical analysis: N. Yoshiyasu, K. Hayashi; analysis and interpretation of the data: N. Yoshiyasu, K. Hayashi, D. Yamada, F. Kojima, T. Bando; drafting the manuscript: N. Yoshiyasu, K. Hayashi, F. Kojima, T. Bando; critical revision of the manuscript: N. Yoshiyasu, D. Yamada, K. Hayashi, F. Kojima, T. Bando.

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Conflicts of Interest
None declared.
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A part of this manuscript can be found on a community-recognized preprint server, Research Square: https://www.researchsquare.com/article/rs-2322616/v1

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Figure 1. Cohort selection diagram.

Abbreviation: CT, computed tomography

Figure 2. (A) Tumor segmentation and voxel histogram using a three-dimensional CT image at a follow-up visit. After the volume of interest is semi-automatically settled for a subsolid nodule, a histogram is semi-automatically created. In the histogram, black voxels (−1000 to −300 HU) represent the area of ground-glass opacity, whereas red voxels (within the −300 HU border) represent that of the solid component. The subsolid nodule had 2.7% solid components (% solid) of the entire tumor volume. (B) A typical
histogram transition for a subsolid nodule based on LD-CT. The change in the solid component is more subtly visible on the axial CT image than in the red area on the histogram. Pathological diagnosis for the nodule reveals an invasive adenocarcinoma; the histogram correspondingly displays increased invasiveness.

Abbreviations: CT, computed tomography; HU, Hounsfield units; LD-CT, low-dose computed tomography.

**Figure 3.** Annual LD-CT imaging variations between the less-invasive and invasive adenocarcinomas followed up for 5 years.

The representative parameters of the radiomics technology include (A) tumor volume (cm$^3$), (B) mean CT value (HU), (C) % solid, (D) kurtosis, (E) skewness, (F) variance, and (G) entropy. The shaded areas represent the 95% confidence intervals.

Abbreviations: CT, computed tomography; HU, Hounsfield units; LD-CT, low-dose computed tomography.
Table 1. Demographics of resected subsolid nodules

<table>
<thead>
<tr>
<th>Clinicopathological and operative data (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Localization of tumors</strong></td>
</tr>
<tr>
<td>Right/left</td>
</tr>
<tr>
<td>29/18 (61.7/31.3%)</td>
</tr>
<tr>
<td>Upper/middle/lower</td>
</tr>
<tr>
<td>24/4/19 (51.1/8.5/40.4%)</td>
</tr>
<tr>
<td><strong>Diameter of tumors on preoperative CT</strong></td>
</tr>
<tr>
<td>Maximum size, mm</td>
</tr>
<tr>
<td>13.7 (9.0–16.1)</td>
</tr>
<tr>
<td>Solid size, mm</td>
</tr>
<tr>
<td>6.4 (0.0–8.9)</td>
</tr>
<tr>
<td><strong>Consolidation-to-tumor ratio</strong></td>
</tr>
<tr>
<td>0.3 (0.0–0.8)</td>
</tr>
<tr>
<td><strong>Clinical T factor (N0M0)</strong></td>
</tr>
<tr>
<td>Tis/T1mi</td>
</tr>
<tr>
<td>19/8 (40.4/17.0%)</td>
</tr>
<tr>
<td>T1a/T1b/T1c</td>
</tr>
<tr>
<td>11/6/3 (23.4/12.8/6.4%)</td>
</tr>
<tr>
<td><strong>Pathological T factor (N0M0)</strong></td>
</tr>
<tr>
<td>Tis/T1mi</td>
</tr>
<tr>
<td>14/10 (29.8/21.3%)</td>
</tr>
<tr>
<td>T1a/T1b/T1c</td>
</tr>
<tr>
<td>16/5/2 (34.0/10.6/4.3%)</td>
</tr>
<tr>
<td><strong>Histological type</strong></td>
</tr>
<tr>
<td>AIS</td>
</tr>
<tr>
<td>14 (29.8%)</td>
</tr>
<tr>
<td>MIA</td>
</tr>
<tr>
<td>10 (21.3%)</td>
</tr>
<tr>
<td>Lepidic-predominant</td>
</tr>
<tr>
<td>3 (6.4%)</td>
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<tr>
<td>Acinar-predominant</td>
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<tr>
<td>3 (6.4%)</td>
</tr>
<tr>
<td>Papillary-predominant</td>
</tr>
<tr>
<td>15 (31.9%)</td>
</tr>
<tr>
<td>Others (solid or invasive mucinous)</td>
</tr>
<tr>
<td>-------------------------------------</td>
</tr>
<tr>
<td><strong>Surgical procedures</strong></td>
</tr>
<tr>
<td>Wedge resection</td>
</tr>
<tr>
<td>Segmentectomy</td>
</tr>
<tr>
<td>Lobectomy</td>
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</tbody>
</table>

Abbreviations: AIS, adenocarcinoma in situ; CT, computed tomography; MIA, minimally invasive adenocarcinoma

Data are reported as the median (interquartile range) or count (percentage).
Table 2. Elements of radiomics for identifying invasive tumors among subsolid nodules

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Univariate logistic regression model</th>
<th>Multivariate logistic regression model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Crude)</td>
<td>(Adjusted)</td>
</tr>
<tr>
<td></td>
<td>(After variable selection)</td>
<td></td>
</tr>
<tr>
<td>Δ tumor volume,</td>
<td>1.360 (0.750–2.460) 0.312 0.877 (0.402–1.910) 0.742</td>
<td></td>
</tr>
<tr>
<td>cm³ per year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ % solid, % per</td>
<td>1.130 (1.030–1.250) 0.011 1.040 (0.814–1.340) 0.737</td>
<td></td>
</tr>
<tr>
<td>year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ mean CT value,</td>
<td>1.010 (0.999–1.010) 0.076 0.998 (0.978–1.020) 0.819</td>
<td></td>
</tr>
<tr>
<td>HU per year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ variance, ×10⁴</td>
<td>1.530 (1.050–2.230) 0.026 1.440 (0.647–3.200) 0.372 1.630 (1.030–2.580) 0.037</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SE)</td>
<td>Lower CI</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------</td>
<td>----------</td>
</tr>
<tr>
<td>Δ kurtosis, per year</td>
<td>0.544 (0.028)</td>
<td>(0.317–0.936)</td>
</tr>
<tr>
<td>Δ skewness, per year</td>
<td>0.107 (0.002)</td>
<td>(0.026–0.445)</td>
</tr>
<tr>
<td>Δ entropy, per year</td>
<td>4.190 (0.025)</td>
<td>(1.190–14.700)</td>
</tr>
</tbody>
</table>
All Cancer Screenings by Low-dose Chest CT from 2014-2019  
\[ n = 51,136 \]

Consultations for Close Investigation by Surgery  
\[ n = 309 \]

Excluded:
- Patients who did not undergo surgery \( (n = 194) \): Continued Observation or Skipped Checkup

Surgeries for Nodules Suspected of Cancer  
\[ n = 115 \]

Excluded:
- No Available Data of Six Times Serial CT for 5 Years \( (n = 53) \)
- Non-Pulmonary Adenocarcinoma \( (n = 15) \): They Included All Patients with Pure Solid Nodule \( (n = 12) \)

Patients with Subsolid Nodules Included in This Study  
\[ n = 47 \times 6 \text{ Times: Total } 282 \]