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Can computed tomography differentiate adenocarcinoma in situ from minimally invasive adenocarcinoma?

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Abstract

Background: Given the subtle pathological signs of adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA), effective differentiation between the two entities is crucial. However, it is difficult to predict these conditions using preoperative computed tomography (CT) imaging. In this study, we investigated whether histological diagnosis of AIS and MIA using quantitative three-dimensional CT imaging analysis could be predicted.

Methods: We retrospectively analyzed the images and histopathological findings of patients with lung cancer who were diagnosed with AIS or MIA between January 2017 and June 2018. We used Synapse Vincent (v. 4.3) (Fujifilm) software to analyze the CT attenuation values and performed a histogram analysis.

Results: There were 22 patients with AIS and 22 with MIA. The ground-glass nodule (GGN) rate was significantly higher in patients with AIS ($p < 0.001$), whereas the solid volume ($p < 0.001$) and solid rate ($p = 0.001$) were significantly higher in those with MIA. The mean ($p = 0.002$) and maximum ($p = 0.025$) CT values were significantly higher in patients with MIA. The 25th, 50th, 75th, and 97.5th percentiles (all $p < 0.05$) for the CT values were significantly higher in patients with MIA.

Conclusions: We demonstrated that quantitative analysis of 3D-CT imaging data using software can help distinguish AIS from MIA. These analyses are useful for guiding decision-making in the surgical management of early lung cancer, as well as subsequent follow-up.

KEYWORDS
adenocarcinoma in situ, computed tomography, minimally invasive adenocarcinoma

INTRODUCTION

It has previously been reported that adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) typically have a similar prognosis. Generally, tumors with solid components on computed tomography (CT) images are histologically diagnosed as AIS, whereas tumors with ground-glass opacities (GGOs) in most areas are histologically diagnosed as MIA. Nevertheless, it is difficult for pathologists to correctly differentiate between AIS and MIA using preoperative CT imaging (Figure 1) because the histopathological findings are very similar, although the histology of MIA is characterized by signs of invasiveness to interstitial tissue (for example, fibrotic changes, such as the appearance of collagen fibers and elastic fibers, and the invasion of cancer cells to the interstitial tissue ≤0.5 cm in any one focus). These subtle pathological changes indicate an important stage at the beginning of invasion and must therefore be carefully considered. Moreover, if pathological changes using CT imaging can be predicted then the appropriate treatments and follow-up plans for patients with pure or part-solid ground-glass nodules (GGNs) can be selected.

Li et al. reported that CT number histogram analysis can reflect nodule distribution and heterogeneity. The 95th,

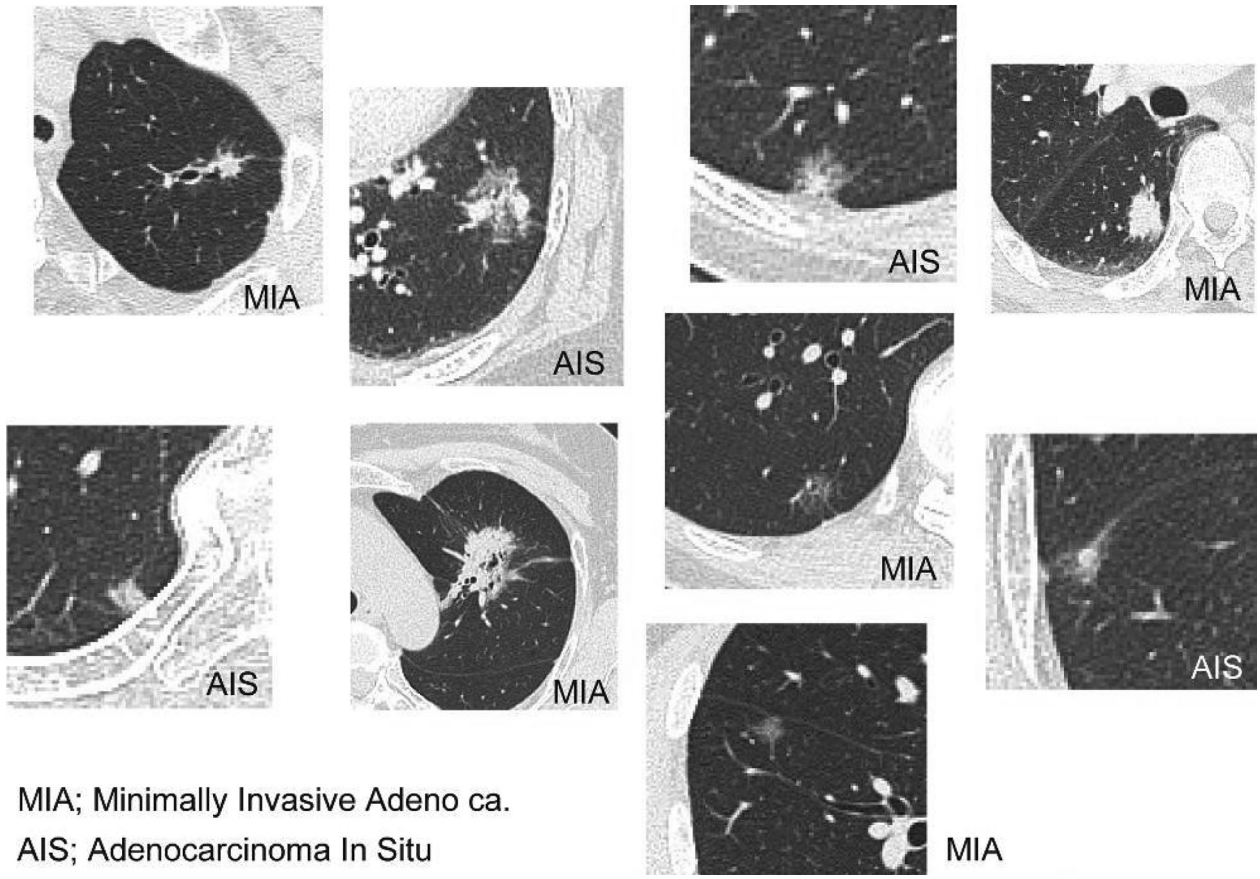


FIGURE 1 In clinical practice, we experience tumors with a histological diagnosis of adenocarcinoma in situ (AIS) but reveal solid components on computed tomography (CT) imaging and tumors with a histological diagnosis of minimally invasive adenocarcinoma (MIA) with ground-glass opacity (GGO) in most areas. Therefore, it is difficult to diagnose AIS and MIA using preoperative CT imaging

98th, and 100th percentiles and the second to 98th, 25th to 75th, and 0th to 100th slopes in preinvasive lesions were significantly different from those in MIA or invasive pulmonary adenocarcinoma (IPA). This is probably because the 95th, 98th, and 100th percentiles indicate the high CT attenuation zone within the tumor, differences in tumor cellularity and alveolar septum thickening, as well as the retained air space among preinvasive lesions. Thus, it may be possible to differentiate between MIA and invasive adenocarcinoma using this information. In contrast, no differences were found between MIA and IPA, likely because of increased central fibrosis and alveolar structural collapse.[1]

Similarly, several recent studies have reported the characteristics of invasive and noninvasive adenocarcinoma imaging patterns.[2–4] Nonetheless, there is insufficient evidence in the current literature about the differences in the rate of recurrence and prognosis between AIS and MIA.[5] Ito et al. suggested that MIA be included with AIS as tumor in situ because of the lack of recurrence in their series.[6] However, according to the International Association for the Study of Lung Cancer (IASLC), the current data are insufficient to make such a proposal. Staging is a method used to document the extent of tumor invasion or spread.[7,8] By definition, invasion has occurred in MIA but not in AIS; hence, these entities need to be staged differently and the implications of staging need to be considered carefully. Tumors with apparent signs of invasion require a carefully considered treatment plan. The ability to distinguish between AIS and MIA on preoperative CT images would enable the selection of an appropriate surgical method and follow-up plan.

There are limitations associated with a two-dimensional (2D)-CT diagnosis. In our experience, many pure GGNs (pGGNs), visually characterized by crystal-clear ground-glass opacity in almost the entire nodule area, are unexpectedly diagnosed as MIA. Thus, macroscopic diagnosis of pGGNs on 2D-CT images is equivocal and not reproducible. In addition, as discussed at a recent Japanese lung cancer conference, the measurement of maximum tumor diameter varies across radiologists because many tumors have an irregular surface and many solid components exist sporadically. Therefore, doctors may detect different slices and different maximum diameters. Diagnosis based on subjective evaluation of doctors does not show reproducibility.

Conversely, software can detect the fine differences in the CT values in pixels that humans cannot. Therefore, in this study, we used quantitative 3D-CT image analysis using Synapse Vincent (Fujifilm) software and investigated its utility for differentiating between AIS and MIA in patients with lung cancer.

In this study, we only focused on AIS and MIA tumors and not on atypical adenomatous hyperplasia and invasive adenocarcinoma tumors as we believe that the differences between AIS and MIA can contribute to treatment policy and follow-up management.

METHODS

Ethical considerations

This retrospective study was approved by the Institutional Review Board (IRB) of our hospital (approval No. 3385). It was a retrospective review of patient medical records from the Tokushima University Hospital. Written informed consent was obtained from the participants whose histological data are presented in this study. Information disclosure documents has been published on the home page of the Tokushima University Hospital's website for patients whose medical information alone was accessed, and the IRB specifically waived the requirement for informed consent from these patients. The aforementioned procedures regarding informed consent were in accordance with the Japanese government's guidelines and were approved by the Ethics Committee of Tokushima University Hospital. The IRB guidelines are equivalent to the guidelines of the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor, and Welfare in Japan.

Study population

We retrospectively reviewed the records of patients with lung cancer who were diagnosed with AIS or MIA from January 2017 to June 2018 at Tokushima University Hospital. This period was selected because the Japanese lung cancer conference revised the terms of the tumor-node-metastasis (TNM) classification from January 2017 (eighth edition). Patients with squamous cell, low-grade, large cell, small cell, adenosquamous, and pleomorphic carcinoma, large cell neuroendocrine carcinoma, and non-small cell lung cancer (NSCLC) were excluded. We included all patients which underwent surgery at this period. Therefore, there was no selection bias in this study (Table 1).

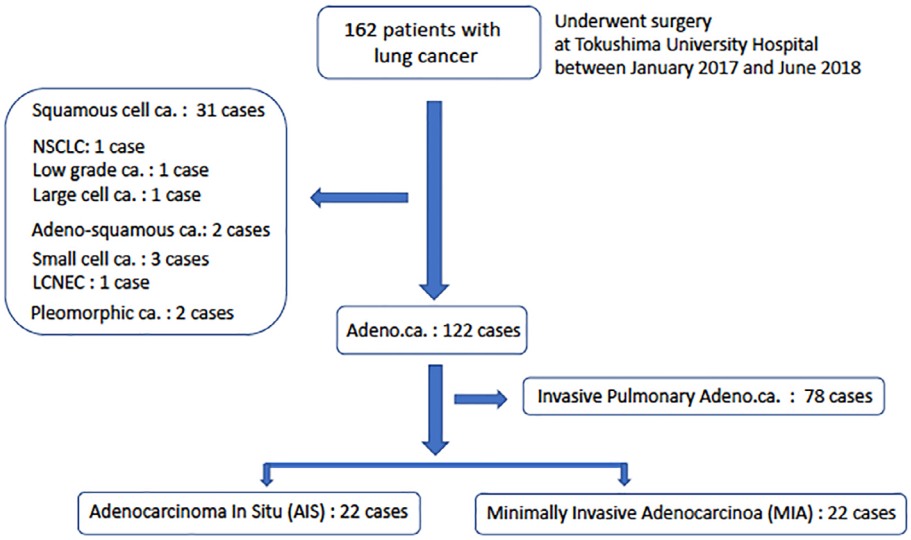
There were no patients who had AIS and invasive carcinoma, MIA and invasive carcinoma. The T1 classification was revised and MIA classification was well defined histologically from the eighth edition. We analyzed the CT images and reviewed the histological results of all patients. All patients had undergone lung surgery by different surgical methods (partial resection, segmentectomy, and lobectomy).

Moreover, we included all patients which underwent surgery at this period. Therefore, there was no selection bias in this study.

CT scanning and analysis

All CT scans were performed from the lung apex to the lung base using Aquillion One (320 line) (Toshiba) without enhancement. The dose of CT: All CT devices had auto exposure control and the standard deviation was eight. Slice thickness was 1 mm slice for all patients. The resolution was 512 × 512 pixels and the number of detectors was 80 lines. The definition of volume using the Vincent software was the volume of voxels on CT images. The mean CT was defined as the mean CT value of all slices. All CT images were analyzed using Synapse Vincent (v. 4.3) (Fujifilm) software which was set to recognize the attenuation areas between −300

TABLE 1 CONSORT diagram



Hounsfield units (HU) and −800 HU as GGN areas using the automatic recognition option. The Vincent software was also used to calculate GGN volume, GGN rate (GGN area [m]/total tumor volume [ml] × 100 [%]), solid volume (ml) (area with CT values less than −300 Hounsfield units [HU]), solid rate (solid area [ml]/total tumor volume [ml] × 100 [%]).

TABLE 2 Quantitative analysis of AIS and MIA

Variable	AIS (n = 22)	MIA (n = 22)
Age (years)	69.3 ± 8.7	66.2 ± 10.2
Histological tumor size (mm)	12.9 ± 4.4	17.3 ± 6.8
Volume (mm^3)	1793 ± 533.3	3021 ± 649.7
GGN volume (mm^3)	1522 ± 463.5	1461 ± 463.0
GGN rate (%)	85.19 ± 3.162	47.45 ± 6.820*
Solid volume (mm^3)	271.3 ± 97.70	1560 ± 394.0**
Solid rate (%)	14.81 ± 3.162	52.55 ± 6.820*

Note: *$p < 0.001$, **$p = 0.001$, Unpaired t-test (nonparametric).
Abbreviations: AIS, adenocarcinoma in situ; GGN, ground-glass nodule; MIA, minimally invasive adenocarcinoma.

Pathological evaluation

Histopathological evaluation was performed by three pathologists at our institution who examined the hematoxylin and eosin-stained slides prepared using formalin-fixed paraffin-embedded tissues. They discussed the results and diagnosed AIS or MIA based on the latest WHO classification guidelines on lung histology.[9] Patients were accordingly classified into two groups: AIS and MIA.

Statistical analysis

Statistical analyses were performed using SPSS software v. 24.0 (IBM Corp., Armonk, NY, USA). Unpaired t-tests

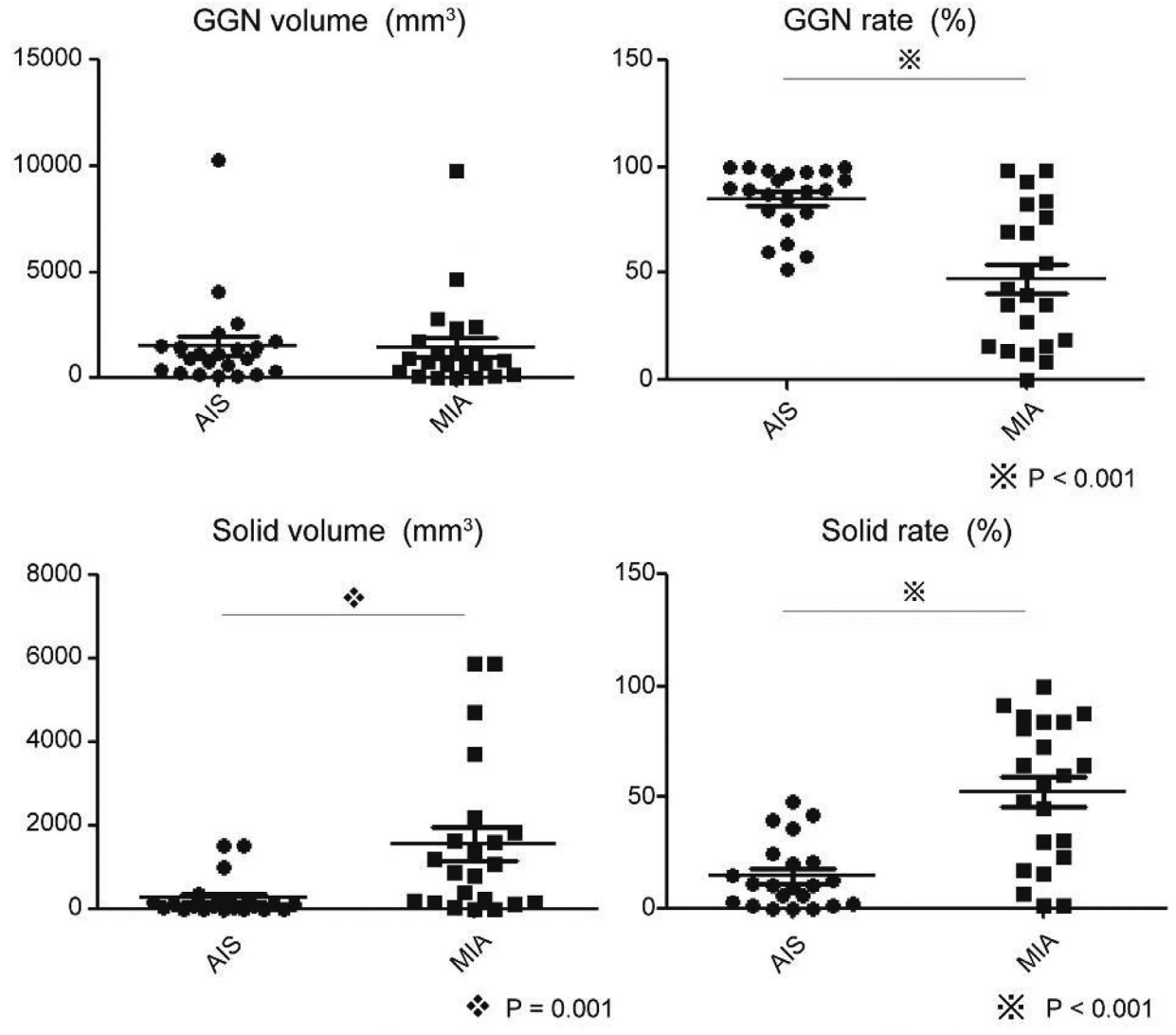


FIGURE 2 The GGN volume (mm^3) does not differ significantly between patients with AIS and those with MIA. The GGN rate (%) is significantly higher in patients with AIS compared to those with MIA ($p < 0.001$), whereas the solid volume (mm^3) and solid rate (%) are significantly higher in patients with MIA compared to those with AIS ($p = 0.001$). AIS, adenocarcinoma in situ; GGN, ground-glass nodule; MIA, minimally invasive adenocarcinoma

were used to compare the patients' demographic and clinical characteristics, as well as the minimum, maximum, and mean CT values between the two groups. A *p*-value of less than 0.05 was considered statistically significant.

The ROC curves of statistically superior parameters were used to determine the cutoff values as the closest values for 1.0 sensitivity.

TABLE 3 Histogram analysis for adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA)

Variable	AIS (n = 22)	MIA (n = 22)	p-value
Mean CT value	−568.3 ± 28.8	−331.4 ± 47.27	$p = 0.002$[a]
Maximum CT value	−568.3 ± 28.28	236.9 ± 44.98	$p = 0.025$[a]
Minimum CT value	−967.2 ± 33.61	−938.2 ± 65.60	$p = 0.70$
2.5th percentile	−941.1 ± 32.03	−910.6 ± 57.12	$p = 0.64$
25th percentile	−701.0 ± 21.81	−585.4 ± 37.51	$p = 0.018$[a]
50th percentile	−434.3 ± 25.96	−319.5 ± 28.87	$p = 0.004$[a]
75th percentile	−167.5 ± 41.53	−49.03 ± 37.22	$p = 0.019$[a]
97.5th percentile	72.55 ± 58.31	245.7 ± 75.43	$p = 0.004$[a]

Abbreviations: AIS, adenocarcinoma in situ; CT, computed tomography; MIA, minimally invasive adenocarcinoma.
[a]Statistically significant.

RESULTS

Of the 162 patients with lung cancer, a total of 44 patients were included in the study; 22 patients with pure AIS and 22 with pure MIA (Table 1). There were no significant differences between the two groups regarding age, histological tumor size, tumor volume (mm^3), and GGN volume (mm^3). The GGN rate was significantly higher in the AIS group (85.19 ± 3.162%) than in the MIA group (47.45 ± 6.820%) ($p < 0.001$). Conversely, the solid volume and solid rate were significantly higher in the MIA group than in the AIS group (1560 ± 394.0 mm^3 and 52.55 ± 6.820% vs. 271.3 ±

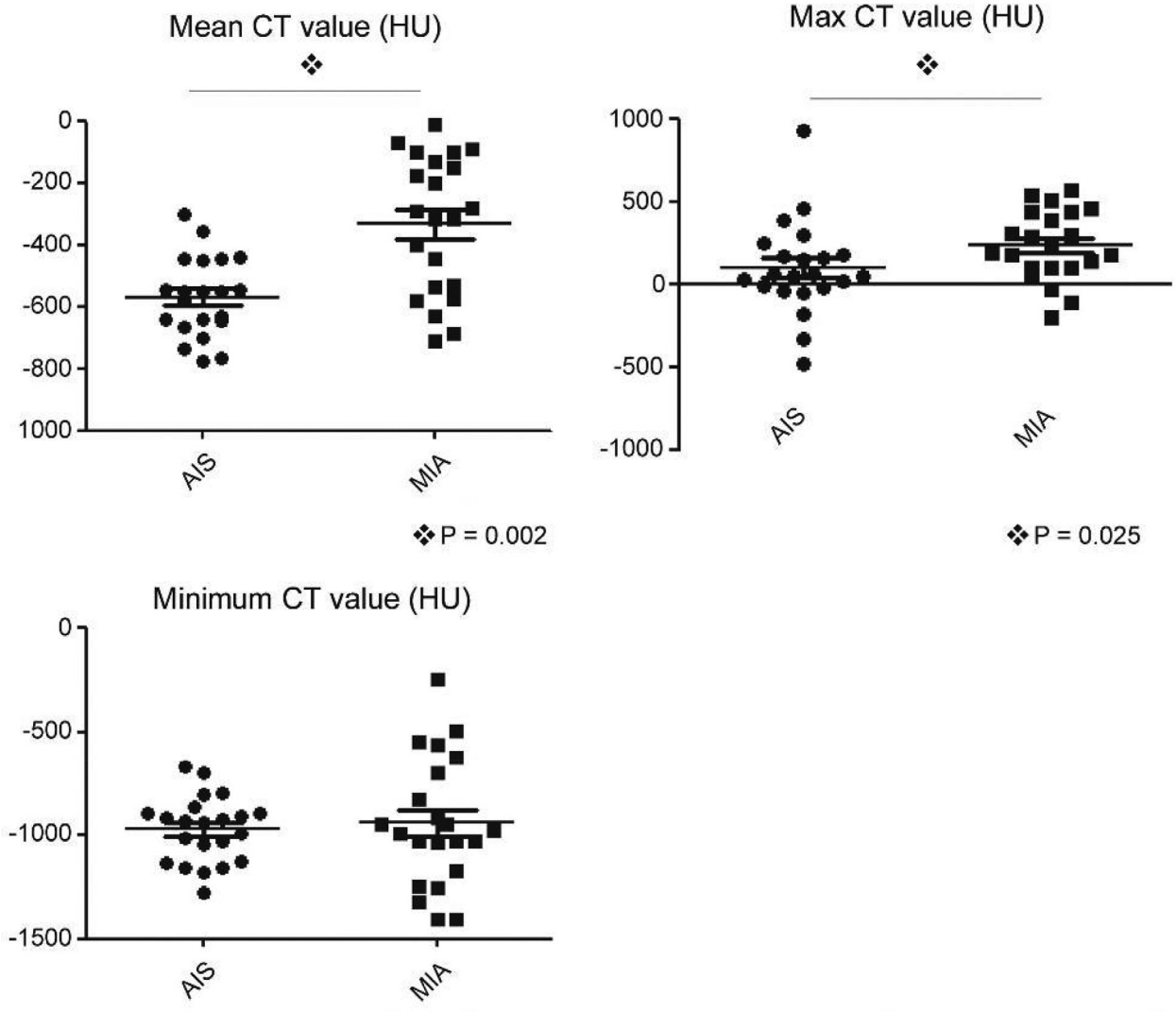


FIGURE 3 In the histogram analysis, the mean and maximum CT values are significantly higher in patients with MIA than in those with AIS. AIS, adenocarcinoma in situ; CT, computed tomography; HU, Hounsfield unit; MIA, minimally invasive adenocarcinoma

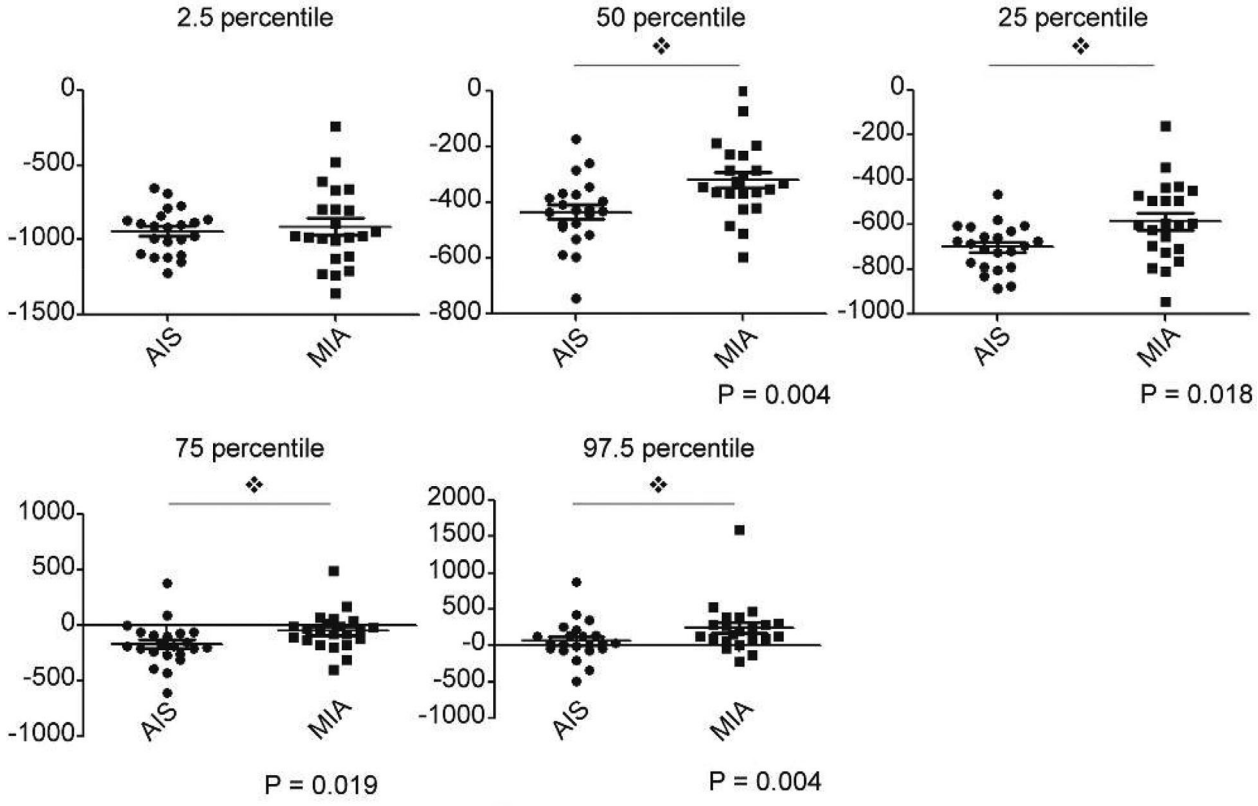


FIGURE 4 The 25th, 50th, 75th, and 97.5th percentiles show significantly higher CT values for patients with MIA than for those with AIS. AIS, adenocarcinoma in situ; CT, computed tomography; MIA, minimally invasive adenocarcinoma

97.70 mm^3 and 14.81 ± 3.162%; $p = 0.001$) (Table 2, Figure 2).

There was no correlation between FDG value and solid rate (parametric analysis, Pearson's $r = -0.145$) in the AIS group. FDG value and solid rate in the MIA group were positively correlated (parametric analysis, Pearson's $r = 0.532$).

In the histogram analysis, the mean and maximum CT values were significantly higher in the MIA group than in the AIS group. The 25th, 50th, 75th, and 97.5th percentiles showed significantly higher CT values for patients with MIA than for those with AIS (Table 3, Figures 3 and 4).

The cutoff value of GGN rate was 72.45%; solid rate was 22.3%; solid volume was 227.75 ml; mean CT value was −418.6 HU; 25th percentile was −602.8750 HU (sensitivity 0.091, 1-specificity 0.591); 50th percentile was −368.25 HU (sensitivity 0773, 1-specificity 0.227); 75th percentile was −139.75 HU (sensitivity 0773, 1-specificity 0.364) and 97.5th percentile was 55.55 HU (sensitivity 0.409, 1-specificity 0.818).

DISCUSSION

In this study, we investigated the possibility of AIS and MIA diagnosis using CT. We demonstrated that quantitative analysis of 3D-CT imaging data using software can help distinguish the histological characteristics of AIS and MIA.

The GGN rate, solid volume, and solid rate significantly differed between AIS and MIA because of the higher pixel density of MIA tumors relative to AIS tumors. This was probably due to the higher rate of fibrotic changes in MIAs compared to AISs. However, these fine differences cannot be recognized visually.

We speculated that the software for quantitative analysis of 3D-CT imaging data could recognize these differences based on the tumor cellularity.

In the process of development of pGGNs, they initially increase in size, and later, a solid volume appears within the GGNs and these areas increase. This process is consistent with our results. With the lung cancer invasion in MIA, increases in volume can occur. In our study, patients with MIA had significantly larger histological tumors and solid volume than did those with AIS.

In this study, in patients with AIS, the typical histopathological findings included solid components in the form of atelectasis and lymph node aggregate areas, as well as areas that showed features characteristic of bronchioloalveolar carcinoma, whereas the CT images showed pGGNs (Figure 5). In contrast, in patients with MIA, almost all solid component areas showed fibrotic changes with an increase in elastic fibers with polymerization and sometimes rupture, and cancer cells invading the interstitial tissue and disturbing its structure, resulting in an increase in collagen fiber content. These changes are significant even if they affect an area of

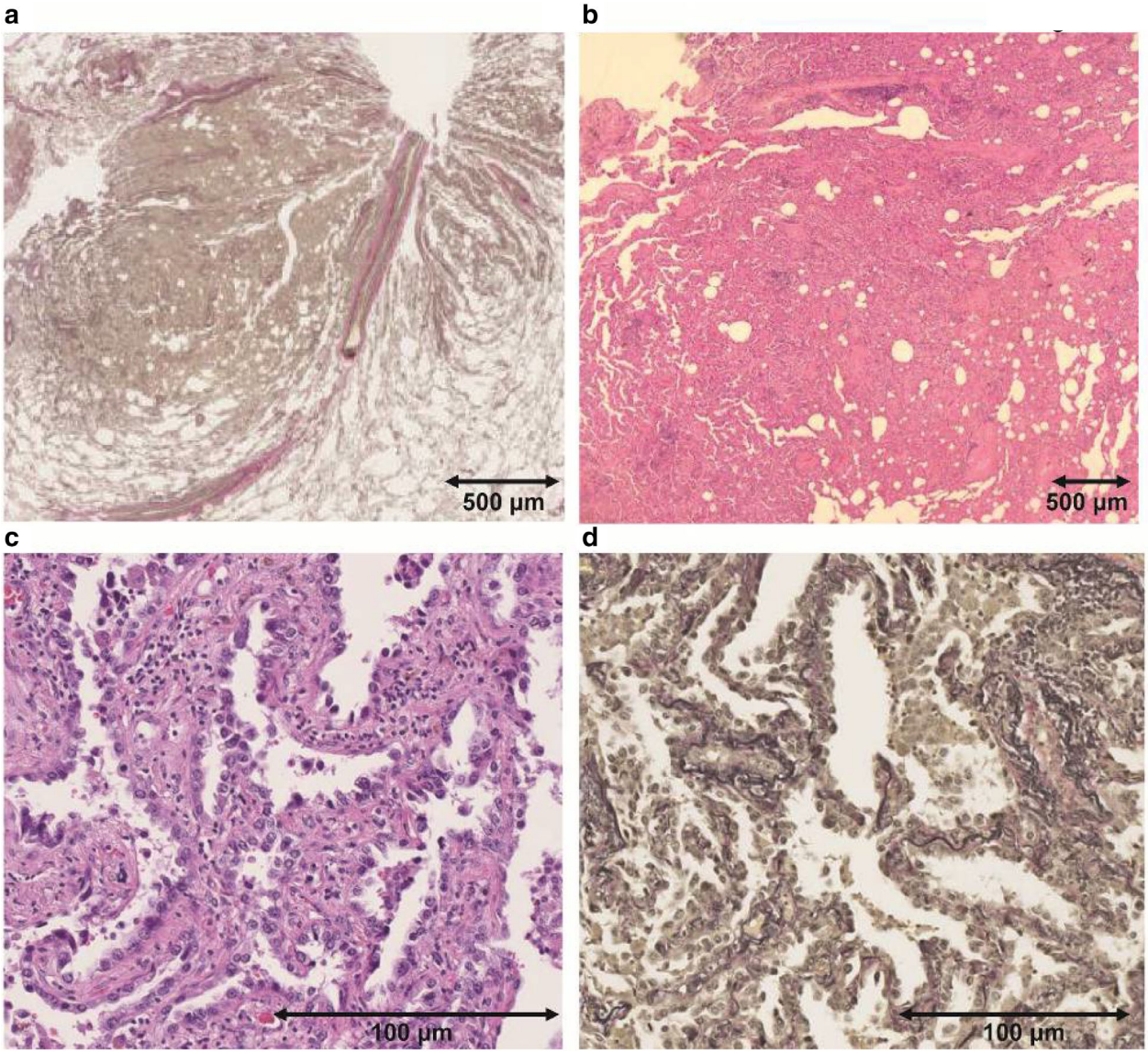


FIGURE 5 AIS pathological features. The typical AIS histological image shows areas that are almost bronchioloalveolar carcinoma (BAC) and CT imaging shows pure GGN (pGGN) (Figure 3 (a), (b); low power, (c), (d); high power). AIS, adenocarcinoma in situ; GGN, ground-glass nodule

less than 5 mm because they represent the first step of cancer invasion into the interstitial tissue (Figure 6).

We believe that the areas with these changes are recognized as solid components on CT images. The solid areas on CT may show collapse and lymphatic invasion. When tumors with these signs are detected, the surgical method must be carefully selected. If we could predict AIS or MIA from preoperative CT images, we would be better able to choose the surgical method preoperatively.

Quantitative image analysis with Synapse Vincent (Fujifilm) using 3D imaging can possibly recognize the minute changes in early disease associated with difficulty in diagnosis (AIS or MIA) and may possibly provide information regarding the situation inside the tumor, which cannot be recognized using 2D-CT imaging.

Li et al. investigated whether quantitative CT analysis can help predict histological invasiveness of pulmonary adenocarcinoma appearing as pGGNs. They concluded that quantitative CT analysis can predict histological invasiveness of pGGNs, particularly the maximum nodule diameter and 100th percentile on the CT value histogram, and that this can guide the surgical management selection and long-term follow-up planning.[1] Studies have reported that a subset of pulmonary pGGNs is associated with pathological invasiveness and that it is difficult to detect invasiveness in pGGNs only using morphological characteristics. In their study, Bak et al. found that nearly half of all resected pulmonary pGGNs (54.5%) were MIA or invasive adenocarcinomas.[10]

The diagnosis of AIS and MIA is a popular topic among pathologists because of the minimal difference in the pathological findings. In our experience, many pGGNs are unexpectedly diagnosed as MIA. In many reports, the maximum nodule diameters, the largest cross-sectional areas, and pGGN mass were significantly larger in IPA compared with

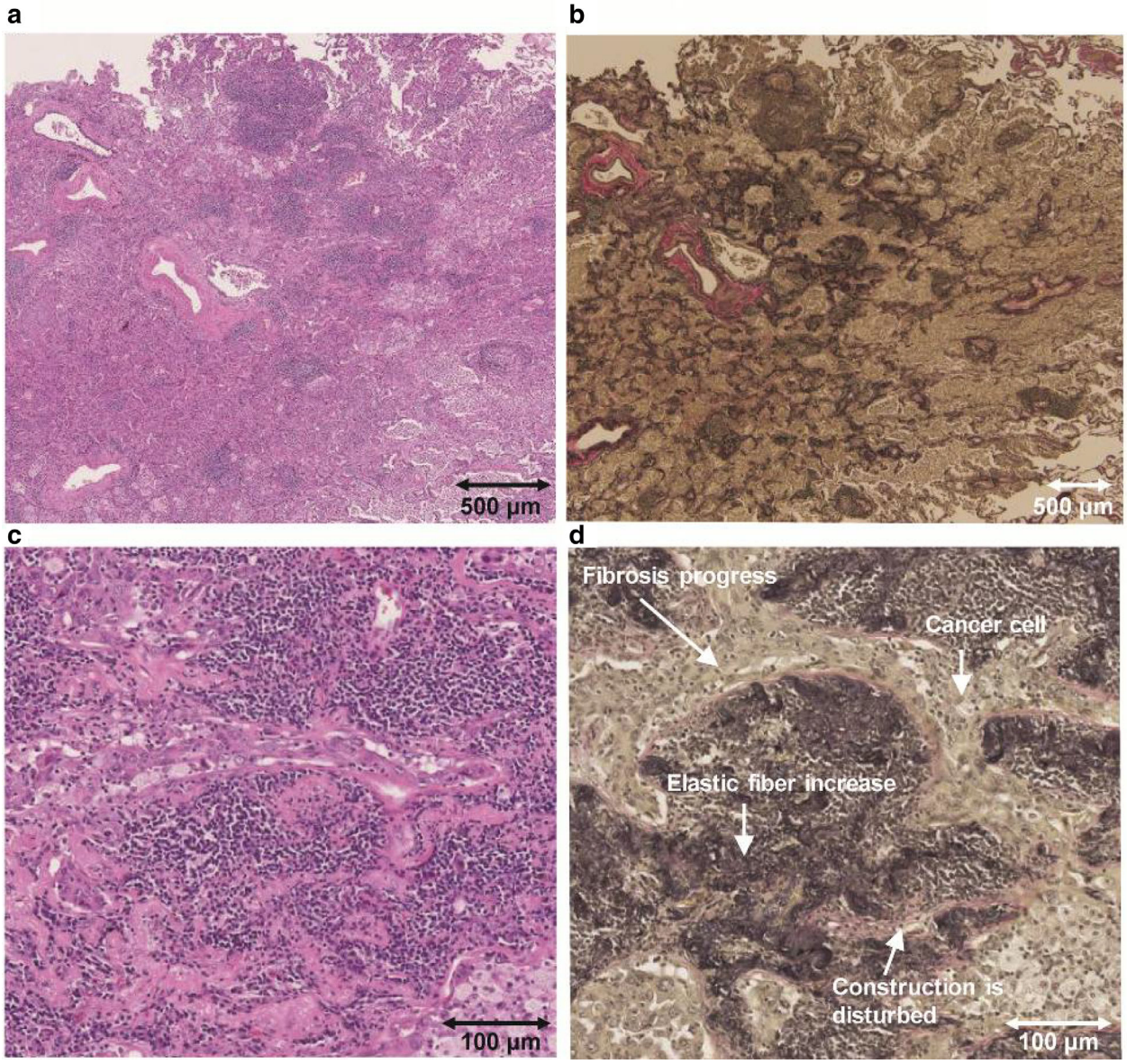


FIGURE 6 MIA pathological features. Almost all solid component areas in MIA show an increase in elastic fibers with polymerization and sometimes with rupture, and cancer cells invading the interstitial tissue and disturbing its construction (Figure 4 (a), (b): low power; (c), (d): high power). Accordingly, increased collagen fibers appear. These histological fibrotic changes are significant even if they affect an area of less than 5 mm because they represent the first step of invasion into the interstitial tissue. MIA, minimally invasive adenocarcinoma

the values obtained in preinvasive adenocarcinoma or MIA. This was caused mainly by an increased tumor tissue component and thickening of the alveolar septa in invasive adenocarcinomas.[1]

The important advantage of CT value histogram analysis is that it can reflect the nodule distribution and heterogeneity. Li et al. reported a percentile analysis for histogram assessment. Their results indicated that the 95th, 98th, and 100th percentiles reflected a high CT attenuation zone within the tumor, differences in tumor cellularity, and alveolar septum thickening, as well as retained air space in preinvasive lesions, and MIA and invasive adenocarcinoma may be detected.[8] The percentile analysis can express the characteristics of entire tumors, which cannot be detected using preoperative 2D-CT.

Nomori et al. examined the peak rather than the mean CT value in clinical T1N0M0 lung adenocarcinoma[11] and concluded that the mean CT value may be affected by the density of vessels or bronchi within the tumor. Tamura et al. showed that a one-dimensional high mean CT value of a GGN was associated with its future change.[12]

We hypothesized that a CT histogram analysis would provide more information on the tumor characteristics because it can objectively reflect various CT densities and pixel distributions and may constitute a more comprehensive modality for assessing intratumoral heterogeneity than

mean CT value. Meanwhile, the CT attenuation slope from the 0th to 100th percentile may reflect a larger difference in the heterogeneity of intratumoral cellularity and density. Furthermore, Li et al. reported that logistic regression analysis showed that the maximum nodule diameter and the 100th percentile on CT value histogram were independent risk factors for histological invasiveness.[1] The histological invasiveness of MIA is associated with minute changes, making the preoperative diagnosis of AIS or MIA difficult.

Other studies proposed that pGGNs should be defined as homogeneous hazy lesions for which CT values are less than −300 HU because −300 HU is the threshold of differentiation of vessels.[13,14] In our study, we used Synapse Vincent (Fujifilm) software that defines the GGN area as −800 to −300 HU. Therefore, it is necessary to validate our evaluation in further studies. However, given that our results showed that quantitative analysis of CT imagin data can help distinguish the histological differences between AIS and MIA, and considering that the histological tumor size (mm), solid rate (%), GGN rate (%), mean CT value, and the 25th, 50th, 75th, and 97.5th percentiles were significantly different, we believe that this method can guide selection of surgical management and long-term follow-up plans.

Bak et al. also investigated whether quantitative analysis of lung adenocarcinoma manifesting as a GGN on initial CT scans can predict further CT scanning changes or rate of growth.[10] They found that the 97.5th percentile and the slope of the CT scanning attenuation values from the 2.5th to the 97.5th percentiles could be helpful in predicting future CT changes and the growth rate of pGGNs.[10] They concluded that patients with pGGNs showing CT scanning attenuation values higher than the 97.5th percentile and steeper slopes of CT scanning attenuation values may require more frequent follow-up than the usual interval of 6 months.[10]

In 2016, Travis et al. reported on the new method of lung cancer staging, the IASLC Lung Cancer Staging Project.[5] They presented the clinical T factor diagnosis of solid components using 2D high-resolution CT. In the past, the clinical T factor was used to diagnose invasive or noninvasive lung cancer using the maximum diameter of the 2D solid components.

For analysis of 2D-CT images, one slice is selected for measurement of the maximum diameter of the solid components. However, currently, the selected maximum solid component differs depending on the reading radiologist. Almost all solid components of maximum diameter show an irregular margin; therefore, different radiologists provide different maximum diameters. This is the main problem associated with 2D-CT reading. Therefore, in this study, we investigated 3D imaging using software. We believe that the maximum diameter should be measured on 3D images for correct diagnosis. Sagittal sectioning may provide the maximum diameter in many patients.

The diagnosis of MIA varies among pathologists based on the relatively large number of GGNs. Therefore, in our institution, three pathologists discuss and diagnose AIS, MIA, and IPA.

Information about the characteristic findings of AIS and MIA is important given that patients have a 100% or near-100% chance of disease-free survival, respectively, if these lesions are completely resected.[4,5] Despite the growing number of published cases, no definitive rates for recurrence have so far been reported in patients with AIS.[15–22] Although rare cases of staple line recurrences have been reported in what may have represented MIA,[23] these cases were not diagnosed according to the IASLC/American Thoracic Society (ATS)/European Respiratory Society (ERS) adenocarcinoma classification; thus, it is not possible to be certain whether some of the exclusion criteria may have been present, such as the recently described invasive pattern of spread through air spaces.[24,25]

Survival analysis of AIS and MIA should be performed using disease-specific survival or recurrence-free probability rather than overall survival because patients typically die of other causes.[15,26] When new lung adenocarcinomas develop after resection of MIA,[27] they may represent a second primary tumor rather than a recurrence or metastasis.[28]

Our study had two limitations which may limit the generalizability of our findings. First, it was retrospective in design, and second, the sample size was relatively small.

In conclusion, we have shown that quantitative analysis of 3D-CT imaging data using software can help distinguish the histological differences of AIS and MIA. In future, the solid component selected using quantitative CT imaging analysis can replace the current 2D-CT solid area for TNM classification. Our method enables preoperative diagnosis of AIS and MIA using CT imaging, which can guide the choice of an appropriate surgical method as well as an appropriate follow-up plan.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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