Analysis of Tumor Size, Computed Tomography (CT) Attenuation and Post-Contrast Attenuation of Pulmonary Pure Ground-glass Nodules for Predicting Pathological Invasiveness

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The aim of this study is to compare and analyze CT characteristics like tumor size, CT attenuation value and post-contrast CT attenuation value of pulmonary pure ground-glass nodules less than or equal to 3 cm in maximum diameter, to study the key in their differential diagnosis and identify factors that predict pathological invasion.

We retrospectively evaluated preoperative CT data of 161 pulmonary pure GGNs less than or equal to 3 cm in maximum diameter from October 2013 to August 2015 and pathologically classified them as adenocarcinoma in situ (AIS; n = 68), minimally invasive adenocarcinoma (MIA; n = 52), or invasive adenocarcinoma (I-ADC; n = 41). The age, sex, smoking history, nodule location, tumor size, and computed tomography (CT) attenuation value in plain CT and contrast enhanced CT of the 3 groups were compared. Tumor size, CT attenuation value in plain CT and CT attenuation value in post-contrast CT was significantly greater in the I-ADC group than in the AIS and MIA groups. From our study, we can conclude that tumor size, CT attenuation value in both plain CT and contrast-enhanced CT could significantly differentiate invasive adenocarcinoma from adenocarcinoma in situ and minimally invasive adenocarcinoma in pulmonary pure ground-glass nodules. The combination of all these factors could facilitate in prediction of pathological invasiveness and that further large-scale studies need to be conducted.

Keywords: adenocarcinoma, CT, invasion, pulmonary pure ground-glass nodules.

Ground-glass opacity is defined as a hazy increased opacity of the lung, with preservation of the bronchial and vascular margins.[1] The International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society introduced a new classification of lung adenocarcinoma.[2] In this classification, adenocarcinoma in situ (AIS) defined as a small (< 3 cm) adenocarcinoma with growth restricted to neoplastic cells along preexisting alveolar structures without stromal, vascular, or pleural invasion,[2]is newly recognized as another preinvasive lesion for pulmonary adenocarcinoma in addition to atypical adenomatous hyperplasia (AAH), replacing the former term of bronchioloaveolar carcinoma (BAC). This conceptual change from BAC to AIS was due to the observation that BACs showed 100% disease-free survival with proper surgical intervention. [3-6]

Classification

The International Association for the Study of Lung Cancer/ American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) proposed a new classification for lung adenocarcinoma which divided lung adenocarcinoma into two main groups: preinvasive lesions, including atypical adenomatous hyperplasia (AAH) and adenocarcinoma in situ (AIS); and invasive lesions, such as minimally invasive adenocarcinoma (MIA), invasive adenocarcinoma, and variants of invasive adenocarcinoma.[3] The term bronchioloalveolar carcinoma (BAC) is no longer used. In the new classification, AIS is equivalent to the formerly used term BAC **(Table 1)**.

Pre-invasive lesions:

Atypical adenomatous hyperplasia (AAH)

AAH is a localized, small (usually 0.5 cm or less) proliferation of mildly to moderately atypical type II pneumocytes and/or Clara cells lining alveolar walls and sometimes, respiratory bronchioles. There is a continuum of morphologic changes between AAH and AIS.[3]

Adenocarcinoma in situ (AIS)

AIS, one of the lesions formerly known as BAC, is a localized small (≤3 cm) adenocarcinoma with growth restricted to neoplastic cells along preexisting alveolar structures (lepidic growth), lacking stromal, vascular, or pleural invasion. AIS is subdivided into nonmucinous and mucinous variants. Virtually, all cases of AIS are nonmucinous, consisting of type II pneumocytes and/or Clara cells.[3]

Invasive lesions:

Minimally invasive adenocarcinoma (MIA)

MIA is a small, solitary adenocarcinoma (≤3 cm), with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension in any one focus. MIA is usually nonmucinous but rarely may be mucinous.[3]

Invasive Adenocarcinoma (I-ADC)

Invasive adenocarcinomas represent more than 70 to 90% of surgically resected lung cases; one of the most important aspects of this classification is to present a practical

(I) Preinvasive lesions
(i) Adenocarcinoma in situ (AIS) —mucinous, nonmucinous, or mixed
(ii) Atypical adenomatous hyperplasia (AAH)
(II) Minimally invasive lesions
(i) Minimally invasive adenocarcinomas (MIA) —mucinous, nonmucinous, or mixed
(III) Invasive adenocarcinoma
(i) Acinar predominant
(ii) Papillary predominant
(iii) Micropapillary predominant
(iv) Solid predominant with mucin production
(v) Lepidic predominant adenocarcinoma (LPA)
(IV) Variants of invasive adenocarcinoma
(i) Invasive mucinous adenocarcinoma
(ii) Colloid, fetal, and enteric
The International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) classification of lung adenocarcinoma.

Table 1: The revised classification of lung adenocarcinoma.

way to address these tumors that are composed of a complex heterogeneous mixture of histologic subtypes. It is a malignant tumor with glandular differentiation or mucin production. This tumor exhibits various patterns and degrees of differentiation, including lepidic, acinar, papillary, micropapillary and solid with mucin formation.[3]

Aims and Objectives

Pulmonary ground-glass nodules (GGNs) are occasionally diagnosed as invasive adenocarcinomas. Serial CT findings have documented that, in subset of patients with adenocarcinoma, stepwise progression of lesions with ground-glass opacity manifests as an increase in size, the appearance or also subsequent increase of solid components. There needs to be an appropriate CT classification, methods for precise measurement of ground-glass nodules, including the extent of both ground-glass and solid components, as well as accurate assessment of the growth rates as means for predicting malignancy and prognosis. In our study, we excluded any ground-glass opacity nodules that have solid component. The aim of our study is to retrospectively evaluate the size, CT attenuation and post-contrast CT attenuation in pulmonary pure ground-glass nodules to identify the differentiating features between adenocarcinoma in situ, minimally invasive adenocarcinoma and invasive adenocarcinoma.

Materials and Methods

Ethics

The study was performed in accordance with the Declaration of Helsinki and was approved by the ethical committees of Shanghai Tongji Hospital and the Tongji University School of Medicine and with the help from Shanghai Pulmonary Hospital affiliated to Tongji University Shanghai, China. All participants provided written informed consent.

Nodule selection and patients

We retrospectively reviewed the chest CT data of patients who were found to have persistent pure GGNs less than or equal to 3 cm in maximum diameter and obtained a definitive pathological diagnosis from October 2013 to August 2015. Pure GGN was defined as a focal dense lesion with homogeneous attenuation on the lung window, and no solid portion within the lesion on the mediastinal window. In total, 161 pure GGNs were selected from 153 patients who were enrolled in the study. Out of these 153 patients, pure GGNs in 62 patients were pathologically diagnosed as adenocarcinoma is situ (AIS), 52 as minimally invasive adenocarcinoma (MIA) and 39 as invasive adenocarcinoma (I-ADC). The patients consisted of 98 women and 55 men with a mean age of 54 years (range, 27–73 years). Thirty four patients were smokers and the rest were nonsmokers. In AIS group, 2 patients had 3 pure GGNs and 2 patients had 2 pure GGNs, in MIA group, all the patients had single pure GGNs, and in I-ADC group, 1 patient had 3 pure GGNs. Therefore, the number of pure GGNs in AIS, MIA and I-ADC group was 68, 52 and 41 respectively. Out of 68 pure GGNs in AIS group, 46 nodules had undergone CT without contrast and 31 nodules with contrast. Similarly, out of 52 pure GGNs in MIA group, 33 nodules had undergone CT without contrast and 20 nodules with contrast. In I-ADC group, out of 41 pure GGNs, 24 nodules had undergone CT without contrast and 21 nodules with contrast. This is because only few nodules had undergone both pre-contrast and post-contrast CT examination. Most nodules had either one.

Criteria of inclusion

(a) Pure ground-glass nodules

(b) Maximum diameter ≤3cm

(c) Pathologically confirmed nodules

(d) Undergone both plain CT and contrast enhanced CT or either.

Criteria of exclusion

Nodules that included both ground-glass and solid components were excluded from the study.

CT selection

In all patients included in the study, CT was performed preoperatively at least once. CT scans were obtained using one of two CT scanners (Sensation 64, Siemens Medical Systems, Erlangen, Germany; Brilliance 40, Philips Medical Systems, Best, The Netherlands). The CT parameters were as follows: section thickness, 1 mm on Sensation 64 and 2 mm on Brilliance 40; tube voltage, 120 kVp; tube current, 40–546 mA; lung window width, 1,500 Hounsfield units (HU) and level, −700 HU; and mediastinal window width, 400 HU and level, 20 HU. Images were taken with and without the use of contrast medium or

either.

Analysis of CT images

Two board-certified radiologists with 5 and 10 years of experience in chest CT scan interpretation independently reviewed the TSCT images. Both radiologists were blinded to the pathological diagnosis. The patients' age and sex, maximum diameter, mean CT value in both plain and post-contrast CT examination or either plain or post-contrast CT examination were recorded. The radiologists independently measured the maximum diameter on the transverse lung window image. The diameters they obtained were averaged for each nodule. They also measured the mean CT value of each nodule on the slice that showed the maximum diameter; values were averaged for each nodule. When the maximum diameter and mean CT value differed between the two radiologists, the chest CT data were reviewed by the radiologists until they reached a consensus.

Histological Examination

All tumors were histologically evaluated by two experienced pathologists, who were blinded to the patients' clinical information. All histological evaluations were performed by examining hematoxylin and eosin stained slides which were prepared using formalin-fixed paraffin-embedded tissues. Adenocarcinoma lesions were classified according to the new lung adenocarcinoma classification proposed by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society (IASLC/ATS/ERS).

Statistical Analysis

All data were processed using SPSS 20.0 statistical software (IBMCorp., Armonk, NY, USA). The tumors were divided into 3 groups according to pathological classifications: (1) adenocarcinoma in situ (AIS), (2) minimally invasive adenocarcinoma (MIA), and (3) invasive adenocarcinoma (I-ADC). Patient characteristics (age, sex, smoking history), tumor size, and mean CT attenuation values in both plain and post-contrast CT examination or either plain or post-contrast CT examination were compared between the 3 groups. Continuous variables were compared using the analysis of variance with Scheffe's post-hoc test, and categorical data were compared using Chi-square tests. Therefore, age, sex, smoking history and CT findings were compared among the AIS, MIA and I-ADC groups by using the F test with Scheffe's post-hoc test (age, maximum diameter and mean CT value), Pearson $\chi 2$ test (sex and smoking history). According to the results obtained, we regrouped the three groups into two groups. Receiver operating characteristic (ROC) curves were plotted for the maximum diameter and mean CT value to confirm the optimal cut-off that differentiated the two groups. The area under the curve (AUC), sensitivity, and specificity were obtained using various cut-off points and the optimal cut-off point was defined as that having the greatest AUC. Measurement data are written in $\bar{x} \pm s$.

Results

	Total (n = 161)	AIS (n = 68)	MIA (n = 52)	I- ADC (n = 41)	p value
Age (years)	54.24±10.27	53.5 ±9.31	52.52±12.03	57.69±8.44	0.044
Sex (male/ female)	55/98	21/41	20/32	14/25	0.879
Smoking history (with/ without)	34/119	12/50	14/38	8/31	0.599
Tumor size (cm)	1.07±0.49	0.86±0.34	0.99±0.38	1.54±0.55	0.000
CT attenuation (HU)	-596.16±114.37	-648.70±80.98	-600.06±109.93	-490.08±105.30	0.000
CT attenuation – contrast (HU)	-553.63±121.19	-604.68±88.79	-582.40±90.06	-450.86±129.03	0.000

Table 2: Patient characteristics and tumor properties

Location	AIS (n = 68)	MIA (n = 52)	I- ADC (n = 41)
RUL	29	15	12
RML	8	4	5
RLL	4	6	4
LUL	17	17	14
LLL	10	10	6

Table 3: Location of tumor, RUL=Right Upper Lobe, RML=Right Middle Lobe, RLL=Right Lower Lobe, LUL=left Upper Lobe, LLL=Left Lower Lobe

Patient Characteristics and Radiological Tumor Properties

The age, sex, smoking history, tumor size, mean CT attenuation value in plain and post-contrast CT studied for each group are summarized in **Table 2**. The location of tumor in each group is summarized in **Table 3.**

The F test, Pearson $\chi 2$ test revealed that maximum diameter (P =0.000), mean CT value in plain CT (P =0.000), mean CT value in post-contrast CT (P =0.000) and age (P =0.044) significantly differed among the AIS, MIA and I-ADC groups. There was no difference in sex (P =0.879) and smoking history (P = 0.599) between the

The reference group is AIS		
MIA	Age	0.876
	Maximum diameter(cm)	0.288
	Mean CT attenuation(HU)	0.094
	Mean CT attenuation-contrast(HU)	0.751
I-ADC	Age	0.132
	Maximum diameter(cm)	0.000
	Mean CT attenuation(HU)	0.000
	Mean CT attenuation-contrast(HU)	0.000
The reference group is MIA		
AIS	Age	0.876
	Maximum diameter(cm)	0.288
	Mean CT attenuation(HU)	0.094
	Mean CT attenuation-contrast(HU)	0.751
I-ADC	Age	0.058
	Maximum diameter(cm)	0.000
	Mean CT attenuation(HU)	0.000
	Mean CT attenuation-contrast(HU)	0.001
The reference group is I-ADC		
AIS	Age	0.132
	Maximum diameter(cm)	0.000
	Mean CT attenuation(HU)	0.000
	Mean CT attenuation-contrast(HU)	0.000
MIA	Age	0.058
	Maximum diameter(cm)	0.000
	Mean CT attenuation(HU)	0.000
	Mean CT attenuation-contrast(HU)	0.001

Table 4: Comparison of patient characteristics and tumor properties for each group

three groups. Since the above tests only identified variables that significantly differed among the three groups and did not identify differences between any two of the three groups, so we also performed Scheffe's post-hoc test. This is a statistical method in which one group is a reference group, and the other groups are compared with the reference group to obtain differences between any two groups. For example, using the AIS group as the reference group, we compared the MIA and

I-ADC groups with the AIS group to identify differences between the AIS and MIA groups and between the AIS and I-ADC groups. The results of Scheffe's post-hoc test are shown in **Table 4**.

Maximum diameter

The maximum diameter significantly differed between the AIS and I-ADC groups (P =0.000) and between the MIA and I-ADC groups (P =0.000), but not between the AIS and MIA groups (P =0.288). We therefore combined the AIS and MIA groups into a single AIS–MIA group. A Receiver Operating Characteristics (ROC) curve was plotted between the I-ADC group and the AIS–MIA group **(Figure 1 A)**. The optimal cut-off for distinguishing between I-ADC and AIS/MIA was 1.2 cm (sensitivity, 68.3%; specificity, 86.7%; area under the curve [AUC], 0.838). Nodules with a maximum diameter <1.2 cm were likely to be AIS or MIA, while nodules with a maximum diameter ≥1.2 cm were likely to be I-ADC. The odds of a lesion being an I-ADC gradually increased with increasing maximum diameter, suggesting that an increase in lesion size increases the possibility of an invasive lesion.

Mean CT value in plain CT

Mean CT value significantly differed between the AIS and I-ADC groups (P =0.000), and the MIA and I-ADC groups (P =0.000) but not between the AIS and MIA groups (P =0.094). We therefore combined the AIS and MIA groups into single AIS – MIA group. A ROC curve was plotted between the I-ADC group and the AIS–MIA group **(Figure 1 B)**. The optimal cut-off for distinguishing between AIS / MIA and I-ADC was −584 HU (sensitivity, 87.5%; specificity, 70.9%; AUC, 0.834). Nodules with a mean CT attenuation value <-584 were likely to be AIS or MIA, while nodules with a mean CT attenuation value ≥-584 were likely to be I-ADC. The odds of a lesion being an I-ADC gradually increased with increasing mean CT attenuation value, suggesting that an increase in lesion mean CT attenuation value increases the possibility of an invasive lesion.

Mean CT value in post-contrast CT

Mean CT value in post-contrast CT

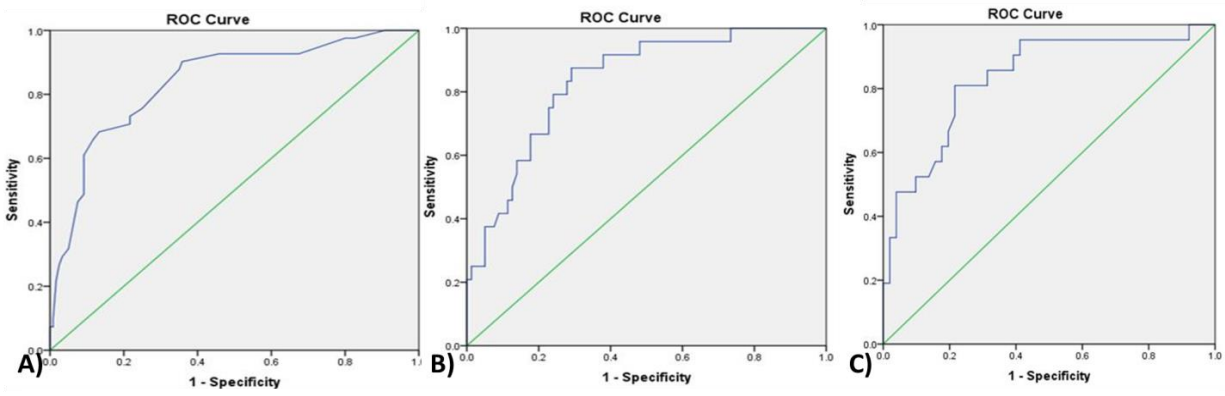

Figure 1: Receiver Operating Characteristics (ROC) curve, X-axis shows specificity and Y-axis shows sensitivity, A) for maximum diameter, B) for mean CT value in plain CT, C) for mean CT value in post-contrast CT

significantly differed between the AIS and I-ADC groups (P =0.000), and the MIA and I-ADC groups (P =0.001) but not between the AIS and MIA groups (P =0.751). We therefore combined the AIS and MIA groups into single AIS – MIA group. A ROC curve was plotted between the I-ADC group and the AIS–MIA group **(Figure 1 C)**. The optimal cut-off for distinguishing between AIS / MIA and I-ADC was −536HU (sensitivity, 81%; specificity, 78.4%; AUC, 0.835). Nodules with a mean CT attenuation value <-536 in post-contrast CT were likely to be AIS or MIA, while nodules with a mean CT attenuation value ≥-536 were likely to be I-ADC. The odds of a lesion being an I-ADC gradually increased with increasing mean CT attenuation value in post-contrast CT, suggesting that an increase in lesion mean CT attenuation value in post-contrast CT increases the possibility of an invasive lesion.

Age

There was no significant difference in age of patients between the three pathological groups. Between AIS and MIA (P =0.876), AIS and I-ADC (P =0.132), MIS and I-ADC (P =0.058). Therefore, there was no role of age of patients in predicting pathological invasiveness.

Sex

There was no difference in sex distribution in the three groups; therefore, there was no role of sex of patients in predicting pathological invasiveness. Moreover, in each group female patient were found to be more than the male patients.

Smoking history

There was no difference in smoking history in the three groups. So, there was no role of smoking history of patients in predicting pathological invasiveness. In each group there were more nonsmokers than smokers.

Location

As shown in Table 3, most of the nodules were located in the right upper lobe, followed by the left upper lobe. The least found location of nodules was right lower lobe, followed by right middle lobe.

Discussion

We found that, in pure pulmonary ground-glass nodules less than or equal to 3 cm in maximum diameter, a maximum diameter less than 1.2 cm was helpful to distinguish AIS and MIA from I-ADC; mean CT value less than −584 HU differentiated AIS and MIA from I-ADC; and in post-contrast CT scan mean CT value less than −536 HU differentiated AIS and MIA from I-ADC. Patient characteristics like age, smoking history were not helpful in differentiating the three groups of pathology. Most of the patients were nonsmokers and female. Nodules were mainly located in the right upper lobe and least in right lower lobe.

In our study, there was no significant difference in the maximum diameter between AIS and MIA group, whereas in study conducted by Eguchi T et al.[7] there was a significant difference in maximum diameter between AIS and MIA groups. In present study, according to analysis of variance (F test) there was significant difference in maximum diameter in the three groups (P =0.000), and with further

Scheffe's post-hoc test, the difference was found between AIS and I-ADC group (P =0.000) and MIA and I-ADC group (P =0.000). The cutoff to differentiate I-ADC from MIA and AIS group was 1.2 cm with sensitivity 68.3%; specificity 86.7%; and area under the curve (AUC) 0.838. In the study conducted by Eguchi T et al.,[7] there was significant difference in maximum diameter between the three groups (P =0.0005), but the difference was found to be between AIS and MIA group (P= 0.0100) and AIS and I-ADC group (P= 0.0025) with cutoff value of 11.0 mm, and the sensitivity and specificity were 95.8% and 46.8%, respectively, with an area under the curve (AUC) of 0.75. In one study, Lee et al.,[8] showed that all 11 pure GGNs 10 mm or smaller were preinvasive lesions consisting of six AAHs and five BACs. Nakata et al.,[9] also showed that 93.0% (53 of 57) of pure GGNs 10 mm or smaller were AAH or BAC.

Again, in our study, there was no significant difference in the mean CT value between AIS and MIA group, which was similar to the study conducted by Eguchi T et al.,[7] there was also no significant difference in mean CT value between AIS and MIA groups. In present study, according to analysis of variance (F test) there was significant difference in mean CT value in the three groups (P =0.000), and with further Scheffe's post-hoc test, the difference was found between AIS and I-ADC group (P =0.000) and MIA and I-ADC group (P =0.000). The cutoff to differentiate I-ADC from MIA and AIS group was −584 HU with sensitivity 87.5%; specificity 70.9%; and area under the curve (AUC) 0.834. In the study conducted by Eguchi T et al.[7] there was significant difference in mean CT value between the three groups (P<0.0001), and the difference was found to be between AIS and I-ADC group (P= 0.0001) and MIA and I-ADC group (P= 0.0129) with cutoff value of –680 HU, and the sensitivity and specificity were 95.8% and 35.1%, respectively, with an area under the curve (AUC) of 0.77. According to their study, combination of tumor size and CT attenuation could be more predictable than tumor size and CT attenuation value alone.

Moreover, in our study we also conducted study in post-contrast enhanced CT, and again there was similar result, there was no significant difference in the mean CT value between AIS and MIA group. According to analysis of variance (F test) there was significant difference in mean CT value in the three groups (P =0.000), and with further Scheffe's post-hoc test, the difference was found between AIS and I-ADC group (P =0.000) and MIA and I-ADC group (P =0.001). The cutoff to differentiate I-ADC from MIA and AIS group was −536 HU with sensitivity 81%; specificity 78.4%; and area under the curve (AUC) 0.835.

Other patient and tumor characteristics like age, sex, smoking history and location were not of use in differentiating AIS, MIA and I-ADC groups. We could see that most of the patients were nonsmokers and female and the most common location was right upper lobe. From our study, we found that tumor size, mean CT value in unenhanced

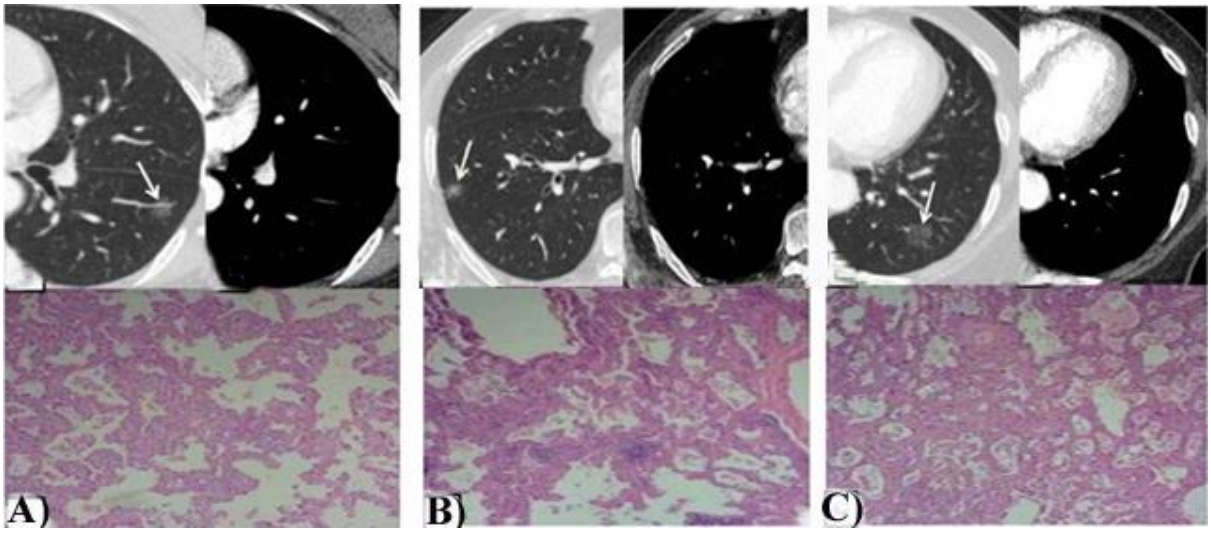

Figure 2: A) CT scan finding of a case of adenocarcinoma in situ showing a 1 cm pure ground-glass nodule and Hematoxylin-eosin stain, ×100 showing no foci of invasion, B) CT scan finding of a case of minimally invasive adenocarcinoma showing a1.3 cm pure ground-glass nodule and Hematoxylin-eosin stain, ×100 showing a small area of invasion, C) CT scan finding of a case of invasive adenocarcinoma showing a 1.6 cm pure ground-glass nodule with higher HU value and Hematoxylin-eosin stain, ×100 showing areas of invasion

and enhanced CT both, were consistent in AIS and MIA group, whereas in the study conducted by Eguchi T et al.,[7] tumor size was similar in MIA and I-ADC group and CT attenuation was similar in AIS and MIA group. They found that the retained air space was larger in non-invasive adenocarcinomas than in invasive adenocarcinomas and that this was largely due to an increased tumor tissue component and thickening of the alveolar septa in invasive adenocarcinomas, resulting in reduced air space. These findings suggested that the high CT attenuation of pure GGNs reflects the large number of tumor cells that grow along alveolar septa, and, in terms of a stepwise progression of adenocarcinoma, indicates that the lesion is progressing to invasive adenocarcinoma.[7,10] As a conclusion drawn from our study and previous studies, we could say that tumor size and CT attenuation value increases as the tumor progresses to its invasive forms. And, the combination of tumor size and CT attenuation value could help in the predictability of pathological invasiveness. The mean CT value in contrast enhanced CT also showed similar result, i.e. the mean CT value in post-contrast enhanced CT was higher in more invasive group.

However, our study has several limitations. Firstly, we only selected pure GGNs diagnosed as AIS, MIA and I-ADC; no cases of atypical adenomatous hyperplasia (AAH) and organizing pneumonia/ fibrosis were included and the small number of patients analyzed and the retrospective nature of the analysis may have affected our results. Secondly, the mean CT values we measured were the average attenuation values on the transverse slices that showed the maximum diameter of the nodule, not the density of the entire nodule. Lastly, we used two CT scanners, whose section

thicknesses were 1 mm and 2 mm; this difference might have affected the mean CT values and led to inaccuracies in measurements. Fleischner Society guidelines recommend that,[11] CT scanners with 1-mm section thickness should be used for examining GGNs. Diagramatic representation of CT images and some pathological slides have been shown in **Figure 2**.

Conclusion

From our study we can conclude that a subset of pulmonary pure GGNs have histological invasive areas that cannot be recognized as solid components on CT, and that tumor size and CT attenuation in both plain and contrast enhanced CT scan, in cases of pure GGNs could successfully predict pathological invasiveness. Maximum diameter ≥1.2 cm, mean CT value ≥-584 in plain CT and mean CT value ≥-536 in post-contrast CT could differentiate I-ADC from AIS and MIA but could not differentiate between MIA and AIS. The combination of these factors might enable a more accurate prediction of invasive adenocarcinoma than the factors individually, and further, large-scale studies should be conducted to confirm these results.

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