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FULL PAPER

Effect of CT window settings on size measurements of the solid component in subsolid nodules: evaluation of prediction efficacy of the degree of pathological malignancy in lung adenocarcinoma

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Objective: To investigate the predictive value of size measurements of the solid components in pulmonary subsolid nodules with different CT window settings and to evaluate the degree of pathological malignancy in lung adenocarcinoma.

Methods: The preoperative chest CT images and pathological data of 125 patients were retrospectively evaluated. The analysis included 127 surgically resected lung adenocarcinomas that manifested as subsolid nodules. All subsolid nodules were divided into two groups: 69 in group A, including 22 adenocarcinomas *in situ* (AIS) and 47 minimally invasive adenocarcinomas (MIA); 58 in group B that included invasive pulmonary adenocarcinomas (IPA). The size of the solid component in the pulmonary subsolid nodules were calculated in one dimensional, two dimensional and three dimensional views using lung and mediastinal windows that were recorded as 1D-SCLW, 2D-SCLW, 3D-SCLW, 1D-SCMW, 2D-SCMW and 3D-SCMW, respectively. Furthermore, the volume of solid component with a threshold of -300HU was measured using lung window (3D-SCT). All the quantitative features were evaluated by the Mann-Whitney *U* test. Multivariate analysis was used

to identify the significant predictor of the degree of pathological malignancy.

Results: The 1D-SCLW, 2D-SCLW, 3D-SCLW, 1D-SCMW, 2D-SCMW, 3D-SCMW and 3D-SCT views of group B were significantly larger than those of group A ($p < 0.001$). The multivariate logistic regression analysis indicated that 3D-SCT (OR = 1.018, 95%CI: 1.005 ~ 1.03, $p < 0.05$) was the independent predictive factor. The larger SCT was significantly associated with IPAs.

Conclusion: 3D-SCT of subsolid nodules during preoperative CT can be used to predict the degree of pathological malignancy in lung adenocarcinoma, which may provide a more objective and convenient selection criterion for clinical application.

Advances in knowledge: Applying threshold of -300 HU with lung window setting would be better than other window setting for the evaluation of solid component in subsolid nodules. Computer-aided volumetry of the solid component in subsolid nodules can more accurately predict the degree of pathological malignancy than the other dimensional measurements.

INTRODUCTION

The eighth edition of tumor, node, and metastasis (TNM) staging of lung cancer states that the clinical T stage should be based on the size of its solid component that is found within the subsolid nodules.¹ The Fleischner society further recommended the measurement of the diameter of the solid portions and the determination of the percentage of solid vs ground glass opacity components of subsolid nodules.² Previous studies have shown that the greater the extent of

the solid component, the higher the probability of nodule malignancy.³⁻⁶ However, certain controversies exist with regard to the measurement of the solid component and the optimal window setting.^{1-3,7-9} The effect of window setting display on the measurement of the subsolid nodule size is apparent. Certain studies have used electronic calipers in order to measure the diameters of the entire subsolid nodule and of the solid component on a lung window,^{3,6} while other studies reported on the use of both lung and mediastinal window settings in order to measure the subsolid

nodule and calculate the tumor disappearance ratio (TDR).^{8,9} Furthermore, Scholten et al used a semiautomatic volumetric measurement in order to identify and quantify a possible solid component under different Hounsfield unit thresholds.¹⁰ The results of this study indicated that a threshold of -300 HU with a sensitivity of 90% and a specificity of 88% provides an optimal compromise between the false positive and false negative predictions.¹⁰ This issue is very important, since the measurement of the solid component of the subsolid nodules correlates with the likelihood of tumor invasion. The present study aimed to assess the predictive value of solid component size of pulmonary SSNs for the evaluation of the pathological grade of lung adenocarcinoma using different preoperative CT window settings.

METHODS AND MATERIALS

Study population

The present retrospective study was approved by the institutional review board of our hospital and informed consent was provided from all participants for their inclusion in the study protocol. A total of 125 patients with subsolid nodules underwent surgical operation between January 2012 and June 2016. The patients were diagnosed with lung adenocarcinoma. For patients with multiple subsolid nodules, only nodules with pathological confirmation were selected. A total of two patients in the sample size exhibited two subsolid nodules each that resulted in a total of 127 subsolid nodules out of 125 patients. The inclusion criteria for the present study were as follows: (a) available thin-section chest CT (slice thickness ≤ 1 mm) prior to treatment; (b) no previous history of therapy; (c) complete surgical resection and pathological diagnosis of adenocarcinoma; (d) The maximum diameter in the transverse plane with lung window settings (window level: -450 HU; window width: 1500 HU) was 3 cm and/or less. The solid component of the subsolid nodules whose distribution was scattered was excluded.

CT scanning

All CT scans were carried out from the lung apex to the base, using three CT scanners (Aquiline 16, Toshiba, Tokyo, Japan; Light Speed 64VCT, GE Healthcare, Freiburg, Germany; Brilliance 128, Philips Medical Systems, The Netherlands). The helical scanning protocols included the following parameters: 120 kVp; 50 to 150 mAs; beam pitch, 0.516 to 0.98; slice thickness, 5 mm; matrix, 512×512 . The imaging data were reconstructed into 0.625 mm and/or 1 mm slice thickness with a soft-tissue algorithm was used for the mediastinal window image, and a lung algorithm for the lung window image.

Image analysis

The thin slice DICOM format data sets were transferred to the united imaging workstation (SW001.001version, China) and processed with the Pulmonary nodules advanced analysis tool software. This application of this software has been described previously¹¹ and was adapted in order to analyze pure ground glass opacity nodules. Initially, the subsolid nodules were segmented manually by delineating the margin with the lung window settings (window level: -450 HU; window width: 1500 HU), sequentially on all axial images. A volume of interest (VOI) was automatically generated around the total nodule and

adjusted to a threshold of -300 HU. The software can automatically detect the component of which the CT value is greater than or equal to -300 HU and calculates the three-dimensional volume (volume of solid component with threshold of -300 HU, 3D-SCT). Furthermore, the solid components that obscure the underlying lung parenchyma were segmented manually sequentially (window level: -450 HU; window width: 1500HU) using lung window settings. Subsequently, the software automatically selects the largest diameter (1D-SCLW), its perpendicular diameter and volume (3D-SCLW) and calculates the 2D-SCLW based on the bidimensional average of the largest and its perpendicular diameter. Moreover, the solid portion was delineated using mediastinal window settings (window level: 40HU, window width: 340HU) and its diameters and volume were recorded (1D-SCMW, 2D-SCMW, 3D-SCMW) (Figure 1).

A manual segmentation was conducted by Dr GU, while margin delineation and exclusion were verified by Dr LQ and Dr FL.

Pathological evaluation

The histological evaluations were carried out by hematoxylin and eosin stained slides, which were prepared using formalin-fixed paraffin-embedded tissues. The histological diagnosis was based on the new classification of lung adenocarcinoma proposed by the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society. The cancer types were classified into adenocarcinoma *in situ* (AIS), minimally invasive adenocarcinoma (MIA), and invasive pulmonary adenocarcinoma (IPA).¹¹ Based on the reported prognosis of lung adenocarcinoma,¹ the cases were divided into 2 groups, group A (AIS +MIA) and group B (IPA).

Statistical analysis

The data are presented as median (interquartile range). Statistical analyses were performed using SPSS 21.0 (IBM, Chicago, IL). All the quantitative features between the two groups were assessed by the Mann-Whitney *U* test. A *p* value of less than 0.05 ($p < 0.05$) was considered statistically significant. Multivariate logistic regression analysis was used in order to identify significant predictors of histological invasiveness and grade. In logistic regression analysis, a forward stepwise selection model was used.

RESULTS

A total of 125 patients (87 females and 38 males) with pulmonary subsolid nodules, ranging from 29 to 78 years (median, 57 years) were included. A total of 127 subsolid nodules were detected in these patients, and the assessment was performed subjectively by two thoracic radiologists. A total of two patients had two lesions each, whereas 69 cases were classified as group A (22 AIS and 47 MIA), while 58 cases were classified as group B.

The parameters 1D-SCLW, 2D-SCLW, 3D-SCLW, 1D-SCMW, 2D-SCMW, 3D-SCMW and 3D-SCT of group B were significantly larger than those of group A (Table 1, $p < 0.001$).

Logistic regression analysis was performed using the histopathological group as the dependent variable. All quantitative measurements were based on different window settings that were entered

Figure 1. Size measurements of the solid component in a 66-year-old male diagnosed with invasive adenocarcinoma in the right lower lobe with different window settings. (a) SCLW: solid component size of lung window setting; (b) SCMW: solid component size of mediastinal window setting; (c) 3D- SCT: volume of solid component with threshold of -300 HU using lung window. (d) The longitudinal axis in the histograms illustrates numbers of pixels within subsolid nodule, the horizontal axis revealed the CT number; The blue area represents the distribution of CT number below -300 HU, whereas the green one represents the distribution of CT number above -300 HU.

as independent variables. Interestingly, 3D-SCT [OR = 1.018, 95% CI: (1.005 ~ 1.03), $p < 0.05$] was the independent predictive factor. The larger SCT was significantly associated with IPAs.

DISCUSSION

The majority of studies have investigated the correlation between total tumor size and solid component size using high-resolution CT for the prediction of pathological malignancy and prognostic outcome, as well as the quantification of the solid component.^{3-6,10} In these multiple studies, it was shown that the solid portion can be viewed with different window settings. However, no consensus has been established regarding the window setting

that is considered as the optimal method for measuring these parameters. The correct recognition and measurement of the solid portion within subsolid nodules is essential for the evaluation of the follow-up, and the management, and prediction of prognosis of the patients. The present study differs from the aforementioned studies in several ways. Firstly, we included AISs and MIAs into the low grade malignancy group, based on the tumor-grading system.¹² Moreover, a -300 HU area and/or higher was defined and calculated as the solid component, according to previous reports and our clinical experience.^{10,13} Furthermore, the volume of the solid portions was measured based on three-dimensional computer-quantified CT number analysis, which can reflect the actual internal distribution of the tumor, resulting in a more objective and convenient method that is required for clinical application.

The NELSON study indicated the effectiveness of 3D volumetric evaluation in the screening and follow-up of lung nodule progression.¹⁴ Lee et al evaluated the solid components of 59 subsolid nodules using CT in three-dimensional (3D), two-dimensional (2D) and one-dimensional (1D) planes, and compared the CT measurements with the pathological measurements.³ The data indicated a significant correlation between the size of the solid component determined by the CT scan and the pathological invasiveness. The 3D measurements tended to be larger than the size of the invasive component. The possibility of the different inflation state of lung tissues must be considered, whereas the shrinkage of the soft tissue may occur in the resected specimens. Furthermore, Shikuma et al reported the use of Hounsfield unit (HU) thresholds of CT images for the prediction of pathological

Table 1. Quantitative measurements between the two groups

	Group A ($n = 69$)	Group B ($n = 58$)	p
1D-SCLW (mm)	5.0 (1.0, 8.0)	13 (9.75, 19.0)	<0.001
2D-SCLW (mm)	4.0 (1.0, 6.25)	11.5 (7.75, 15.125)	<0.001
3D-SCLW (mm^3)	31.0 (1.45, 119.95)	460.55 (168.725, 914.9)	<0.001
1D-SCMW (mm)	0.00 (0.00, 2.0)	8.5 (3.0, 12.25)	<0.001
2D-SCMW (mm)	0.0 (0.0, 1.5)	6.5 (2.0, 10.0)	<0.001
3D-SCMW (mm^3)	0.0 (0.0, 5.25)	155.75 (7.65, 337.0750)	<0.001
3D-SCT (mm^3)	3.0 (0.0, 64.5)	525 (174.75, 942.5)	<0.001

Data are presented as median (interquartile range).

lymph node metastasis and tumor invasiveness of cT1N0M0 lung adenocarcinoma.¹³ These findings were based on 1D, 2D and 3D evaluations.¹³ It was deduced that 3D volumetric evaluations were useful for predicting pathological lymph node metastases and tumor invasiveness. Therefore, in the present study, the solid component size was measured using 3D volumetric evaluations in order to obtain less variance in the measurements. Moreover, HU thresholds were adopted for the measurements. The present analysis demonstrated that the 1D-SCLW, 2D-SCLW, 3D-SCLW, 1D-SCMW, 2D-SCMW, 3D-SCMW and 3D-SCT of IPA were significantly larger than those of AIS and MIA.

It is important to note that in the present routine clinical work, certain ground glass opacity nodules (GGN) were encountered that manifested as a “solid” portion, which obscured the underlying lung structure with lung window settings. These nodules could not be identified with mediastinal window settings, resulting in a controversial GGNs classification. Consequently, in the present study, the use of the threshold of –300 HU was applied in order to define the solid component. The threshold of –300 HU was quoted according to previous reports by Shikuma et al and Scholten et al.^{10,13} The prior investigator reported that the threshold values of –800 and –300 HU were useful for the prediction of the pathological lymph node metastasis and tumor invasiveness of lung adenocarcinoma based on 3D evaluations. It is interesting to note that tumors with a threshold value of –300 HU and/or higher were defined as solid tumors, and those with threshold values between –800 and –301 HU were defined as ground glass opacity tumors.^{10,13} Subsequent studies suggested that the segmentation of –300 HU could be selected for the measurement of the diameter of the solid component. Therefore, we believe that the threshold of –300 HU was essential for the distinction of the solid part from the GGO portion. However, with regard to the estimation of the solid component, the previous clinical experience and the majority of the studies have demonstrated that its size that was displayed at the lung window setting, correlated with that of the pathological invasiveness compared with other window settings.^{3,7,8,15} Thus, we evaluated all the size measurements of the solid component with different window settings using logistic regression analysis.

The data indicated that 3D-SCT was an independent predictor of pathological high-grade malignancy. A larger 3D-SCT was significantly associated with IPAs.

The current study has several limitations. Firstly, this is a single center study and further studies that will include patients from multiple centers are required to confirm the present results, notably the conclusions with regard to the objective definition and predictive value of the volume of solid component with a threshold of –300 HU in the subsolid nodule. Furthermore, this is a retrospective study and includes inevitable selection bias, which requires the exclusion of the cases with scatter consolidation. These cases were difficult to measure on thin-section CT images. Finally, we did not perform the imaging-pathology correlation study, since a single representative pathology slide was used for each case, which may not be accurate and cannot reflect the measurements, whereas the pathological specimens were not consecutively sectioned in the same slice as the CT image.

In conclusion, 3D volume measurements of the solid component with a threshold of –300 HU can be used to predict the degree of pathological malignancy, which may provide a reference for operation. These findings imply that the application of the threshold of –300 HU with the lung window setting would be better than the mediastinal window setting for the evaluation of solid components in subsolid nodules. The external validation is required to assess whether this selection could be adopted for the measurement of the solid components in subsolid nodules.

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