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Optimization of CT windowing for diagnosing invasiveness of adenocarcinoma presenting as sub-solid nodules

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ABSTRACT

Purpose: To evaluate the optimal window setting to diagnose the invasiveness of lung adenocarcinoma in sub-solid nodules (SSNs).

Methods: We retrospectively included 437 SSNs and randomly divided them 3:1 into a training group (327) and a testing group (110). The presence of a solid component was regarded as indicator of invasiveness. At fixed window level (WL) of 35 Hounsfield Units (HU), two readers adjusted the window width (WW) in the training group and recorded once a solid component appeared or disappeared on CT images acquired at 120 kVp. The optimal WW cut-off value to differentiate between invasive and pre-invasive lesions, based on the receiver operating characteristic (ROC) curve, was defined as "core" WW. The diagnostic performances of the mediastinal window setting (WW/WL, 350/35 HU) and core window setting were then compared in the testing group.

Results: Of the 437 SSNs, 88 were pre-invasive [17 atypical adenomatous hyperplasia (AAH) and 71 adenocarcinoma in situ (AIS)], 349 were invasive [233 minimally invasive adenocarcinoma (MIA), 116 invasive adenocarcinoma (IA)]. In training group, the core WW of 1175 HU was the optimal cut-off to detect solid components of SSNs (AUC:0.79). In testing group, the sensitivity, specificity, positive, negative predictive value, and diagnostic accuracy for SSN invasiveness were 49.4%, 90.5%, 95.7%, 29.7%, and 57.3% for mediastinal window setting, and 87.6%, 76.2%, 91.6%, 76.2%, and 85.5% for core window setting.

Conclusion: At 120 kVp, core window setting (WW/WL, 1175/35 HU) outperformed the traditional mediastinal window setting to diagnose the invasiveness of SSNs.

1. INTRODUCTION

Pulmonary sub-solid nodules (SSNs) on chest computed tomography (CT) are grouped into non-solid nodules [synonymous with pure ground-glass nodules (GGN)] and part-solid nodules; adenocarcinoma is the most common underlying histology type [1]. The International

Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society proposed a new classification system for lung adenocarcinoma in 2011, dividing lung adenocarcinoma into two main groups: pre-invasive lesions, including atypical adenomatous hyperplasia (AAH) and adenocarcinoma in situ (AIS); and invasive lesions, including minimally invasive adenocarcinoma (MIA) and invasive

Abbreviations: SSN, sub-solid nodule; AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; IA, invasive adenocarcinoma

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adenocarcinoma (IA) [2]. Several studies have shown that the presence of the solid component is related to the probability of nodule invasiveness [1,3–5]. The use of mediastinal window setting to depict solid component of SSNs allows better agreement between radiologists [6]. However, it is known that SSNs are rendered partially invisible when viewed on mediastinal window setting, where small solid components that represent early signs of invasiveness may be missed [4,7]. The traditional mediastinal window setting (WW 350HU, WL 35HU) displays solid lesion components with density above -140HU [8]. Previous studies found a lower density range (-400 or -300HU) to be more appropriate for the distinction of part-solid lesions from GGNs [3,9,10]. An optimized CT window setting is necessary to determine the presence of a solid component in SSNs.

This study aimed to optimize the CT window setting at 120 kVp, by assessing the best window width to detect the solid lesion component as indicator of invasiveness of lung adenocarcinoma in SSNs, with histopathology as reference standard.

2. MATERIALS AND METHODS

2.1. Study population

We reviewed patients with resected SSNs from Tianjin Medical University Cancer Institute and Hospital who were evaluated from November 2011 to October 2017. All SSNs were confirmed by post-operative histopathological analysis to be early stage adenocarcinomas (pre-invasive lesions: AAH, AIS; invasive lesions: MIA, IA). All patients underwent CT scanning within 3 weeks of surgery. The included SSNs were randomly divided (3:1 ratio) into a training group and a testing group. The institutional review board approved the study and waived the need for informed consent because of its retrospective design and the use of anonymized data.

2.2. CT protocol

Non-contrast chest CT examinations were conducted using a Discovery CT750 HD (GE Medical Systems), Lightspeed 16 (GE Medical Systems, Milwaukee, WI), or Somatom Sensation 64 (Siemens Healthineers, Forchheim, Germany) CT system. The scan range was from pulmonary apex level to below the diaphragm. The scanning protocol was as follows: tube voltage 120 kVp with automatic tube current modulation. For the GE CT systems, pitch was 0.984, the reconstructed slice thickness 1.25 mm, and the reconstruction algorithm were “Standard” for mediastinal window setting and “Lung” for lung window setting. For the Siemens CT system, pitch was 0.95, the reconstructed slice thickness 1.5 mm, and the reconstruction algorithms were “B30f” for mediastinal window setting and “B60f” for lung window setting.

2.3. CT image analysis

Two radiologists (X.C., S.F.) with 5 and 9 years of experience in chest radiology, respectively, reviewed the CT images without knowledge of the pathology result. SSNs were identified in lung window setting. Each SSN was first classified as a part-solid or non-solid nodule according to the presence or absence of a solid component observed in the mediastinal window setting [window width (WW)/window level (WL), 350/35 HU]. In case of disagreement, final classification was determined by consensus of the two radiologists. Thereafter, the individual radiologists adjusted WW (at fixed WL of 35 HU) in the training group and recorded once a solid component appeared or disappeared on CT images acquired at 120 kVp; the mean WW for the two radiologist HU values was considered as final result (Fig. 1).

2.4. Histopathological evaluation

The diagnosis and categorization of the pathological specimens were evaluated by two lung pathologists (one junior, one senior). The specimens were fixed in formalin and embedded in paraffin. The adenocarcinoma classification was followed by the IASLC/ATS/ERS adenocarcinoma classification [2]. Immunohistochemistry was performed in case of equivocal histopathological classification under light microscopy.

2.5. Statistical analysis

All nodules ($n = 437$) were randomly divided (3:1) into a training group ($n = 327$) and testing group ($n = 110$) by using a random number generator in SPSS. Data were reported as numbers (%) for categorical variables. The Pearson's Chi-square test was used to test for the difference between categorical variables. Normally distributed data were presented as mean (standard deviation [SD]) and were compared using Student's t-test. Non-normally distributed data were presented as medians (inter-quartile range [IQR]) and were evaluated by Mann-Whitney U test. Interobserver agreement regarding the presence or absence of the solid component in the mediastinal window setting was evaluated using Cohen's kappa test and the WW value was evaluated using intraclass correlation coefficient (ICC). The kappa or ICC value was divided into: poor agreement ($\text{kappa} \leq 0.40$); fair agreement ($> 0.40, \leq 0.60$); good agreement ($> 0.60, \leq 0.75$); and excellent agreement (> 0.75) [11]. A receiver operating characteristic (ROC) curve was constructed to assess the optimal WW cut-off value for the detection of a solid component on CT images as indicator of invasiveness, based on pathology results as reference. The optimal WW cut-off value (with WL 35 HU) was defined as “core” window setting. The diagnostic performances of the mediastinal window setting (WW/WL, 350/35 HU) and core window setting were then compared in the testing group. All statistical analyses were performed using SPSS software version 20.0 (IBM, New York, US).

3. Results

3.1. Clinical and nodule characteristics

A total of 437 resected SSNs in 396 patients were identified. These nodules were confirmed to be pre-invasive lesions in 88 cases (17 AAH, 71 AIS) and invasive lesions in 349 cases (233 MIA; 116 IA), none of them were invasive mucinous adenocarcinoma. The median diameter (IQR) of the lesions was 13.3 (9.6–18.4) mm. Patients had a mean age of 56.9 years (SD, 9.2), 73.2% were female (290/396). The training group ($n = 327$) included 67 pre-invasive lesions (13 AAH, 54 AIS) and 260 invasive lesions (174 MIA; 86 IA), and the testing group ($n = 110$) included 21 pre-invasive lesions (4 AAH, 17 AIS) and 89 invasive lesions (59 MIA; 30 IA).

3.2. Performance in the training group

3.2.1. Mediastinal window setting

As shown in Table 1, based on mediastinal window setting, 180 nodules were categorized as non-solid nodules, and 147 were categorized as part-solid nodules. The kappa value for the agreement in presence of a solid component between the two readers was 0.87. Pathology results in the non-solid nodules showed 13 cases of AAH, 42 AIS, 119 MIA, and 6 IA, and in the part-solid nodules, 0 cases of AAH, 12 AIS, 55 MIA, and 80 IA. For mediastinal setting, sensitivity, specificity, PPV, NPV, and diagnostic accuracy to discriminate between pre-invasive and invasive lesions were 51.9%, 82.1%, 91.8%, 30.6%, and 58.1%, respectively.

Fig. 1. A: 65-year old male patient with SSN (AIS) in the right upper lobe identified in lung window setting, and no solid component in mediastinal window setting. The solid component lesion became visible at window width of 1495 HU (A4: reader 1) and 1512 HU (A5: reader 2), with final window width 1504 HU. B: 49-year old female patient with SSN (MIA) in the left lower lobe identified in lung window setting, and no solid component in mediastinal window setting. The lesion became visible at window width of 484 HU (B4: reader 1) and 502 HU (B5: reader 2), with final window width 493 HU. C: 58-year old female patient with SSN (IA) in the right upper lobe identified in lung window setting, and presence of solid component in mediastinal window setting. The lesion disappeared at window width of 96 HU (C4: reader 1) and 81 HU (C5: reader 2), with final window width 89 HU.

3.2.2. Core window setting

The ICC value for the agreement of WW between two readers was 0.98. The ROC curve analysis showed that a WW of 1175 HU (AUC: 0.79) was the best cut-off for the detection of a solid component on CT images as indicator of invasiveness, based on pathology results as reference (Fig. 2). Using this as the core window setting (WW/WL, 1175/35 HU), 69 nodules were categorized as non-solid, and 258 were categorized as part-solid. Pathology results in the non-solid nodules,

showed 11 cases of AAH, 26 AIS, 31 MIA, and 1 IA, and in the part-solid nodules, 2 cases of AAH, 28 AIS, 143 MIA, and 85 IA as shown in Table 1. For core window setting, sensitivity, specificity, PPV, NPV, and diagnostic accuracy for discrimination between pre-invasive and invasive lesions were 87.7%, 55.2%, 88.4%, 53.6%, and 81.0%, respectively.

Table 1

Overview of the differentiation of histopathological subtype in SSNs per window setting in the training group

Parameter	Pre-invasive lesions		Invasive lesions	
	AAH (n = 13)	AIS (n = 54)	MIA (n = 174)	IA (n = 86)
Mediastinal window setting				
Non-solid	13 (100.0%)	42 (77.8%)	119 (68.4%)	6 (7.0%)
Part-solid	0 (0.0%)	12 (22.2%)	55 (31.6%)	80 (93.0%)
Core window setting				
Non-solid	11 (84.6%)	26 (48.1%)	31 (17.8%)	1 (1.2%)
Part-solid	2 (15.4%)	28 (51.9%)	143 (82.2%)	85 (98.8%)

SSN: sub-solid nodule; AAH: atypical adenomatous hyperplasia; AIS: adenocarcinoma in situ; MIA: minimally invasive adenocarcinoma; IA: invasive adenocarcinoma.

Fig. 2. The receiver operator characteristic curve accuracy of mediastinal window setting and new WW setting.

Table 2

Overview of the differentiation of histopathological subtype in SSNs per window setting in the testing group.

Parameter	Pre-invasive lesions		Invasive lesions	
	AAH (n = 4)	AIS (n = 17)	MIA (n = 59)	IA (n = 30)
Mediastinal window setting				
Non-solid	4 (100.0%)	15 (88.2%)	39 (66.1%)	6 (20.0%)
Part-solid	0 (0.0%)	2 (11.8%)	20 (33.9%)	24 (80.0%)
Core window setting				
Non-solid	4 (100.0%)	12 (70.6%)	11 (18.6%)	0 (0.0%)
Part-solid	0 (0.0%)	5 (29.4%)	48 (81.4%)	30 (100.0%)

SSN: sub-solid nodule; AAH: atypical adenomatous hyperplasia; AIS: adenocarcinoma in situ; MIA: minimally invasive adenocarcinoma; IA: invasive adenocarcinoma.

3.3. Performance in the testing group

As shown in Table 2, when using the mediastinal window setting, 64 nodules were categorized as non-solid nodules (4 AAH, 15 AIS, 39 MIA and 6 IA), and 46 were categorized as part-solid nodules (0 AAH, 2 AIS, 20 MIA and 24 IA). The sensitivity, specificity, PPV, NPV, and diagnostic accuracy for discrimination between pre-invasive and invasive lesions were 49.4%, 90.5%, 95.7%, 29.7%, and 57.3%, respectively. On core window setting, 27 nodules were non-solid (4 AAH, 12 AIS, 11 MIA and 0 IA); 83 nodules were categorized as part-solid (0 AAH, 5 AIS, 48 MIA and 30 IA). The sensitivity, specificity, PPV, NPV, and diagnostic accuracy for discrimination between pre-invasive and invasive lesions were 87.6%, 76.2%, 94.0%, 76.2%, and 85.5%, respectively.

4. Discussion

This study demonstrated that an optimized, ‘core’ window setting (WW 1175 HU; WL 35 HU) outperformed the traditional mediastinal window setting in determining the solid component of an SSN. The solid component in SSNs is directly related to the invasiveness of the lesion. In the training group, 1175 HU was found to be the best window width cut-off to detect a solid component. Compared to mediastinal window setting, core window setting improved the sensitivity for invasive SSNs (87.6% vs. 49.4%) in the testing group, especially for MIA (81.4% vs. 33.9%), and improved the diagnostic accuracy (85.5% vs. 57.3%).

The Eighth Edition Lung Cancer Stage Classification [12] classified MIA for the first time as T1a (mi), where resection is now indicated [13]. Near 100% survival can be achieved after resection of MIA. Many studies have verified the correlation between the presence of a solid component of SSNs in CT and the invasiveness of lesions [14]. Thus, distinction between MIA and pre-invasive lesions by accurate detection of a solid component of SSNs in CT is essential. However, small solid or semisolid components may be invisible in mediastinal window setting. This is especially the case for the histopathology subtype MIA [5,15–17]. Our study showed a similar result; while in 80.0% (24/30) of IAs a solid component was identified when evaluated in mediastinal window setting, this was the case in only 33.9% (20/59) of MIAs. The sensitivity and diagnostic accuracy for the differentiation between pre-invasive and invasive adenocarcinoma were 49.4–51.9% and 57.3–58.1%, respectively, in the regular mediastinal window setting. This improved to 87.6–87.7% and 81.0–85.5% in core window setting. This comes, however, at a slight decrease in specificity for pre-invasive lesions (from 82.1–90.5% to 55.2–76.2%).

In order to improve diagnostic performance for invasive SSNs, a better method to determine the presence of a solid component is needed. It is well recognized that the apparent size of a lesion in a CT image can be altered by adjusting the window width and window level [18]. The window level, also known as window center, is the midpoint of the range of the HU displayed. The window width, as the name suggests, is the measure of the range of HU that an image contains. A wider window width will display a wider range of HU and provide more precise detail [19,20]. The previous studies used three-dimensional CT segmentation techniques and thresholds density from -166 to -800 HU to find the optimal window setting for measuring the SSNs [3,9,17,21–23]. One prior study evaluated the possibility of a new window setting for detection of solid components in SSN [24]. This study showed that a window width of 1250 HU and window level of 40HU was useful for viewing the invasive components of SSNs. However, this study had several limitations. First, the diagnostic performance of the mediastinal window setting and the new window setting was not compared, leaving open what is the best window setting to analyze the presence of a solid component in SSNs. Second, the size of the study population was relatively small, 209 cases were analyzed (102 pre-invasive; 107 invasive). In our study, we provided an optimized window level cut-off to differentiate invasive from pre-invasive

lesions, and directly compared its performance with mediastinal window width as current reference standard, with a training group and a testing group for validation.

Based on our study results, we propose adjustment of the window width as an easy and useful method for diagnosing the invasiveness of SSNs. The use of the improved window setting will change some of our past perceptions. For example, we know that, beyond the presence of a solid component, the solid diameter of SSN is related to the nodule invasiveness. The Lung CT screening reporting and data system (LungRADS 1.1) [25] considers a solid component diameter of 6 mm in part-solid nodules as a cut-off value between probably benign (LungRADS 3) and suspicious (LungRADS 4) in screen-detected lesions. In addition to the size, visual assessment of the radiologist of suspicious imaging features justifies an upgrade to a higher risk category. Although several previous studies have shown that morphological features can be useful in differentiating pre-invasive from invasive SSNs [26,27], how to quantify these features, which are currently rather subjective, is still a challenge. Our core window setting based on the adjustment of window width results in a new feature for differentiating pre-invasive from invasive SSNs. If and how size criteria and morphological features can further improve differentiation between pre-invasive and invasive lesions in core window setting deserves additional research.

Our study has several limitations. First, our study population may reflect a degree of selection bias since our data only included SSNs with known pathology from a tertiary referral cancer center, and most SSNs were confirmed to be invasive lesions. Second, our study did not consider the impact of different CT scan parameters. Since the increased utilization of low-dose CT lung cancer screening programs, the influence of more image noise and low tube voltage (100kVp with or without Sn filter) should be considered in future studies. In addition, this is a single-center study; the effectiveness of our results needs to be further verified in other centers and in Western populations.

5. Conclusions

A core window setting (WW/WL, 1175/35 HU) outperformed the traditional mediastinal window setting (WW/WL, 350/35 HU) for detecting a solid component of SSNs as indicator of invasiveness at 120 kVp. In core window setting, MIA could be well differentiated from pre-invasive lesions.

CRedit authorship contribution statement

Xiaonan Cui: Conceptualization, Methodology, Writing - original draft, Formal analysis. **Shuxuan Fan:** Validation, Writing - review & editing. **Marjolein A. Heuvelmans:** Writing - review & editing, Supervision. **Daiwei Han:** Writing - review & editing. **Yingru Zhao:** Resources, Data curation. **Harry J.M. Groen:** Writing - review & editing. **Monique D. Dorrius:** Writing - review & editing. **Matthijs Oudkerk:** Supervision. **Geertuida H. de Bock:** Supervision, Writing - review & editing. **Rozemarijn Vliegthart:** Supervision, Writing - review & editing, Project administration. **Zhaoxiang Ye:** Investigation, Supervision, Project administration.

Declaration of Competing Interest

All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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