Original Article

The predictive value of computed tomography value on high-resolution images in differentiating invasive from indolent lung adenocarcinoma

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Background: Invasive adenocarcinoma (IA) has a worse prognosis and different clinical management strategies compared to indolent lung adenocarcinoma including adenocarcinoma in situ (AIS) and minimally IA (MIA). The purpose of this study was to evaluate the predictive value of computed tomography (CT) value in differentiating invasive from indolent lung adenocarcinoma.

Methods: The pathological diagnoses and imaging data of confirmed lung adenocarcinomas manifested as lung nodules with homogeneous internal density which were surgically resected between August 2021 and July 2022 were retrospectively analyzed. Differences in CT values between invasive and indolent lung adenocarcinomas were compared in the primary cohort (n=766), and receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off value. The predictive performance of the cut-off value was evaluated in the validation cohort (n=341).

Results: A total of 1,107 lung nodules from 1,014 patients were included in the total cohort. The CT values had a significant difference between invasive and indolent lung adenocarcinomas (P<0.001). Using the primary cohort, we determined the optimal cut-off value of –415 Hounsfield units (HU) of the CT value based on ROC curve, which showed good discrimination between IA and AIS/MIA in both the primary and validation cohorts (sensitivity, 85.98% and 87.42%, specificity, 87.67% and 84.74%, respectively).

Conclusions: The CT value of >–415 HU could be an effective predictor of invasive lung adenocarcinoma, thereby providing an appropriate clinical decision guide.

Keywords: Lung adenocarcinoma; computed tomography (CT); differential diagnosis; invasiveness

Submitted Aug 27, 2023. Accepted for publication Nov 17, 2023. Published online Jan 04, 2024.
doi: 10.21037/tcr-23-1548
View this article at: https://dx.doi.org/10.21037/tcr-23-1548

Introduction

According to the 8th edition of the tumour, node, and metastasis (TNM) staging of lung cancer, adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) are grouped into the category of Tis-T1mi and assumed to be indolent lesions due to the extremely good prognosis (1). In contrast to the poor prognosis of invasive adenocarcinoma (IA), patients would have a nearly 100% disease-free survival if these indolent lesions were completely resected (2,3). In addition, previous evidences also supported that sublobar resection was appropriate for indolent lung adenocarcinoma (3). Therefore, when pulmonary nodules are encountered in clinical practice, it is of great significance to accurately judge the degree

of infiltration of malignant lesions to determine optimal follow-up or resection strategies.

High-resolution thin-section computed tomography (CT) allows comprehensive and non-invasive display of characteristics of pulmonary nodules. Based on this, a considerable effort has been exerted to distinguish invasive and indolent lesions. Both CT features such as tumor diameter, irregular shape, and standardized uptake value and quantitative analysis have showed an association with pathological invasiveness (4-7). It is worth noting that the value of mean CT (mCT) value has been demonstrated in previous studies in predicting the invasiveness of lung adenocarcinoma (5,6,8). A previous study even showed that the mCT value was the only significant predictor (9). However, pulmonary nodules with heterogeneous density, such as mixed ground glass nodules, may have significant internal heterogeneity and mCT values are not a good indicator of pathological invasiveness.

Following this idea and avoiding pathological heterogeneity as much as possible, pulmonary nodules with homogeneous internal density were selected as research objects in the present study to identify an optimal point in the entire continuous CT value cohort for differentiating invasive from indolent lung adenocarcinoma, and to test its predictive value in another cohort. We present this article in accordance with the STARD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1548/rc).

Highlight box

Key findings

- The computed tomography (CT) value can be used as an effective tool to predict the pathological invasiveness of lung adenocarcinoma.

What is known and what is new?

- Large tumor diameter, irregular shape, and high density are generally considered markers of aggressiveness. The value of CT values in this regard has been reported in several previous studies, but no commonly accepted reference value has yet been established. The results of our study demonstrated that the CT value of >−415 Hounsfield units was an effective predictor of invasive lung adenocarcinoma.

What is the implication, and what should change now?

- Whether the lesions have progressed to invasive adenocarcinomas needs to be considered when the higher CT attenuation of internal components exceeds the critical value. Therefore, CT values could help clinicians choose an appropriate surgical method and follow-up plan.

Methods

Patients

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China (No. 2023-736). Individual informed consent was waived due to the retrospective nature of this study.

The clinical data of patients who underwent pulmonary nodule resection in our hospital between August 2021 and July 2022 were continuously reviewed. Lesions with the following criteria were included in this study: (I) pathologically confirmed lung adenocarcinomas, including AIS, MIA, and IA; (II) high-resolution CT examination within 1 month before surgery; (III) the maximum diameter of the lesion was ≤3 cm; (IV) no biopsy or any anti-tumour treatment was performed before surgery. The exclusion criteria were as follows: (I) pulmonary nodules with heterogeneous internal density, such as mixed ground glass nodules or with distinct cystic airspace; (II) there were diffuse lesions distributed around lung nodules; (III) lung nodules with an extremely irregular shape, of which the CT value was difficult to be measured. Finally, 1,107 eligible lung nodules in 1,014 patients were included in the present study, as shown in *Figure 1*. The entire cohort was divided into the primary cohort (August 2021 to April 2022, n=766) and the validation cohort (May 2022 to July 2022, n=341).

CT image acquisition and analysis

Preoperative chest non-enhanced CT scans were performed from lung apex to base at mid-inspiration during a held breath using a Lightspeed CT system (General Electric Healthcare, Milwaukee WI, USA) or Brilliance CT 64 (Philips Medical Systems, Best, the Netherlands) with a section thickness of 1.0 or 1.25 mm. The readings were based on the lung window setting [width, 1,500 Hounsfield units (HU); level, −500 HU] and mediastinal window setting (width, 400 HU; level, 40 HU). The HU, also referred to as the CT unit, is a relatively quantitative measurement of density used by radiologists in the interpretation of CT images. Distilled water (at standard temperature and pressure) is arbitrarily defined as 0 HU, and air is defined as −1,000 HU.

Two thoracic surgeons independently viewed these images and selected eligible lung nodules. CT parameters were measured independently by two observers, who were

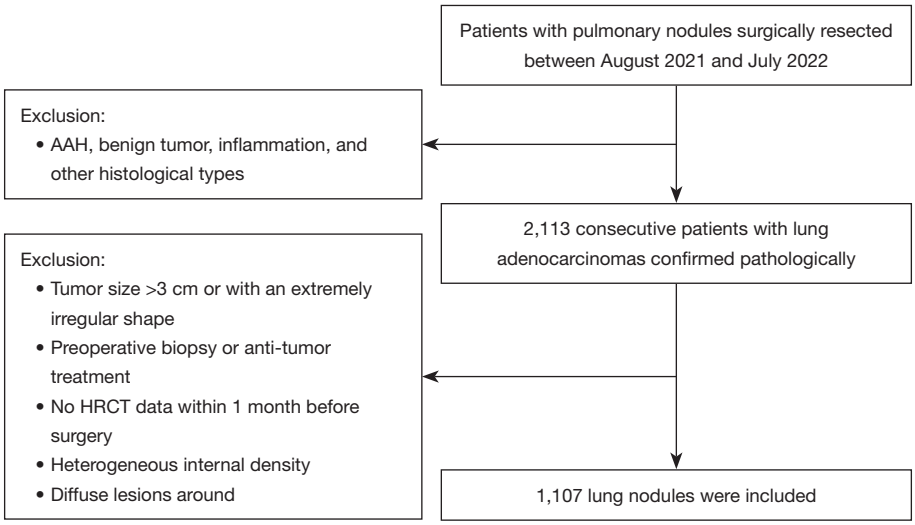

Figure 1 Patient flowchart. AAH, atypical adenomatous hyperplasia; HRCT, high-resolution computed tomography.

blinded to the histopathological results. Discrepancies in measurement and interpretation between observers were resolved by consensus. The CT value was measured by using the circle region of interest (ROI) cursors to trace along the inner edge of lung nodules as large as possible on the axial section with the maximum diameter and upper and lower adjacent slices on the lung window, avoiding the portions of apparent vessels and bronchioles (*Figure 2*). The measurement variation was corrected by calculating the mean value from the two observers. In addition, the maximum diameter of lung nodules was also recorded.

Pathological evaluation

The specimens used for pathological diagnosis were derived from surgical resection. All specimens were evaluated by two pathologists at our institution after pathological preparation with formalin fixation and haematoxylin and eosin (HE) staining was completed. Any disagreement was resolved by a mutual consensus or consulting with a third senior pathologist. Pathological diagnoses were based on the criteria of the latest World Health Organization (WHO) classification of lung tumors and classified as AIS, MIA, and IA. In the present study, AIS and MIA were classified as indolent adenocarcinomas.

Statistical analysis

Clinical characteristics of patients and lung nodules were statistically described using the mean ± standard deviation (SD) and frequency (percentage). The differences in CT values between invasive and indolent lung adenocarcinomas were analyzed using the Mann-Whitney *U* test. Receiver operating characteristic (ROC) curve and the area under the curve (AUC) were used to evaluate the differentiating capacity of the CT value. The optimal cut-off value was determined by the maximum value of the Youden's index. The sensitivity and specificity of the primary cohort and the validation cohort were obtained using the cut-off value. A P value of less than 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS 25.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

A total of 1,107 lung nodules in 1,014 patients were included in the present study. All patients underwent surgical resection and all lesions were pathologically confirmed as lung adenocarcinoma. Other lesions such as benign lesions or atypical adenomatous hyperplasia (AAH) were excluded. There were 766 lung nodules in the primary cohort and 341 lung nodules in the validation cohort. Patients' baseline characteristics in the primary and validation cohorts are listed in *Table 1*. In the primary cohort, the mean age at diagnosis was 53.22±13.187 years (range, 17–84 years); 235 lesions were in men and 531 in women. The maximum diameter of lung nodules was 11.09±5.688 mm (range, 3–

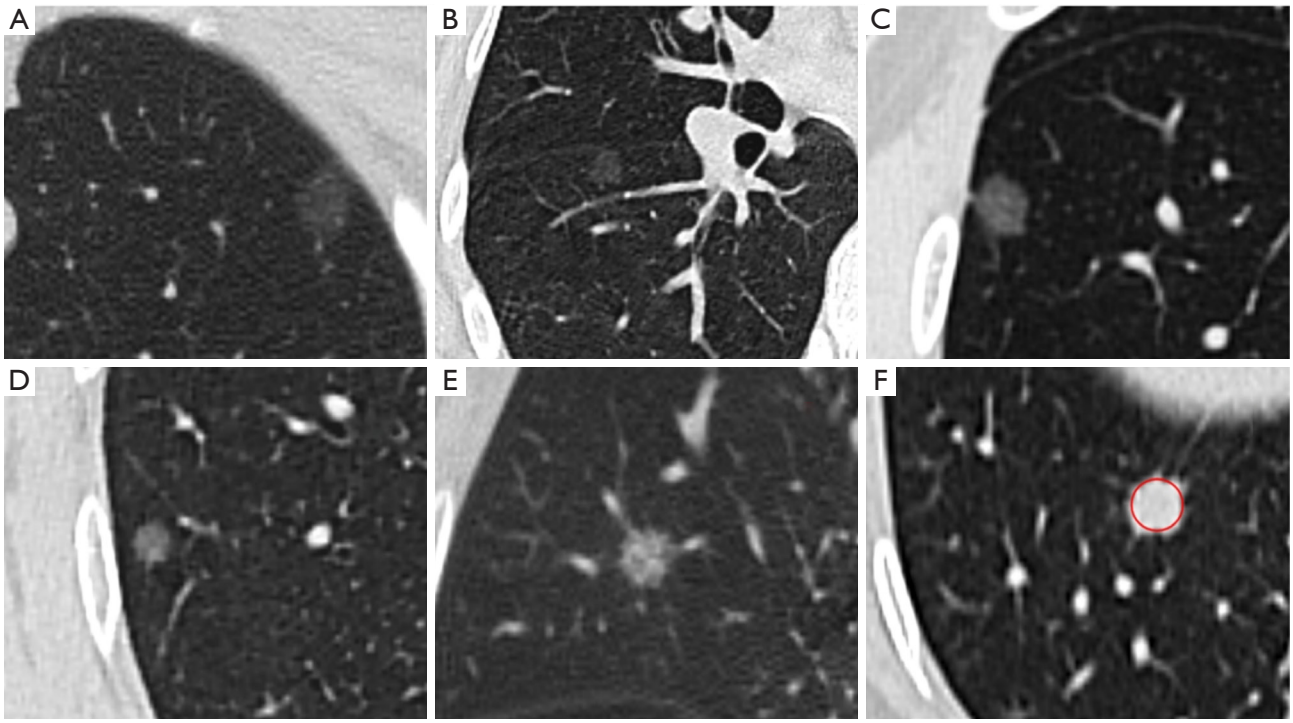

Figure 2 The measurement method of CT value and typical HRCT images of different pathological subtypes of lung nodules with homogeneous internal density. The CT value was measured by using the circle ROI cursors to trace along the inner edge of lung nodules as large as possible on the slice containing the maximum tumour diameter [as shown by the red circle in (F)]. (A) AIS with a diameter of 10 mm and −698 HU CT value in a 25-year-old female. (B) MIA with a diameter of 9 mm and −763 HU CT value in a 42-year-old female. (C) MIA with a diameter of 10 mm and −506 HU CT value in a 28-year-old male. (D) MIA with a diameter of 6 mm and −446 HU CT value in a 47-year-old male. (E) IA with a diameter of 10 mm and −272 HU CT value in a 66-year-old female. (F) IA with a diameter of 11 mm and 61 HU CT value in a 51-year-old female. CT, computed tomography; HRCT, high-resolution computed tomography; ROI, region of interest; AIS, adenocarcinoma in situ; HU, Hounsfield units; MIA, minimally invasive adenocarcinoma; IA, invasive adenocarcinoma.

30 mm). In the validation cohort, the mean age at diagnosis was 53.35±13.161 years (range, 17–83 years); 91 lesions were in men and 250 in women. The maximum diameter of lung nodules was 11.32±5.394 mm (range, 4–30 mm).

Differences in CT value between IA and AIS/MIA

In the primary cohort, the median of CT values was −547.950 HU (range, −789.5 to −173.0 HU) in AIS/MIA patients (n=438) and 2.600 HU (range, −747.1 to 153.8 HU) in IA patients (n=328). In the validation cohort, the median of CT values was −553.800 HU (range, −771.2 to −60.3 HU) in AIS/MIA patients (n=190) and −90.100 HU (range, −757.4 to 86.9 HU) in IA patients (n=151). Significant differences were observed in CT values between the AIS/MIA and IA patients in both the primary and validation cohorts (P<0.001) (*Figure 3*).

ROC analysis for the CT value in the primary cohort

A ROC curve analysis was performed using the primary cohort to evaluate the differentiating capacity of the CT value. The AUC of the ROC curve was 0.923 [95% confidence interval (CI): 0.902–0.944] (*Figure 4*). The optimal cut-off value was identified as −415 HU. The sensitivity and specificity at this point were 85.98% and 87.67%, respectively. Details are given in *Table 2*.

Validation of the cut-off value

In the validation cohort, we verified the differentiating capacity of this cut-off value, showing sensitivity and specificity of 87.42% and 84.74%, respectively. The positive and negative predictive value were 81.99% and 89.44%, respectively. Details are given in *Table 2*. In addition, we

Table 1 Clinical characteristics of patients and lung nodules in the primary and validation cohorts

Characteristics	Primary cohort	Validation cohort
No. of patients	706	308
Total No. of lung nodules	766	341
No. of lung nodules per patient		
1	652	276
2	48	31
3	6	1
Age at diagnosis (years)[a]	53.22±13.187 [17–84]	53.35±13.161 [17–83]
Male: female, n	235:531	91:250
Location of lung nodules, n		
Left upper lobe	208	86
Left lower lobe	119	54
Right upper lobe	216	98
Right middle lobe	68	30
Right lower lobe	155	73
Maximum diameter of lung nodules (mm)[a]	11.09±5.688 [3–30]	11.32±5.394 [4–30]

[a], data are mean ± standard deviation [range].

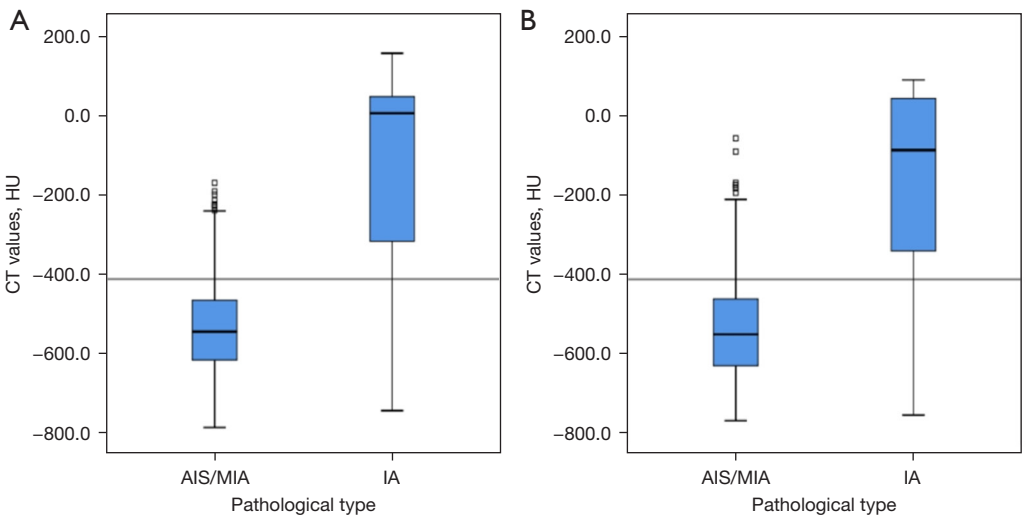

Figure 3 Comparison of the CT values between IA and AIS/MIA patients in (A) the primary cohort and (B) the validation cohort. CT, computed tomography; HU, Hounsfield units; IA, invasive adenocarcinoma; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma.

analyzed the proportion of IA in different ranges of CT value. The curve in *Figure 5* showed the trend of the proportion of IA with the increase of CT value. The results demonstrated that the proportion of IA in the range of –415 to –300 HU was significantly different from that in each range of CT value less than –415 HU, and this difference was statistically significant (*Table 3*). Similarly, we verified this difference in the validation cohort (*Table 3*).

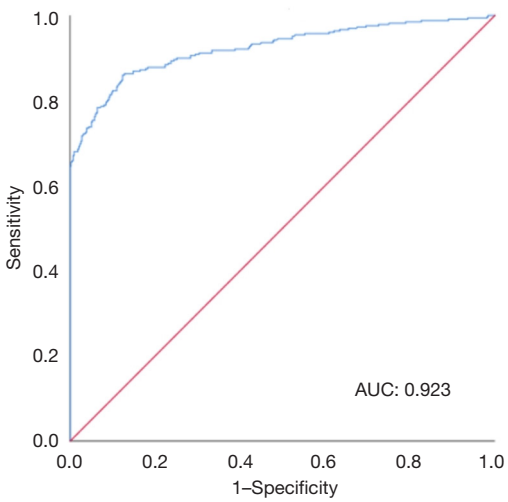

Figure 4 The ROC curve for the CT value in the primary cohort. AUC, area under the curve; ROC, receiver operating characteristic; CT, computed tomography.

Performance in small size nodules

In particular, we evaluated the differentiating capacity of the cut-off value of –415 HU in small size nodules with a maximum diameter ≤10 mm. The sensitivity and specificity were 80.49% and 88.08% in the primary cohort and 76.92% and 83.63% in the validation cohort, respectively. Details are listed in *Table 2*.

Discussion

Adenocarcinoma is the most common pathological subtype of lung cancer and is generally considered to develop via tumorigenesis and progression from AAH to AIS, MIA, and ultimately to IA with a lepidic pattern (10). During this progressive process, tumor tissue components increase, alveolar septa thicken, and air spaces decrease, which can be shown as an increase in size and density on CT images (11). Therefore, the degree of malignancy can be judged by observing these changes of lung lesions. Many previous studies have made great efforts to explore the correlation between histological invasiveness and CT features based on

Table 2 The performance of the cut-off value of –415 HU in predicting pathological types

Pathological type	No. of lung nodules			
	>–415 HU	≤–415 HU	>–415 HU*	≤–415 HU*
Primary cohort				
AIS (n)	2	87	2	80
MIA (n)	52	297	44	260
IA (n)	282	46	66	16
Sensitivity, % (95% CI)	85.98 (81.63–89.45)		80.49 (69.96–88.10)	
Specificity, % (95% CI)	87.67 (84.14–90.53)		88.08 (84.33–91.06)	
Validation cohort				
AIS (n)	0	29	0	26
MIA (n)	29	132	28	117
IA (n)	132	19	30	9
Sensitivity, % (95% CI)	87.42 (80.80–92.06)		76.92 (60.28–88.29)	
Specificity, % (95% CI)	84.74 (78.65–89.38)		83.63 (77.03–88.67)	

*, the performance of the cut-off value of –415 HU in predicting pathological types in small size nodules. HU, Hounsfield unit; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; IA, invasive adenocarcinoma; CI, confidence interval.

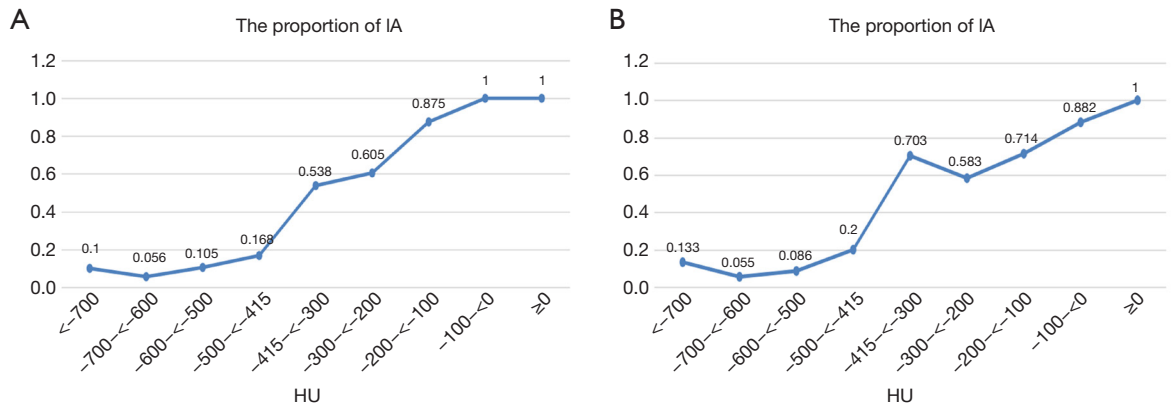

Figure 5 The trend of the proportion of IA with the increase of CT value in (A) the primary cohort and (B) the validation cohort. IA, invasive adenocarcinoma; CT, computed tomography; HU, Hounsfield units.

Table 3 Comparison of pathological types between other CT value ranges and the CT value of –415 to –300 HU

CT value (HU)	Primary cohort			Validation cohort		
	No. of IA (n)	No. of AIS/MIA (n)	P value	No. of IA (n)	No. of AIS/MIA (n)	P value
<–700	2	18	<0.001	2	13	<0.001
–700 to <–600	7	119	<0.001	3	52	<0.001
–600 to <–500	18	153	<0.001	6	64	<0.001
–500 to <–415	19	94	<0.001	8	32	<0.001
–415 to <–300	43	37	–	26	11	–
–300 to <–200	23	15	0.488	14	10	0.338
–200 to <–100	14	2	0.096	15	6	0.926
–100 to <0	37	0	<0.001	15	2	0.189
≥0	165	0	<0.001	62	0	<0.001

CT, computed tomography; HU, Hounsfield unit; IA, invasive adenocarcinoma; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma.

qualitative and quantitative analyses. High CT attenuation, larger tumour size, and irregular shape are generally considered important CT features of IA. Furthermore, the value of mCT values in this regard has been confirmed by many studies. Tamura *et al.* reported that the mCT value of ground glass opacity (GGO) was a risk factor associated with their future change and was a sensitive marker for predicting tumour recurrence (12,13). Some studies have indicated that mCT values show superior sensitivity and specificity over those of consolidation/tumor ratio (CTR) and maximum diameter in predicting the histological invasiveness of GGO. In addition, in the study of Sun *et al.*, the mCT attenuation was the only valuable parameter to preoperatively identify IA among pure ground glass masses (9).

Multiple previous studies, particularly focusing on pure GGO, confirmed that an increase in mCT values reflected a stepwise progression of lung adenocarcinoma (6,8). However, for pulmonary nodules with heterogeneous density, there is significant internal heterogeneity, and indolent and invasive components may co-exist. Therefore, the mCT value is not a good indicator of the pathological invasiveness of these pulmonary nodules. In the present study, pulmonary nodules with homogeneous internal density were used to avoid the existence of tumor internal heterogeneity as much as possible, so that the

measured mCT values could represent the entire internal characteristic of pulmonary nodules. Based on this, we attempted to explore the correspondence between CT values and the degree of pathological invasiveness.

All lung nodules with homogeneous internal density were analyzed in our study, including ground glass nodules, solid nodules, and those with a higher density between GGO and solid tumor. This is due to the fact that adenocarcinoma progression is a continuous process, and sometimes it is difficult to distinguish them accurately in clinical practice. Our aim is to find a suitable critical value across the entire continuous CT value cohort to differentiate IA with different clinical management strategies and outcomes from indolent adenocarcinoma. In our study, the cut-off value of –415 HU showed a good predictive performance in both the primary cohort and the validation cohort.

For lung nodules with heterogeneous internal density, such as mixed GGO, mCT values alone may not be a good predictor of invasiveness. CTR is also an important predictor. Ichinose *et al.* reported the value of maximum CT value for predicting histological invasiveness (14). It is not always possible to measure the size of the solid part of the tumor when the nodule comprises a heterogeneous mixture of GGO and solid tumor. Therefore, the CT value is a good supplement to the CTR. Although the quantitative CT value can be slightly affected by the densities of vessels or bronchi within the tumor, this method is easy to use, and can similarly evaluate lung nodules with heterogeneous internal density. Our study showed that the CT value of >–415 HU was an effective predictor of invasive lung adenocarcinoma. Therefore, for those nodules with heterogeneous internal density, whether the lesions have progressed to IAs needs to be considered when the higher CT attenuation of internal components exceeds the critical value. Zhang *et al.* also reported that the CT value could be used to distinguish lepidic predominant from non-lepidic predominant IA (15).

It has been reported that tumor size is also a predictor of histological invasiveness. Hsu *et al.* reported that the mean diameter of IA was significantly higher than that of AIS/MIA (16). In the study of Ren *et al.*, the maximum diameter could differentiate between IAs and preinvasive lesions (17). Furthermore, we also verified the predictive value of the critical value of –415 HU in small size lung nodules with a maximum diameter ≤10 mm, showing satisfactory sensitivity and specificity. In general, small size nodules that show the emergence of solid component or apparent growth are indications for surgical resection. Therefore, even for lesions that were 10 mm or smaller in size, if the CT value gradually increases and exceeds the critical value of –415 HU, it may be better to stop follow-up and consider excision of lesions.

CT features established based on radiomics have been reported to help predict the histological invasiveness and have shown satisfactory performance (18). However, the radiomics method is a complicated and time-consuming process compared to the preoperative measurement of the CT value using CT images. It is not always realistic to popularize it in clinical practice under the condition that a complete system has not been established at present. In contrast, the measurement of the CT value is limited and imperfect, but is still an easy-to-use and effective tool that can help clinicians make a preliminary judgment.

This study has two limitations that should be considered. First, only surgical nodules were included and lesions diagnosed as benign or AAH were excluded. Thus, some selection bias may be unavoidable. Second, our study was a retrospective analysis, and although the cut-off value was verified in another cohort, larger prospective studies are still necessary in the future.

Conclusions

In conclusion, the results of this study demonstrated that the CT value of >–415 HU was an effective predictor of invasive lung adenocarcinoma, which might help clinicians choose an appropriate surgical method and follow-up plan.

Acknowledgments

Funding: This work was supported by the National Natural Science Foundation of China (Grant No. 31700690, 82002927) and Zhejiang Provincial Natural Science Foundation (No. LQ19H160023).

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1548/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1548/dss

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1548/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1548/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China (No. 2023-736). Individual informed consent was waived due to the retrospective nature of this study.

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Cite this article as: Gao S, Wu Y, Li H, Zhou Y, Du C, Yang R, Wu Y. The predictive value of computed tomography value on high-resolution images in differentiating invasive from indolent lung adenocarcinoma. Transl Cancer Res 2024;13(1):268-277. doi: 10.21037/tcr-23-1548

