



Diagnostic performance of a deep learning-based method in differentiating malignant from benign subcentimeter (≤ 10 mm) solid pulmonary nodules

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Background: This study assessed the diagnostic performance of a deep learning (DL)-based model for differentiating malignant subcentimeter (≤ 10 mm) solid pulmonary nodules (SSPNs) from benign ones in computed tomography (CT) images compared against radiologists with 10 and 15 years of experience in thoracic imaging (medium-senior seniority).

Methods: Overall, 200 SSPNs (100 benign and 100 malignant) were retrospectively collected. Malignancy was confirmed by pathology, and benignity was confirmed by follow-up or pathology. CT images were fed into the DL model to obtain the probability of malignancy (range, 0–100%) for each nodule. According to the diagnostic results, enrolled nodules were classified into benign, malignant, or indeterminate. The accuracy and diagnostic composition of the model were compared with those of the radiologists using the McNemar-Bowker test. Enrolled nodules were divided into 3–6-, 6–8-, and 8–10-mm subgroups. For each subgroup, the diagnostic results of the model were compared with those of the radiologists.

Results: The accuracy of the DL model, in differentiating malignant and benign SSPNs, was significantly higher than that of the radiologists (71.5% vs. 38.5%, $P < 0.001$). The DL model reported more benign or malignant deterministic results and fewer indeterminate results. In subgroup analysis of nodule size, the DL model also yielded higher performance in comparison with that of the radiologists, providing fewer indeterminate results. The accuracy of the two methods in the 3–6-, 6–8-, and 8–10-mm subgroups was 75.5% vs. 28.3% ($P < 0.001$), 62.0% vs. 28.2% ($P < 0.001$), and 77.6% vs. 55.3% ($P = 0.001$), respectively, and the indeterminate results were 3.8% vs. 66.0%, 8.5% vs. 66.2%, and 2.6% vs. 35.5% (all $P < 0.001$), respectively.

Conclusions: The DL-based method yielded higher performance in comparison with that of the radiologists in differentiating malignant and benign SSPNs. This DL model may reduce uncertainty in diagnosis and improve diagnostic accuracy, especially for SSPNs smaller than 8 mm.

Keywords: Computed tomography (CT); differential diagnosis; solitary pulmonary nodule; artificial intelligence (AI); deep learning (DL)

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Introduction

With the wide application of chest computed tomography (CT) and popularization of low-dose CT (LDCT), the detection rate of solid pulmonary nodules has increased remarkably. A study from the Early Lung Cancer Action Project showed that solid nodules accounted for 81% of all nodules detected at baseline (1). Solid nodules are extremely common, with a malignancy rate of approximately 30% (range, 23–75%) (2). It is often difficult to differentiate between benign and malignant solid pulmonary nodules in clinical practice. Malignant solid nodules usually show high-grade malignancy, early metastasis, rapid growth, and poor prognosis (3–5). According to the 8th edition of the tumor-node-metastasis (TNM) classification for lung cancer, the 5-year survival rate of stage IA1 lung cancer is 90%, and 12% in stage IIIC, demonstrating the increased urgency for early diagnosis (6). For T1aN0M0 lung cancer, the recurrence risk of solid nodules is higher than that of part-solid and pure ground-glass nodules, although the diameter of solid nodules is ≤ 10 mm (7). Lymph nodal metastasis can occur even in subcentimeter solid non-small cell lung cancer (8). Hence, the prognosis of patients can be effectively improved if malignant solid nodules are diagnosed and treated at the subcentimeter stage.

However, the diagnosis of subcentimeter (≤ 10 mm) solid pulmonary nodules (SSPNs) remains challenging. The differential diagnosis of nodules is primarily dependent upon their CT features, including nodule size, density,

lobulation, and spiculation (9). Unfortunately, these features are not typical in most SSPNs, making diagnosis difficult for radiologists. For the majority of SSPNs that cannot be determined qualitatively, follow-up observation is often recommended (10–13). However, no consensus has been reached, and follow-up causes additional radiation exposure and psychological and financial burdens for patients (14). Invasive biopsies and surgeries can lead to overtreatment and subsequent unnecessary complications for patients with benign nodules that are misdiagnosed as malignant, or who require surgical diagnosis (15). Hence, a more accurate and safe diagnostic approach is needed for SSPN patients.

Recently, with the advancement of artificial intelligence (AI), deep learning (DL) has achieved multilayer nonlinear transformation without requiring time-intensive manual feature extraction, and has shown high efficiency and robustness (16,17). DL models can extract and learn image features imperceptible to the human eye, avoid subjective influences, and assist radiologists in diagnosis (18), proving effective in differentiating malignant from benign nodules (19–22). For instance, Tang *et al.* (19) proposed a DL model to improve the classification performance for benign and malignant pulmonary nodules, which achieved an accuracy, sensitivity, specificity, and receiver operating characteristic (ROC) area under the curve (AUC) of 94.4%, 90.9%, 92.6%, and 0.931, respectively. However, few studies have evaluated the performance of DL models in diagnosing SSPNs. Our prior study has shown that the accuracy of the DL model is comparable to that of radiologists, but only 11 SSPNs were included in the test set (23). Thus, the model's diagnostic efficiency for SSPNs remains unknown.

This study aimed to assess the diagnostic performance of the previously proposed DL model for differentiating malignant SSPNs from benign ones by comparing it against the performance of radiologists in clinical practice. We present this article in accordance with the STARD reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-985/rc>).

Methods

Nodule selection

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical

Highlight box

Key findings

- A deep-learning (DL) method could more accurately differentiate between benign and malignant subcentimeter (≤ 10 mm) solid pulmonary nodules (SSPNs) using computed tomography than radiologists with 10 and 15 years of experience in thoracic imaging and reduce uncertainty in diagnosis.

What is known and what is new?

- The diagnosis of SSPNs remains challenging, and misdiagnoses can lead to severe negative consequences for patients. The diagnosis of SSPNs using the DL method provides a more accurate diagnosis of benign or malignant SSPNs with reduced uncertainty. Unlike the human performance, the performance of the DL model is not affected by nodule size.

What is the implication, and what should change now?

- This DL method may reduce uncertainty in diagnosis and improve diagnostic accuracy, especially for SSPNs smaller than 8 mm.

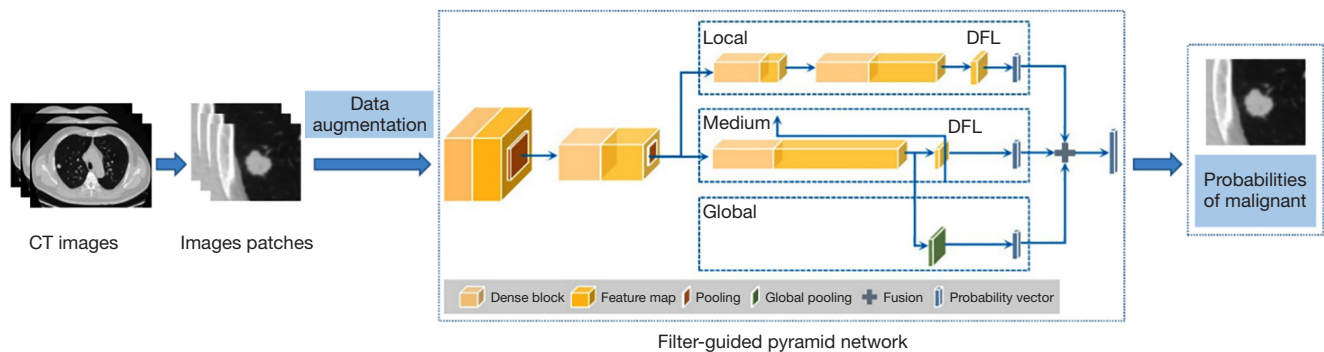


Figure 1 The framework of the proposed DL model. CT, computed tomography; DFL, discriminative filter bank; DL, deep learning.

Sciences and Peking Union Medical College (No. 21/473-3144), and individual consent for this retrospective analysis was waived. We retrospectively selected 200 cases of SSPNs (100 benign and 100 malignant), confirmed by surgical pathology or follow-up, between April 2011 and November 2021 from our database. The inclusion criteria for the nodules were as follows: (I) mean solid nodule diameter ≤ 10 mm; (II) malignant and benign nodules confirmed by surgical pathology, with nodules that remained stable for more than 2 years after follow-up or that disappeared for less than 2 years of follow-up considered benign; and (III) chest CT slice thickness ≤ 1.25 mm with a 50% overlap reconstruction. The exclusion criteria were as follows: (I) metastases confirmed histologically by surgical resection or that could not be excluded by follow-up; (II) poor image quality or evident artifacts on CT images; and (III) calcified nodules. All images were interpreted by two radiologists. The diagnostic reports were given by a junior radiologist and confirmed by a medium-senior radiologist. The CT reports were retrospectively reviewed.

Image acquisition and equipment

Chest CT images were obtained using 8-detector (LightSpeed Ultra, General Electric Medical Systems, GE HealthCare, Anaheim, CA, USA), 16-detector (ProSpeed or Discovery ST, General Electric Medical Systems), and 64-detector (LightSpeed VCT or Optima CT660, General Electric Medical Systems; Toshiba Aquilion, Toshiba Medical Systems, Toshiba International Corporation, Houston, TX, USA) multi-sliced scanners and were reconstructed using standard algorithms at 120 kVp and 250–350 mA. Reconstruction thicknesses were 0.625, 0.75, 1.00, or 1.25 mm at a 0.8-mm interval. For CT-enhanced scanning, 80–100 mL contrast agent was injected intravenously at

2.5 mL/s, and imaging was performed 25–30 s after injection.

Chest CT image analysis

The results of the clinical CT reports were divided into three groups: benign (radiologists diagnosed the lesion as benign or indicated a high probability of benignity), malignant (the radiologists diagnosed the lesion as malignant or indicated a high probability of malignancy), and indeterminate (the report did not offer a definitive diagnosis, except suggesting follow-up, or showed that benign and malignant remained to be distinguished).

All pulmonary nodules included in this study were processed by DL-based AI software, “Dr. Wise System” (National Device Registration Approval No. 20203210920), which was developed by the Deepwise AI Lab and has been applied to clinical work. The DL-based model tested in this study for diagnosing SSPNs adopted a filter-guided pyramid network with DenseNet (24) as the backbone, which can relate local features to global context (Figure 1). The DL model included 4,978 pulmonary nodules for training, and the validation set contained another 500 nodules. Its diagnostic accuracy for all types of pulmonary nodules was confirmed as comparable with the radiologists (70% vs. 64%, $P=0.243$), and more details of the model were presented elsewhere (23). The model provided the ability to determine the malignant probability (0–100%) of each nodule. The diagnostic criteria of the model were as follows: benign, (malignant probability of 0–39.9%), indeterminate (malignant probability of 40–59.9%), and malignant (malignant probability of 60–100%).

The diagnostic results of the model for all nodules were compared to those of the radiologists. Considering the mean diameter of each nodule, the 200 nodules were divided into three size groups: 3–6-, 6–8-, and 8–10-mm.

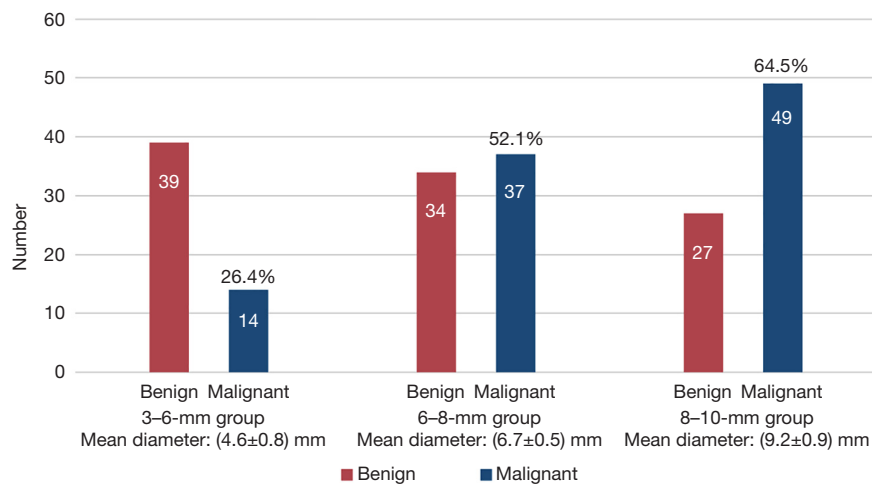


Figure 2 Proportion of benign and malignant nodules in each group. Diameters are expressed as mean ± standard deviation.

Table 1 Clinical characteristics of patients and nodules

Clinical characteristics	Value
Age (years)	56.5±10.1
Sex	
Male	79 (43.6)
Female	102 (56.4)
Diameter (mm)	7.1±2.0
Nodule location	
RUL	35 (17.5)
RML	18 (9.0)
RLL	59 (29.5)
LUL	40 (20.0)
LLL	48 (24.0)

Data are expressed as mean ± SD or n (%). RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; SD, standard deviation.

For each group, the results of the model were compared to those of the radiologists.

Statistical analyses

Statistical analyses were performed using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA) and MedCalc version 19.2.6 (MedCalc Software Ltd., Ostend, Belgium). Diagnostic differences between the AI model and the radiologists were examined using the McNemar-Bowker

test, and the differences in the composition of diagnostic results between the two methods were evaluated using the McNemar test. Taking the results of histopathology and follow-up as the gold standard, the diagnostic accuracy of the model and radiologists for benign nodules (benign *vs.* malignant and indeterminate nodules) was evaluated using the ROC curve, and the AUCs of the two methods were compared using the Delong test. The chi-squared or Fisher's exact test was used to evaluate the differences in diagnostic results among the 3-6-, 6-8-, and 8-10-mm groups. All statistical tests were two-sided, and values of $P < 0.05$ were considered significant.

Results

Clinical and histopathological characteristics

In total, 200 SSPNs were included. The distribution of benign and malignant nodules in the three groups is shown in *Figure 2*. The clinical characteristics of the patients and nodules are shown in *Table 1*. The histopathological findings of the 43 benign nodules and 100 malignant nodules are summarized in *Figure 3*, and the remaining 57 nodules were proven to be benign by follow-up.

Diagnostic results of the AI model

The AI model could automatically detect nodules in CT images without manual segmentation, with all the 200 nodules detected successfully. The model diagnosed 124 (62.0%) as benign, 66 (33.0%) as malignant, and 10

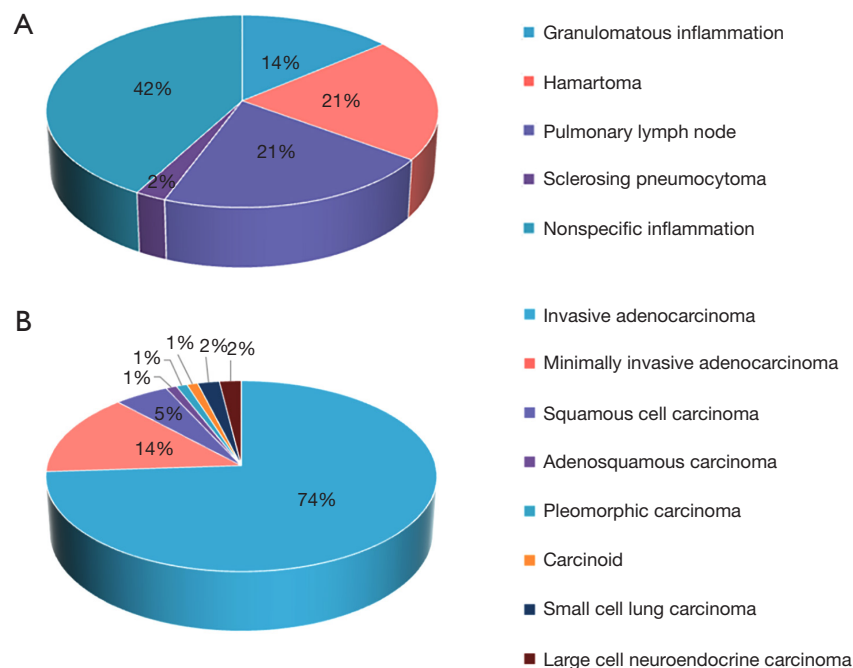


Figure 3 Proportion of histopathological findings in benign and malignant nodules. (A) Benign nodules. (B) Malignant nodules.

as indeterminate (5.0%), of which 7 were malignant and 3 were benign. Regarding indeterminate results as errors, the diagnostic accuracy of the model was 71.5% (143/200). The diagnostic accuracies of the model for the 3–6-, 6–8-, and 8–10-mm groups were 75.5% (40/53), 62.0% (44/71), and 77.6% (59/76), respectively. There were no diagnostic differences for nodules among the three size groups ($P=0.083$). Rates of indeterminate diagnoses for the three nodule groups were 3.8% (2/53), 8.5% (6/71), and 2.6% (2/76), respectively, and the difference in the results among these groups was not significant ($P=0.29$).

Diagnostic results of the radiologists

The radiologists diagnosed 44 (22.0%) benign, 47 (23.5%) malignant, and 109 indeterminate (54.5%) lesions, of which 55 were malignant and 54 were benign. Regarding indeterminate results as errors, the diagnostic accuracy of the radiologists was 38.5% (77/200). The diagnostic accuracies of the radiologists for the 3–6-, 6–8-, and 8–10-mm groups were 28.3% (15/53), 28.2% (20/71), and 55.3% (42/76), respectively. The results for the three nodule size groups were not completely equivalent ($\chi^2=14.548$, $P=0.001$). Multiple comparison analysis showed that the radiologists' diagnostic accuracy for the 8–10-mm group

was higher than that for the 6–8- and 3–6-mm groups, with these differences being statistically significant ($\chi^2=11.049$, $P=0.001$; $\chi^2=9.203$, $P=0.002$). However, there was no significant difference between the radiologists' accuracy for nodules in the 6–8- and 3–6-mm groups ($P=0.98$). The indeterminate diagnoses of the radiologists for the three size groups were 66.0% (35/53), 66.2% (47/71), and 35.5% (27/76), respectively, and the differences among the three groups were statistically significant ($\chi^2=17.796$, $P<0.001$). The results of the multiple comparison analysis showed that the radiologists' indeterminate diagnoses for the 8–10-mm group were less than those for the 6–8- and 3–6-mm groups ($\chi^2=13.813$, $P<0.001$; $\chi^2=11.645$, $P=0.001$). However, there was no significant difference between the 6–8- and 3–6-mm groups ($P=0.98$).

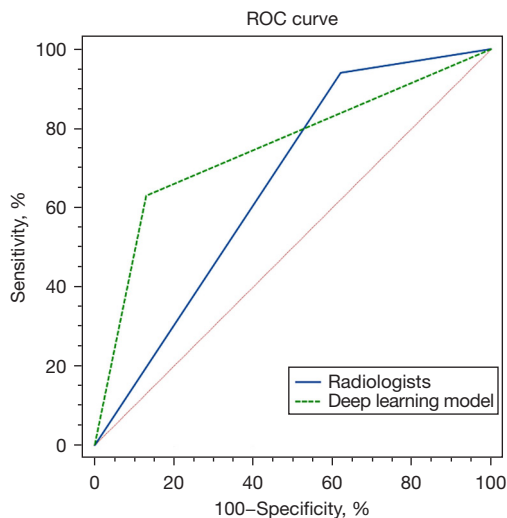
Comparison of diagnostic performance between the AI and radiologists

Both the AI model and the radiologists' diagnoses were benign, malignant, and indeterminate. The results of the McNemar-Bowker test indicated that the diagnostic difference between the two methods was statistically significant ($\chi^2=98.345$, $P<0.001$). Regarding the composition of the diagnostic results, the benign and malignant results

Table 2 Comparisons of diagnostic results between AI model and radiologists

Diagnostic results	AI model	Radiologists	P value
Benign	124 (62.0)	44 (22.0)	<0.001
Malignant	66 (33.0)	47 (23.0)	0.011
Indeterminate	10 (5.0)	109 (54.5)	<0.001
Accuracy	143 (71.5)	77 (38.5)	<0.001

Data are expressed as n (%). $P < 0.05$ indicates significant difference. AI, artificial intelligence.

**Figure 4** The ROC curve of the DL model and radiologists. ROC, receiver operating characteristic; DL, deep learning.

of the model were higher than those of the radiologists, whereas its indeterminate results were lower than those of the radiologists, with statistically significant differences ($\chi^2=66.426$, $P < 0.001$; $\chi^2=6.353$, $P=0.01$; $\chi^2=91.467$, $P < 0.001$). Regarding indeterminate results as errors, the diagnostic accuracy of the model was higher than that of the radiologists, and the difference between the two methods was statistically significant (71.5% vs. 38.5%, $\chi^2=49.128$, $P < 0.001$). The above results are summarized in *Table 2*.

ROC curves were drawn to compare the diagnostic accuracy of the model and that of the radiologists (benign vs. malignant and indeterminate), as shown in *Figure 4*. The AUCs of the DL-based model and the radiologists were 0.750 [95% confidence interval (CI), 0.648–0.808] and 0.660 (95% CI, 0.590–0.725), respectively. The difference in the AUCs between the two methods was statistically significant ($P=0.02$). The sensitivities, specificities of the model and

Table 3 Comparisons of diagnostic accuracy and indeterminate results between AI model and radiologists among three nodule size groups

Groups	AI model	Radiologists	P value
3–6 mm			
Accuracy	40 (75.5)	15 (28.3)	<0.001
Indeterminate	2 (3.8)	35 (66.0)	<0.001
6–8 mm			
Accuracy	44 (62.0)	20 (28.2)	<0.001
Indeterminate	6 (8.5)	47 (66.2)	<0.001
8–10 mm			
Accuracy	59 (77.6)	42 (55.3)	0.001
Indeterminate	2 (2.6)	27 (35.5)	<0.001

Data are expressed as n (%). AI, artificial intelligence.

radiologists were 63% (63/100) and 87% (87/100) vs. 94% (94/100) and 38% (38/100), respectively, with significant differences in all parameters between the two methods ($P < 0.001$).

Regarding indeterminate results as errors, for the 3–6-mm group, the diagnostic accuracies and indeterminate results of the model and the radiologists were 75.5% and 28.3% vs. 3.8% and 66.0%, respectively, with significant differences in results between the two methods ($\chi^2=21.333$, $P < 0.001$; $\chi^2=29.257$, $P < 0.001$). For the 6–8-mm group, the diagnostic accuracies and indeterminate results of the model and the radiologists were 62.0% and 28.2% vs. 8.5% and 66.2%, respectively. Significant differences were found between the results of the two methods ($\chi^2=15.559$, $P < 0.001$; $\chi^2=35.556$, $P < 0.001$). For the 8–10-mm group, the accuracies and indeterminate results of the model and radiologists were 77.6% and 55.3% vs. 2.6% and 35.5%, respectively. The results of the two methods were significantly different ($\chi^2=10.240$, $P=0.001$; $\chi^2=23.040$, $P < 0.001$). These results are summarized in *Table 3*. Some examples of nodules diagnosed by the AI model and the radiologists are shown in *Figure 5*.

Discussion

This study aimed to test the diagnostic performance of the DL model by comparing it with that of radiologists in differentiating benign from malignant SSPNs. The results revealed that the model provided a more accurate diagnosis of benign or malignant SSPNs with reduced uncertainty.

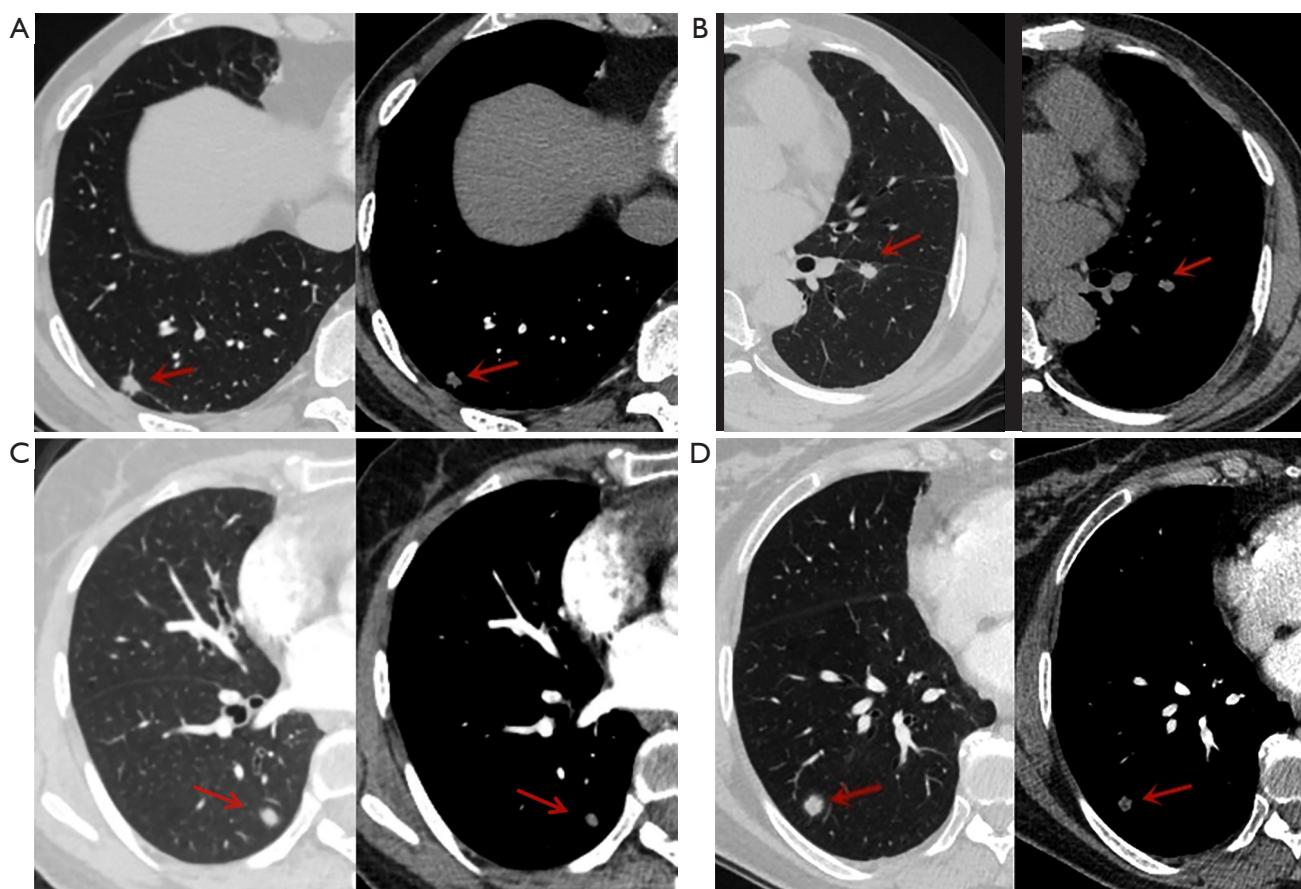


Figure 5 Examples of nodules diagnosed by the AI model and the radiologists. Red arrows point to the target nodule. (A) A nodule in RLL of a 46-year-old male, with mean diameter of 8.5 mm. The AI model diagnosed it as malignant, while the radiologists provided an indeterminate result. Histopathological finding: invasive adenocarcinoma. (B) A nodule in LLL of a 58-year-old male, with mean diameter of 8 mm. The AI model diagnosed it as benign, while the radiologists diagnosed it as malignant. Histopathological finding: pulmonary lymph node. (C) A nodule in RLL of a 58-year-old female, with mean diameter of 6.5 mm. The AI model diagnosed it as malignant, while the radiologists diagnosed it as malignant. Histopathological finding: invasive adenocarcinoma. (D) A nodule in RLL of a 53-year-old female, with mean diameter of 8.5 mm. The AI model diagnosed it as malignant, while the radiologists provided an indeterminate result. Histopathological finding: nonspecific inflammation. AI, artificial intelligence; RLL, right lower lobe; LLL, left lower lobe.

Unlike the radiologists, the performance of the model was not affected by nodule size.

Recently, DL has made significant advancements in the classification of benign and malignant pulmonary nodules (25). Nevertheless, most studies on DL have focused on all types of nodules, rather than specifically exploring SSPNs. In most recent studies, nodules were diagnosed as benign or malignant (26,27). Large nodules can be qualitatively determined by their shape, margins, contour, and other characteristics, whereas most SSPNs are not morphologically typical. Radiologists tend to diagnose indeterminate nodules and recommend further follow-up

or examination because malignancy cannot be ruled out in clinical work. Therefore, it fits better with the actual clinical condition to classify the results into benign, malignant, and indeterminate. Based on a prior study, we considered the interval of 40–59.9% malignancy as the indeterminate diagnosis for the model (23).

Considering the indeterminate results as errors, the diagnostic accuracy of the model was significantly higher than that of the radiologists. Compared with previous outcomes, there was little difference in the diagnostic accuracy of the model for different types of nodules, whereas the radiologists' accuracy decreased considerably

for SSPNs (23), due to the increased uncertain diagnoses. The above results demonstrate that the DL model can assist radiologists in enhancing the diagnostic accuracy of SSPNs and reducing uncertain diagnoses. The ROC curve, which was used to compare the diagnostic performance of benign nodules (benign *vs.* malignant and indeterminate) of the model and radiologists, revealed that the model had a higher accuracy and AUC than the radiologists, indicating that it achieves better diagnostic performance. In addition, the model showed lower sensitivity and higher specificity than the radiologists because of their conservative diagnosis; they were more cautious and tended to recommend follow-up for nodules that could not be judged as benign.

In this study, 200 subcentimeter solid nodules were divided into three groups based on size. The results showed that the radiologists' diagnostic accuracy for the 8–10-mm group was higher than that for the 6–8- and 3–6-mm groups, and the indeterminate results of the radiologists for the 8–10-mm group were lower than that of the 6–8- and 3–6-mm groups. No statistically significant difference was found in the diagnostic accuracy and indeterminate results of the radiologists between the 3–6- and 6–8-mm groups, suggesting that the radiologists' diagnosis is susceptible to the size of the nodules, especially nodules <8 mm, and diagnostic efficiency might be further impaired. In contrast, the model showed similar diagnostic accuracy and indeterminate results among the three nodule size groups, indicating stable diagnostic efficacy for nodules of different sizes. The analysis for each group revealed that the model had higher accuracy and reported fewer indeterminate results than the radiologists, especially for nodules <8 mm, which may give the radiologists confidence.

Although the AI model outperformed the radiologists in diagnosis, the number of misdiagnoses (malignant nodules diagnosed as benign or vice versa) was higher for the model than for the radiologists. Compared to the radiologists, it was more common for the model to misdiagnose the malignant nodules as benign (37/100), and the benign nodules were misdiagnosed as malignant less frequently (10/100). Moreover, the corresponding results for the radiologists' diagnoses were 6/100 and 8/100. This is probably because the radiologists were more cautious and would comprehensively evaluate patients' medical history, serological indicators, and related clinical information, whereas the model's judgments were simply based on CT images, which is a deficiency. If the indeterminate results were classified as errors, the misdiagnosis rate of the model would be lower than that of the radiologists. The numbers

of the model misdiagnosing malignancy as benign or indeterminate and misdiagnosing benign as malignant or indeterminate were 44/100 and 13/100, respectively, and the corresponding results for the radiologists' diagnoses were 61/100 and 62/100, respectively. These results suggest that radiologists are conservative in diagnosing nodules without typical imaging and clinical characteristics, and the model can effectively reduce this uncertainty. In the future, a multimodal DL model can be developed to overcome the above shortcomings and further improve efficiency by incorporating patients' clinical information.

This study has some limitations. First, this was a single-center retrospective study of nodules selected from an oncology center. There might be bias in the database, which can be resolved by using a larger sample size from multiple centers. Prospective studies are necessary to better observe the diagnostic value of DL methods in patients with SSPNs. Besides, it is difficult to characterize SSPNs for malignancy or benign due to the small size in clinical practice, because some morphological features of SSPNs such as margin, border, etc. are difficult to determine. What's more, because few DL models have been developed for SSPNs, this study lacks effective comparisons to other studies. Although the DL-based model was superior to the radiologists in achieving differential diagnosis, the model was trained and validated using solid and subsolid nodules of different sizes instead of only SSPNs, which might lead to insufficient training of the model for SSPNs and hinder the model from achieving optimal diagnostic performance. The development of a DL model dedicated exclusively to SSPNs is expected to further improve diagnostic accuracy for small nodules.

Conclusions

In summary, this study indicates that compared to radiologists, the DL diagnostic method is more effective in differentiating benign and malignant subcentimeter solid nodules in clinical practice, which can effectively reduce uncertainty for radiologists while improving their accuracy, make up for deficiencies in established diagnoses, and mitigate follow-up pressures on patients to some extent.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-985/rc>

Data Sharing Statement: Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-985/dss>

Peer Review File: Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-985/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-985/coif>). ZZ is an employee of Beijing Deepwise & League of PhD Technology Co., Ltd., Beijing, China. The other 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 Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. 21/473-3144) and individual consent for this retrospective analysis was waived.

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