RESEARCH ARTICLE

Combination diagnosis of multi-slice spiral computed tomography and secretory phospholipase A2-IIa for solitary pulmonary nodules

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Introduction: This study was aimed to compare the diagnostic value of multi-slice spiral computed tomography (CT) and secretory phospholipase A2-IIa (sPLA2-IIa) in differentiating between malignant and benign solitary pulmonary nodules (SPNs).

Methods: A total of 223 patients with SPNs (91 patients with malignant SPNs and 132 patients with benign SPNs) were included from Weihai Central Hospital during October 2014 to December 2016. SPN diagnosis was confirmed in all patients using needle biopsy, surgery and bronchoscopy. The patients were managed with dynamic multi-slice CT scans, and their sPLA2-IIa levels were also detected. By selecting the area of interest of focus, the perfusion parameters of multi-slice CT targeting the focus were obtained.

Results: The levels of MTT, PS, BV, BF and sPLA2-IIa significantly increased with increasing severity of SPNs ($P < .05$). Notably, BV (area under the ROC curve [AUC]=0.915; 95%CI: 0.88-0.95; sensitivity=91.21%; specificity=78.79%) showed a higher potential to discriminate patients with malignant SPNs from those with benign SPNs than did BF (AUC=0.712; 95%CI: 0.65-0.78; sensitivity=72.50%; specificity=59.10%), PS (AUC=0.772; 95%CI: 0.71-0.84; sensitivity=65.93%; specificity=82.58%) and MTT (AUC=0.600; 95%CI: 0.52-0.68; sensitivity=52.75%; specificity=78.03%). Finally, the combined diagnostic value of BV and sPLA2-IIa was quite ideal (AUC=0.947; 95%CI: 0.92-0.97; sensitivity=85.70%; specificity=92.70%) for malignant and benign SPNs.

Conclusions: The combined diagnostic value of BV and sPLA2-IIa appeared as a desirable detection method for malignant and benign SPNs.

KEYWORDS

combined diagnosis, multi-slice spiral computed tomography, secretory phospholipase A2-IIa, sensitivity, solitary pulmonary nodules

1 | INTRODUCTION

Solitary pulmonary nodules (SPNs) appear as ≤ 3 cm isolated lesions occurring in the lung, and round- or quasi-circular-shaped lesions are usually not accompanied by pulmonary atelectasis, satellite lesions and lymphadenopathy.¹ In general, the pathology of SPNs includes types of lung carcinoma (eg lung bronchogenic cancer) and benign nodules (eg tuberculosis and hamartoma). Swensen et al. reported that among

patients who underwent surgical removal of SPNs, there were 52% of patients with benign SPNs, whereas only one-third of them suffered from lung cancer.² Hence, it is highly imperative to pre-operatively distinguish between benign and malignant SPNs to reduce the surgical rates for benign SPNs and to remove malignant nodules as early as possible.

The increasing use of computed tomography (CT) has been documented to correctly diagnose 57% of lung cancer cases among SPNs, which remarkably outweighed the detectable rate, just

10%, of chest radiograph. Moreover, the lesions detected by CT were primarily central squamous cell carcinomas located in the primary bronchus, which were mostly at their early age with a size of <2 cm.³ Recent advances in post-treatment techniques of multi-spiral CT, such as maximum intensity projection and multi-planar reconstruction, have also further improved the detection rate of SPNs.⁴ Specifically, multi-spiral CT has primarily enhanced the scanning efficiency via injecting contrast media through the vein, thereby resulting in high-definition images. Thus, the haemodynamic changes and micro-vascular distribution of the focal areas could be delineated through intensive and dynamic measurement of the observation area, ultimately providing haemodynamic information for a clinical diagnosis. However, there is a lack of consistency in both regional and worldwide studies regarding the data obtained from multi-slice spiral CT imaging for SPN diagnosis, though it has been widely applied in the clinical settings.⁵ Furthermore, diagnosis using CT imaging has primarily depended on morphological alterations, calcification and necrosis of lesions, and current demands of explaining the pathological nature of the lesions could not be fulfilled based on the levels of functional imaging and molecular imaging.

Secretory phospholipase A2-IIa (sPLA2-IIa) is a phospholipid hydrolase enzyme, and its product, eicosanoid, has been reported to be involved in various physiological processes, including inflammatory, immune and tumour reactions.^{6,7} For instance, elevated levels of prostaglandins, a type of eicosanoid, were documented to regulate the development of lung cancer.⁸ Over-expressed sPLA2-IIa was also observed in prostate cancer specimens in comparison to adjacent normal tissues.^{9–11} In addition, immunohistochemistry analysis also confirmed that expression levels of sPLA2-IIa were up-regulated in lung cancer compared to those in SPNs, indicating that sPLA2-IIa is a relatively sensitive and specific biomarker for benign and malignant SPNs.¹² However, till date, only few studies have reported about the combined diagnostic value relevant to sPLA2-IIa for lung cancer and SPNs.

Altogether, there are differences in the principles of multi-slice CT perfusion imaging and sPLA2-IIa levels in detecting SPNs, and they might complement each other's defects. However, so far, no study has been conducted to explore the combined diagnostic value of multi-slice CT perfusion imaging and sPLA2-IIa for SPN diagnosis. Therefore, the present study was designed to compare the diagnostic values of multi-slice CT perfusion imaging, sPLA2-IIa and multi-slice CT perfusion imaging combined with sPLA2-IIa for assisting in early diagnosis and treatment of SPNs.

2 | METHODS

2.1 | Clinical features of included subjects

This study included 223 patients with SPNs and 45 healthy controls who attended to the Weihai Central Hospital from January 2014 to December 2016. According to the pathological diagnoses, patients with SPNs comprised 91 patients with malignant SPNs and

132 with benign SPNs. Malignant SPNs were primarily manifested as symptoms of adenocarcinoma, squamous carcinoma, metastatic carcinoma and small cell carcinoma, while the principal symptoms of benign SPNs were detected as tuberculoma, hamartoma and fibrous induration. All participants signed the informed consents, and the study was approved by the ethics committee of Weihai Central Hospital.

2.2 | Inclusion criteria

All the patients with SPNs recruited in this study should have met the following inclusion criteria: (i) patients were clinically diagnosed with SPNs after clinical CT scanning or examination of X-ray, but the focal properties were not detected; (ii) the diameters of solid nodules were ≤ 3 cm; (iii) patients could autonomously operate CT scanning after respiratory training, and they were not hypersensitive to contrast agents; (iv) the subjects should undergo operative treatment within 2 weeks after assessment of CT perfusion; (v) patients did not receive other therapies before interposing puncture or resection operation, such as chemotherapy and radiotherapy; (vi) all the patients should possess complete materials regarding clinical diagnosis and treatment; and (vii) patients did not have contradictions that did not adjust to enhancement, including functional failure of the heart, liver and kidney.

2.3 | Perfusion scanning

The parameters of dynamic scan for a selected focus were set as follows: (i) layer thickness was set as 5 mm with eight layers per circle; (ii) the voltage/current was set as 120 kV/70 mA; (iii) the scanned area was mostly 3.2 cm distance from the locus centre; and (iv) a low-dose scan was used to reduce radiation for patients. The patients were given 60 mL of the contrast agent through perfusion, including 40 mL Ultravist (Schering Pharmaceutical Ltd, Germany; specification: 300 mg/mL) and 20 mL normal saline. The double-syringe power injector was applied to inject the contrast agent through the median cubital vein, and the perfusion flow rate was managed at 4 mL/s. The scan time for the patients was 0.45s/r, and the total exposure time was 45 seconds. The scan was initiated about 4 seconds after injection of the contrast agent, and multi-level scanning was processed for the preselected focus using the software of perfusion scanning. Sequential dynamic scanning was conducted every 4 seconds, and the total scanning time was 40 seconds. During the subsequent scanning, the scanning was sequentially proceeded 30 times, and after 4 seconds, another 10 times of sequential scanning were sustained with an interval of 10 seconds. The scanning time was ensured to be within 5 minutes.

2.4 | Image post-processing

Related data were uploaded to the GE AW4.2 workstation, and the collected images were systematically analysed using the CT Perfusion-3 tumour perfusion software. The largest layer of the focus was

accurately measured and analysed. The inflow artery selected was ventriculus dexter or the aortic trunk of the layer, and the outflow artery was selected according to the descending aorta. After avoiding visible images such as calcification, cavity, necrotic blood vessel and artefacts, the threshold range of CT was determined as -28~160Hu. In addition, after selecting the area of interest of focus, the perfusion parameters of focus were obtained, including mean transit time (MTT) of blood, permeability surface (PS) of blood vessels, blood volume (BV) and blood flow (BF).

2.5 | Detection of sPLA2-IIa

An enzyme immunoassay kit (Cayman Chemical Company, America; batch number: 22069A-63789) was used for the detection of sPLA2-IIa, and a fully automated enzyme immunoassay analyser (Alisei Q.S, Italy) was used for analysing the levels of sPLA2-IIa.

2.6 | Statistical analysis

All the statistical analyses in this study were performed using SPSS 16.0 software. The differences in the levels of MTT, PS, BV, BF and sPLA2-IIa among patients with malignant SPNs and benign SPNs and

healthy controls were analysed by Student's *t* test. Chi-square test was also used for assessment of the enumerated data. Results were deemed statistically significant when *P* value was <.05. Receiver operating characteristic (ROC) curves were derived in line with MTT, PS, BV, BF and sPLA2-IIa levels among the three groups of subjects. Area under the ROC curve (AUC) was calculated to evaluate the diagnostic values of MTT, PS, BV, BF and sPLA2-IIa levels. In addition, the cut-off levels for MTT, PS, BV, BF and sPLA2-IIa levels were determined by the Youden index.

3 | RESULTS

3.1 | Clinical features of study subjects

There were no significant differences among patients with malignant SPNs and benign SPNs and healthy controls in terms of their mean age and sex ratio (*P*>.05) (Table 1). However, a significantly higher proportion of smokers were observed among patients with malignant SPNs than among those with benign SPNs and healthy controls (*P*<.05). Among the patients with malignant SPNs, 75 patients and 16 patients had histologically confirmed NSCLC (eg adenocarcinoma and squamous carcinoma) and SCLC, respectively. In addition, the subjects

TABLE 1 Demographic characteristics of patients and healthy controls

Characteristics	Malignant SPNs	Benign SPNs	Healthy control
N	91	132	45
Age	62.09±10.43	61.36±9.43	64.19±7.06
Sex			
Male	59 (65.56%)	76 (57.58%)	53 (60.92%)
Female	32 (34.44%)	56 (42.42%)	34 (39.08%)
Smoking History			
Smoker	48 (52.75%)	62 (46.97%)	21 (46.67%)
Nonsmoker	43 (47.25%)	70 (53.03%)	24 (53.33%)
Pack years	11.25±3.41	8.50±4.31	9.06±4.08
Histological types of malignant SPNs			
NSCLC	75		
Adenocarcinoma	30		
Squamous carcinoma	34		
Other NSCLC	11		
SCLC	16		
Stage			
I	35		
II	24		
III+IV	32		
Diagnosis of benign SPNs			
Inflammatory lesion		86	
Hamartoma		16	
Tuberculoma		17	
Lung abscess		13	

SPNs, solitary pulmonary nodules; NSCLC, non-small cell lung carcinoma; SCLC, small cell lung cancer.

could be classified into those in stage I (n=35), stage II (n=24) and stage III+IV (n=32) according to the severity of SPNs. Furthermore, the symptoms of benign SPNs could be subdivided into inflammatory lesions (n=86), hamartoma (n=16), tuberculoma (n=17) and lung abscess (n=13).

FIGURE 1 Plasma sPLA2-IIa expression of patients and healthy controls

3.2 | MTT, PS, BV, BF and sPLA2-IIa levels for susceptibility to SPNs

The plasma sPLA2-IIa levels (Figure 1) showed differences among patients with malignant SPNs and benign SPNs and healthy controls. Moreover, as shown in Table 2, MTT, PS, BV, BF and sPLA2-IIa levels of patients with malignant SPNs were significantly higher than the levels in those with benign SPNs ($P < .05$), and the levels of all these parameters were also significantly higher in patients with benign SPNs than those in healthy controls ($P < .05$).

3.3 | Diagnostic performance of MTT, PS, BV, BF and sPLA2-IIa levels for SPNs

Among the four indicators of multi-slice CT perfusion imaging (Table 3), BV (AUC=0.915; 95%CI: 0.88-0.95; sensitivity=91.21%; specificity=78.79%)(Figure 2) showed a higher potential to discriminate patients with malignant SPNs from those with benign SPNs than did BF (AUC=0.712; 95%CI: 0.65-0.78; sensitivity=72.50%; specificity=59.10%), PS (AUC=0.772; 95%CI: 0.71-0.84; sensitivity=65.93%; specificity=82.58%) and MTT (AUC=0.600; 95%CI:

TABLE 2 Results of CT perfusion imaging parameters of SPNs and healthy controls

Group	BF	BV	PS	MTT	sPLA2-IIa (ng/mL)
Malignant SPNs	86.52±14.26	14.61±4.12	21.92±10.12	11.49±5.21	3.47±0.96
Benign SPNs	72.97±18.73	7.01±3.76	12.71±6.52	8.67±2.86	2.18±1.02
Healthy control	16.58±9.40	2.92±1.66	5.08±1.95	4.65±1.35	0.38±0.46

SPNs, solitary pulmonary nodules; BF, blood flow; BV, blood volume; PS, permeability surface; MTT, mean transit time; sPLA2-IIa, secretory phospholipase A2-IIa.

TABLE 3 Sensitivity and specificity of five parameters in different comparison

Parameter	Comparison	Threshold	SEN	SPE	AUC	95% CI
BF	Malignant vs Benign	>78.00	72.50%	59.10%	0.712	0.65-0.78
	Malignant vs Healthy	>56.39	98.90%	100%	0.998	0.99-1.00
	Benign vs Healthy	>35.74	97.70%	100%	0.997	0.99-1.00
BV	Malignant vs Benign	>9.891	91.21%	78.79%	0.915	0.88-0.95
	Malignant vs Healthy	>5.514	98.90%	97.78%	0.987	0.91-0.99
	Benign vs Healthy	>4.453	75.00%	95.56%	0.838	0.78-0.90
PS	Malignant vs Benign	>18.21	65.93%	82.58%	0.772	0.71-0.84
	Malignant vs Healthy	>10.11	87.90%	100%	0.945	0.90-0.99
	Benign vs Healthy	>8.691	71.21%	97.78%	0.847	0.79-0.90
MTT	Malignant vs Benign	>11.82	52.75%	78.03%	0.6	0.52-0.68
	Malignant vs Healthy	>6.984	76.92%	91.11%	0.844	0.78-0.91
	Benign vs Healthy	>6.811	84.09%	88.89%	0.914	0.87-0.96
Spla2-IIa	Malignant vs Benign	>2.747	81.32%	70.45%	0.821	0.77-0.88
	Malignant vs Healthy	>1.881	95.60%	100.00%	0.996	0.99-1.00
	Benign vs Healthy	>1.089	84.85%	93.62%	0.944	0.91-0.98

BF, blood flow; BV, blood volume; PS, permeability surface; MTT, mean transit time; sPLA2-IIa, secretory phospholipase A2-IIa; SEN, sensitivity; SPE, specificity; AUC, area under the curve; CI, confidence interval.

(A) Malignant SPNs vs. Benign SPNs **(A) Malignant SPNs vs. Benign SPNs** **(B) Malignant SPNs vs. Healthy Control** **(B) Malignant SPNs vs. Healthy Control** **(C) Benign SPNs vs. Healthy Control** **(C) Benign SPNs vs. Healthy Control**

FIGURE 2 Determination of blood volume to predict lung cancer by ROC analysis. (A) Malignant SPNs relative to Benign SPNs; (B) Malignant SPNs relative to Healthy Control; (C) Benign SPNs relative to Healthy Control

FIGURE 3 Determination of blood flow to predict lung cancer by ROC analysis. (A) Malignant SPNs relative to Benign SPNs; (B) Malignant SPNs relative to Healthy Control; (C) Benign SPNs relative to Healthy Control

(A) Malignant SPNs vs. Benign SPNs **(A) Malignant SPNs vs. Benign SPNs** **(B) Malignant SPNs vs. Healthy Control** **(B) Malignant SPNs vs. Healthy Control** **(C) Benign SPNs vs. Healthy Control** **(C) Benign SPNs vs. Healthy Control**

FIGURE 4 Determination of permeability surface of blood vessels to predict lung cancer by ROC analysis. (A) Malignant SPNs relative to Benign SPNs; (B) Malignant SPNs relative to Healthy Control; (C) Benign SPNs relative to Healthy Control

FIGURE 5 Determination of mean transit time of blood to predict lung cancer by ROC analysis. (A) Malignant SPNs relative to Benign SPNs; (B) Malignant SPNs relative to Healthy Control; (C) Benign SPNs relative to Healthy Control

0.52-0.68; sensitivity=52.75%; specificity=78.03%) (Figures 3-5). However, the diagnostic performances of MTT, PS, BV and BF were fairly approximate among patients with malignant SPNs and benign SPNs and healthy controls based on the double comparisons of malignant vs healthy and benign vs healthy. Interestingly, sPLA2-IIa was not only slightly better than MTT, PS and BF in diagnosing malignant SPNs from benign SPNs (AUC=0.821; 95%CI: 0.77-0.88; sensitivity=81.32%; specificity=70.45%), but it also showed better efficiency in differentiating between malignant vs healthy (AUC=0.996; 95%CI: 0.99-1.00; sensitivity=95.60%; specificity=100.00%) and benign vs healthy (AUC=0.944; 95%CI: 0.91-0.98; sensitivity=84.85%; specificity=93.62%)(Figure 6). Hence, the combined diagnostic value of BV and sPLA2-IIa appeared quite favourable (AUC=0.947; 95%CI: 0.92-0.97; sensitivity=85.70%; specificity=92.70%) for diagnosing malignant SPNs vs benign SPNs (Figure 7).

4 | DISCUSSION

This study demonstrated that the levels of MTT, PS, BV, BF and sPLA2-IIa increased with the severity of SPNs, providing evidence that MTT, PS, BV, BF and sPLA2-IIa levels are viable in the preliminary screening of SPNs. Moreover, the diagnostic performance of BV and sPLA2-IIa seemed to be most desirable, and their combined diagnostic value was more ideal than any single parameter in differentiating between malignant SPNs and benign SPNs.

In general, differences in the structure and function between normal vessels and new vessels in tumour-bearing hosts are considered to account for the varying results of CT perfusion imaging.¹³ Specifically, the pulmonary artery supplies blood to the malignant tumours within the lung, and there is a decrease in either the number of micro-vessels within the tumours or in the expansion of bronchial arteries within the lung. Moreover, lymph vessels within and out of the tumours are decreased, with increased permeability of BV, stimulation of angiogenesis factors and growing nodular blood vessels. All these findings were identified as contributing to the significantly increased levels of BV, BF, PS and MTT in the present study (Table 2). In fact, BV has been defined as the volume of blood within the vasculature of organs or tissues and was shown to be easily affected by the size of blood capillaries and the number of open vessels.¹⁴ Moreover, BF was shown to be representative of the BF rate within the organs or tumours, and its levels were closely associated with the lymphatic return, draining vein and BV.¹⁵ Regarding MTT, this indicator primarily refers to the MTT of red blood cells within the micro-circulation of the lung or the time that blood takes to pass through the vasculature; however, the diagnostic value of MTT appears to be the least among all the indicators.⁵ PS indicates the one-way transmission rate of contrast agents, and it could accurately reflect the permeability and integrity of vascular endothelial cells, as well as the inter-cellular space within the tumours.¹⁶ Since contrast agents enter the tissue space primarily through the incomplete capillary basement membrane, higher PS

(A) Malignant SPNs vs. Benign SPNs

(B) Malignant SPNs vs. Healthy Control

(C) Benign SPNs vs. Healthy Control

FIGURE 6 Determination of plasma sPLA2-IIa to predict lung cancer by ROC analysis. (A) Malignant SPNs relative to Benign SPNs; (B) Malignant SPNs relative to Healthy Control; (C) Benign SPNs relative to Healthy Control

Combination of BV and sPLA2-IIa

FIGURE 7 Combination of blood volume and plasma sPLA2-IIa in differentiating solitary pulmonary nodules by ROC analysis

could be detected in the lung carcinoma when compared with benign SPNs. Therefore, it is convincing to mechanistically explain that MTT, PS, BV, BF and sPLA2-IIa levels could be highly potential markers to discriminate among patients with malignant SPNs and benign SPNs and healthy controls, though their performances were different.

Regarding sPLA2-IIa, this molecule widely participates in the signalling pathway related to lipid metabolism of cells, and it was also shown to be involved in the regulation of malignant tumours, cell apoptosis, inflammation, atherosclerosis and functional failure of the immune systems.¹⁷ The majority of eukaryocyte membranes exist in the form of asymmetric and bi-layer structures. In other words, under normal circumstances, amino acid phospholipids are situated inside the cyto-membrane and are in contact with the cytoplasm, while lecithin is located outside the cell membrane. During cell ageing and cell death, re-arrangement and reversal of membrane phospholipids could lead to disappearance of the cell membranes' asymmetric structure, which enables the amino acid phospholipids that display high-affinity binding with sPLA2 to lie outside the cell membrane and sPLA2 to act as a catalyst after its contact with cell membrane.¹⁸ Maybe this mechanism could partly explain the role of sPLA2-IIa in stimulating the growth of tumour cells and in differentiating between malignant SPNs and benign SPNs.¹⁹

Most importantly, the novelty of this study is using BV and sPLA2-IIa levels for the combined diagnosis of malignant SPNs in comparison with healthy controls, and the diagnostic performance was higher than that with any single parameter. Moreover, this study compared between patients with malignant SPNs and benign SPNs and healthy controls, and its reference value was far beyond the classification of patients with SPNs and healthy controls. In addition, this study incorporated a relatively large sample size, though still limited, which can provide a reliable study result. However, this study was limited in not

exploring the inherent mechanism of the correlation between sPLA2-IIa and transition from malignant SPNs to benign SPNs. In conclusion, the combined diagnosis could serve as a potential clinical diagnostic method targeting malignant and benign SPNs; however, further studies with a larger sample are needed, and the molecular action imposed by sPLA2-IIa on the development of malignant SPNs should also be investigated.

ACKNOWLEDGMENTS

None.

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How to cite this article: Hou H, Xu Z, Zhang H, Xu Y.

Combination diagnosis of multi-slice spiral computed tomography and secretory phospholipase A2-IIa for solitary pulmonary nodules. *J Clin Lab Anal.* 2018;32:e22250. <https://doi.org/10.1002/jcla.22250>