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Correlation study between dual source CT perfusion imaging and the microvascular composition of solitary pulmonary nodules

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ABSTRACT

Objective: To explore the correlation between dual source computed tomography perfusion imaging (CTPI) and microvascular parameters, and evaluate the value of CTPI in the differential diagnosis of solitary pulmonary nodule (SPN).

Methods: 65 consecutive patients with SPN who successfully underwent pre-operative CT perfusion imaging with dual source CT and received a final diagnosis by postoperative pathology. The cases were divided into malignant, benign and inflammatory groups according to the pathological results. CT perfusion parameters, such as blood flow (BF), blood volume (BV), mean transit time (MTT) and permeability surface (PMB) were obtained by performing CTPI of SPNs. The postoperative specimens of SPNs were immunohistochemically stained for CD34 and SMA to detect microvessel density (MVD) and luminal vascular parameters, such as luminal vascular number (LVN), luminal vascular area (LVA) and luminal vascular perimeter (LVP). The receiver operating characteristic (ROC) curve was used to assess the diagnostic efficiency of CT perfusion parameter in diagnosing malignant SPNs.

Results: In these 65 cases, malignant, benign and inflammatory SPNs were respectively 39, 14 and 12 cases. Significant difference was observed in LVN/MVD, LVA and LVP among the three groups ($P < 0.05$). The correlation between CT perfusion parameters (BF, BV and PMB) and the luminal vascular parameters was stronger than that with MVD ($P < 0.05$). PMB has the strongest correlation with LVN/MVD. Using BF ≥ 60ml/100ml/min, BV ≥ 6.34ml/100ml and PMB ≥ 13.35ml/100 ml/min for the diagnosis, the area under the curve (AUC) of the ROC curve was 0.760, the sensitivity was 82% and the specificity was 61%.

Conclusions: The main indicators reflecting blood perfusion of SPN are the degree of lumen or maturity of microvessels (LVN, LVA and LVP), not just the number of microvessels (e.g. MVD). CT perfusion imaging can be used as an important method to non-invasively evaluate tumour angiogenesis and help to distinguish malignant SPNs from benign and inflammatory SPNs.

1. Introduction

A solitary pulmonary nodule (SPN) is defined as a single, spherical, well-circumscribed, radiographic opacity ≤3 cm in diameter surrounded by aerated lung without atelectasis, hilar enlargement, or pleural effusion [1]. SPN is a common imaging signs, and the detection rates are gradually increasing due to the development of imaging technology and improvement of people's physical examination consciousness. Malignant tumors in SPNs are detected by imaging is 5–40%, and most of them are peripheral lung cancers [2]. The five-year

Abbreviations: AUC, area under the curve; BF, blood flow; BV, blood volume; CT, computed tomography; CTDIvol, volume computed tomography dose index; CTPI, computed tomography perfusion imaging; DLP, dose length product; LVA, luminal vascular area; LVN, luminal vascular number; LVP, luminal vascular perimeter; MTT, mean transit time; MVD, microvessel density; PMB, permeability surface; ROC, receiver operating characteristic; ROI, region of interest; SMA, smooth muscle action; SPN, solitary pulmonary nodule; VPCT, volume perfusion computed tomography

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survival rate of patients with early lung cancer can reach up to 54–73%, while patients with advanced lung cancer have a poor prognosis and a 5-year survival rate of only 2% [3,4]. Therefore, early detecting, diagnosing and treating lung cancer are vital, which not only can enhance the therapeutic effect of malignant tumors and improve the prognosis, but also can avoid the physical and economic burden caused by overtreatment of benign lesions. Chest CT is the most common examination of SPN, but the qualitative diagnosis of SPN is challenging if it mainly depending on the imaging morphology or enhancement degree of SPN. Tumor angiogenesis is closely related to the characteristic of tumor, which is an important factor affecting tumor growth, invasion, metastasis and prognosis. Microvessel density (MVD) and luminal vascular parameters including the luminal vessels number (LVN), the luminal vessels area (LVA) and the luminal vessels perimeter (LVP) are important indicators of tumor angiogenesis [5–7]. But this method belongs to invasive examination, and can not dynamically observe the angiogenesis of living tissues. CT perfusion imaging can reflect non-invasively the tumor angiogenesis and has important application value in quantitative and qualitative research of tumor [8,9]. However, clinical application of CT perfusion imaging has been limited because of its higher X-ray dose. The advanced low dose technology of flash dual source CT can greatly reduce the radiation dose caused by CT perfusion imaging, which can protect the patients' health and safety on the greatest extent, and is beneficial to carry out CT perfusion imaging study of SPN. Therefore, this study intends to introduce the microvascular parameters (MVD, LVN, LVA and LVP) to quantitatively analyze the microvascular structure of SPN and to make correlation analysis with dual source CT perfusion parameters in order to provide the theoretical basis in studying the dual source CT perfusion imaging characteristics of SPN, then to evaluate better the value of the dual source CT perfusion parameters for the diagnosis and differential diagnosis of SPN.

2. Material and methods

2.1. Patients

This study has been approved by the ethics committee of our university. And written informed consent was obtained from each patient or the patient’s family before performing the pre-operative CT scan. Sixty-five consecutive patients with SPNs who successfully underwent pre-operative CT perfusion imaging with dual source CT and received a final diagnosis by pathology (43 men, 22 women, age range 23–74 years, mean age 51.27 years) were enrolled between January 2015 and September 2016 according to the following criteria: (a) SPN detected by chest CT scan, successful pre-operative CT perfusion imaging and accepted surgical treatment; (b) no pre-operative treatment, such as chemotherapy or radiotherapy; (c) less than 2 weeks between the time of the CT perfusion imaging and the operation; (d) absence of calcification, necrosis, cavity or excision; (e) absence of severe heart, lung or kidney insufficiency.

2.2. Equipment and methods

2.2.1. Computed tomography scanning

The images of the patients were obtained using Germany's Siemens SOMATOM Definition Flash dual source CT scanner with the Care Dose 4D and X-care technique. All patients received breath training before performing the plain CT scanning. First, plain CT scanning of the chest was performed to determine the section of perfusion scan at an initial tube voltage of 120 kV, the tube current was automatically adjusted according to the patients' personal condition and 8-mm section thickness. And its’ scanning range was from the thoracic inlet to the bottom of the lung. Second, a perfusion CT scan in the condition of breathless which covered upper and lower poles of the tumor (range level fluctuation at the center of the nodule 3.5 cm) was performed with following parameters: 80 kV, the tube current was automatically adjusted according to the patients' personal condition, 3-mm scanning slice thickness and B20f smooth Eva image reconstruction method after injecting contrast medium (iohexol) 2–4 seconds. In total, 50 ml of iohexol were applied at a rate of 5 ml/s through the antecubital vein after the SPN was detected as non-ionic contrast material. The data acquisition time of 45 s. In our study, CTDIvol is(60.28 ± 9.35)mGy and DLP is (535.06 ± 45.63)mGy.cm.

2.2.2. Image post-processing

We transferred the scan images to the workplace (Siemens Syngo Multimodality workplace) and used volume perfusion software (VPCT body) for the data processing. The region of interest (ROI) of reference blood vessel was set in the thoracic aorta (if the plane of lung tumor was not present in the thoracic aorta, the arteria carotis or truncus brachiocephalicus was chosen). And the ROI of lung tumor was drawn freehand around the boundary (2–3 mm from the edge of the tumor) of the tumor (avoid necrosis area, calcification areas) in the maximum section(If any artifact interference, the section will is not regarded as the analysis section). Finally, we obtained the perfusion parameters, such as the blood flow (BF), blood volume (BV), permeability (PMB) and mean transit time (MTT), using the deconvolution method. The deconvolution model [8,10] could reflect the continuous changes of contrast agent in the arterial and venous phases, taking into account the inflow and outflow of blood vessels in the actual situation. Two experienced radiologists (both more than six years of experience and same level in interpreting CT perfusion imaging) were invited to do the experiments without knowing the patients’ information and take the average value from them as the final data. The two experienced radiologists would be asked to calculate again if the difference between their data beyond 10%.

2.3. Immunohistochemical staining

SPN specimens corresponding to the ROI of the CT imaging section were prepared, fixed with a 10% formaldehyde solution for 24 h, embedded in paraffin and sliced at a thickness of 4–6 μm. Using the PV-9000 two-step immunohistochemical test system, two slices of each specimen were stained for CD34 and SMA [11,12]. The anti-CD34 and anti-SMA kits were purchased from ZSGB-BIO Company (ZSGB-BIO, China). The slides were examined at a low-power magnification(×40 or ×100). The two most vascularized areas in the slice centre and the four most vascularized areas in the slice periphery were selected. The microvessels in these six areas were counted at ×200 magnification. The average counts were recorded as the values of MVD and luminal vascular parameters, which were obtained by staining for CD34 and SMA, respectively. Any CD34 highlighted endothelial cell or cell cluster that was apparently separate from peripheral tissues and connective tissues was counted as a single microvessel and branch construct with discrete breaks was also counted as a single microvessel. Taking the mean value of the data that came from the six fields above as the final MVD. For LVN, LVP and LVA, only microvessels with a discernible lumen and one or more complete layer(s) of α-smooth muscle actin stained pericytes and smooth muscle cells (regarded as relatively mature tumor vessels) will be counted. The corresponding counts were obtained by software processing. Two pathologists (both more than 15 years of experience and same level in lung pathology) were invited to count each slice respectively. If the difference between the two results is more than 10%, they would be asked to do it again. The mean of the two or four results is the final histologic data.

2.4. Statistical analysis

All data were analysed using SPSS 17.0 statistical software (IBM, Armonk, New York) and are expressed as the means ± standard deviation. $P < 0.05$ is considered statistically significant. First, all parameters underwent a normality test. Then, all parameters were compared among the three groups of SPNs by performing a Kruskal-Wallis H test, and H test comparisons of any two groups of these three types of SNPs were performed using Mann-Whitney-U tests. The correlations among the CT perfusion parameters and MVD, luminal vascular parameters and LVN/MVD of the three types of SPNs were analysed by performing Spearman correlation analyses. Finally, ROC curve was used to assess the diagnostic efficiency of CT perfusion parameter in differentiating malignant nodules and non-malignant nodules (benign and inflammatory nodules).

3. Results

3.1. Size and classification of SPNs

In our study, the SPN diameters ranged between 10–30 mm, and the average was 21.3 mm. Among the sixty-five patients with SPNs, 39 nodules were malignant (21 adenocarcinoma, 12 squamous carcinoma, 1 adenosquamous carcinoma, 2 large cell neuroendocrine carcinoma, 1 small cell carcinoma, 1 carcinoid and 1 sarcomatoid), 14 nodules were benign (9 tuberculoma, 1 hamartoma, 1 aspergillosis, 1 inflammatory myofibroblastic tumour, 1 sclerosing haemangioma and 1 neuroinoma) and 12 nodules were inflammatory.

3.2. CT perfusion parameters and microvascular parameters of SPNs

In the three groups of malignant, inflammatory and benign SPNs, MVD, LVA, LVP and LVN/MVD were normally distributed, except for BF, BV, PMB, MTT and LVN. BF, BV, MVD, LVN, LVA and LVP values in the malignant and inflammatory groups were statistically significantly higher than those in the benign group ($P < 0.05$). PMB values in the malignant group were higher than those in the inflammatory group, but LVA, LVP and LVN/MVD values were lower than those in the inflammatory group, and all differences were statistically significant ($P < 0.05$). However, no significant difference was observed in BF, BV, MTT, MVD and LVN values between the two groups. PMB in the malignant group was significantly higher than that in the benign group ($P < 0.05$), while no significant difference was observed between the benign group and inflammatory group ($P > 0.05$). MTT values did not significantly differ among the three groups (Table 1) (Fig. 1 and 2).

3.3. Correlation between CT perfusion parameters and the microvascular parameters of SPNs

Spearman's correlation coefficients (r) and P-values among the four perfusion parameters (BF, BV, MTT and PMB) and MVD and luminal vascular parameters of the SPNs are summarized in Table 2. BF and BV were both correlated with LVN, LVA, LVP, MVD and LVN/MVD ($P < 0.05$), and BF was most strongly correlated with the LVN, which is similar to BV and LVA. PMB was associated with LVN/MVD, LVN, LVA and MVD ($P < 0.05$), and the correlation between PMB and LVN/MVD was the most relevant. No correlation was observed between MTT and MVD or luminal vascular parameters ($P > 0.05$) (Table 2).

3.4. Efficacy of dual source CT perfusion parameters in diagnosing malignant SPNs

We divided the SPNs into malignant and non-malignant (benign and inflammatory) groups. BF, BV and PMB significantly differed between the two groups (Table 3). Therefore, we considered BF, BV and PMB as estimating indexes of malignant SPNs, and their areas under the curve (AUC) were 0.717, 0.646 and 0.749, respectively ($P < 0.05$) (Fig. 3). Using the ROC curve, the reference thresholds of BF, BV and PMB in judging malignant SPNs were obtained. BF ≥ 56 ml/100 ml/min as the cut-off point to predict malignant SPNs, the sensitivity was 85% and the specificity was 54%. BV ≥ 6.34 ml/100 ml/min as the cut-off point to predict malignant SPNs, the sensitivity was 82% and the specificity was 54%. PMB ≥ 8.88 ml/100 ml/min as the cut-off point to predict malignant SPNs, the sensitivity was 100% and the specificity was 50%. The combination of BF ≥ 60 ml/100 ml/min, BV ≥ 6.34 ml/100 ml and PMB ≥ 13.35 ml/100 ml/min for diagnosis resulted in an AUC of 0.760, sensitivity of 82% and specificity of 61%.

4. Discussion

4.1. Tumor angiogenesis and microvessel maturity of SPN

Tumour growth depends on angiogenesis. Tumour angiogenesis is closely related to biological behaviour and plays a key role in tumour growth [13,14]. When tumor reaches a certain size, the oxygen content in it is insufficient, in order to meet the needs of growth, tumor began to form new blood vessels to provide nutrients to meet the need of its growth. Tumor angiogenesis is closely related to the characteristic of tumor, which is an important factor affecting tumor growth, invasion, metastasis and prognosis [15,16].

It was found that benign, inflammatory and malignant SPN are significantly different in growth, development and morphological characteristics of microvessels by means of immunohistochemistry study. The microvascular maturity differs among the different types of SPNs. Malignant SPNs have many immature tumour microvessels. Inflammatory SPNs have many mature distended capillaries. Benign SPNs have only a few blood vessels [17,18]. MVD reflects tumour angiogenesis, but the tumour blood perfusion is reflected by the degree or maturity of the tumour microvascular cavity [18]. The degree of microangiogenesis and the vascular maturity of SPNs can be quantitatively analysed by detecting MVD, LVN, LVA, LVP and LVN/MVD. LVN/MVD is a luminal vascular ratio and the main index reflecting the degree or maturity of the microvascular cavity. As shown in this study, MVD, LVN, LVA and LVP in the malignant and inflammatory groups were significantly higher than those in the benign group. LVA, LVP and

Table 1
The microvascular parameters and CT perfusion parameters of SPNs (mean ± SD).

Parameters	Benign group	Inflammatory group	Malignant group
BF(ml/100 ml/min)	43.59 ± 38.56	101.21 ± 96.76[a]	104.89 ± 64.55[a]
BV(ml/100 ml)	4.96 ± 4.98	10.06 ± 4.86[a]	9.64 ± 4.46[a]
PMB(ml/100 ml/min)	10.37 ± 16.47	14.83 ± 7.50	24.65 ± 22.43[a,b]
MTT(s)	9.53 ± 7.46	8.24 ± 3.54	7.19 ± 3.79
LVN(bar/vision)	4.76 ± 2.45	8.95 ± 2.87[a]	7.59 ± 2.26[a]
LVA(μm^2/vision)	4333.77 ± 1977.31	8788.39 ± 2702.26[a]	6000.16 ± 1549.6[a,b]
LVP(μm/vision)	509.33 ± 258.39	1454.86 ± 400.52[a]	746.96 ± 152.77[a,b]
MVD(bar/vision)	45.81 ± 35.18	110.92 ± 33.71[a]	146.13 ± 58.89[a]
LVN/MVD	0.13 ± 0.06	0.08 ± 0.02[a]	0.05 ± 0.01[a,b]

[a] vs. benign group, $P < 0.05$.
[b] vs. inflammatory group, $P < 0.05$.

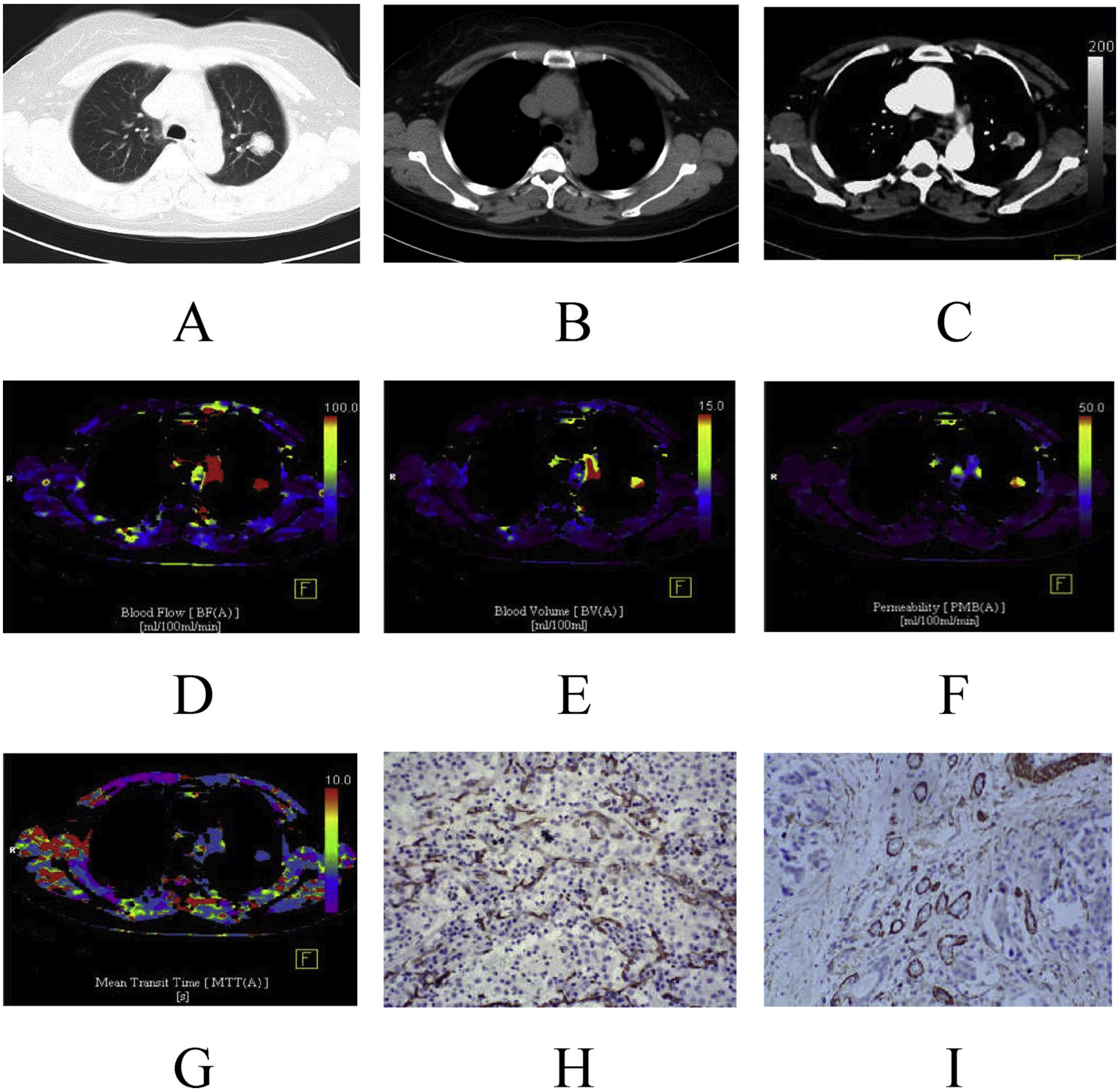

Fig. 1. Adenocarcinoma in a 48-year-old woman.
Note (1) A and B: The mediastinal window and lung window in a CT scan showing a nodule in the left upper lobe; C: The SPN exhibits a relatively obvious enhancement after the injection of the contrast medium; D-G: Corresponding functional colour maps of SPN characteristics, including BF, BV, PMB and MTT. H: CD34 immunohistochemical staining – microvessels are defined as single brown-stained endothelial cells and small clusters of brown-stained endothelial cells representing the MVD (×200); I: SMA immunohistochemical staining – the positive vessels are stained brown,and the yellow particles are the luminal vascular parameters (×200). (2) The mean MVD was 138.312 bar/vision, the mean LVN was 9 bar/vision, the mean LVA was 6204.708 μm2/vision and the mean LVP was 830.298 μm/vision.

LVN/MVD in the malignant group were lower than those in the inflammatory group, but no significant differences were detected in the values of MVD and LVN. Therefore, identifying SPNs requires CTPI indexes associated with LVA, LVP and LVN/MVD rather than CTPI indexes associated with MVD or LVN, which is a theoretical basis for identifying SPNs using CTPI. In this study, BF, BV and PMB were strongly correlated with LVN, LVA and LVN/MVD, respectively, further confirming that tumour blood perfusion truly reflects the degree or maturity of the microvascular cavity rather than simply the number of microvessels.

4.2. The value of CT perfusion parameters in evaluating the microvascular composition of SPNs and diagnosing malignant SPNs

In this study, BV and BF values of the SPNs in the malignant and inflammatory groups were significantly higher than those in the benign group, which is consistent with previous reports [19,20]. Of the computed tomography perfusion parameters used in this study, PMB was the only index that significantly differed between the malignant and inflammatory groups. PMB mainly reflects the integrity of vascular endothelial cells and the permeability of the vascular wall. Due to the low vascular maturity in malignant SPNs and the relatively mature blood vessels and low permeability of blood vessel walls in inflammatory and benign SPNs, PMB in the malignant group were higher than those in the inflammatory and benign groups, but the difference in PMB between the inflammatory group and benign group was not significant [14,21]. PMB is an important index for identifying inflammatory and malignant SPNs using CT perfusion parameters.

MTT reflects mainly the time required for the contrast material to enter the blood capillaries. In the malignant and inflammatory groups, the blood vessels were abundant, and the blood flowed quickly. However, many blood vessels were observed in the benign group (such as sclerosing haemangioma). Therefore, MTT value greatly overlapped among the three different types of SPNs, and the practical application

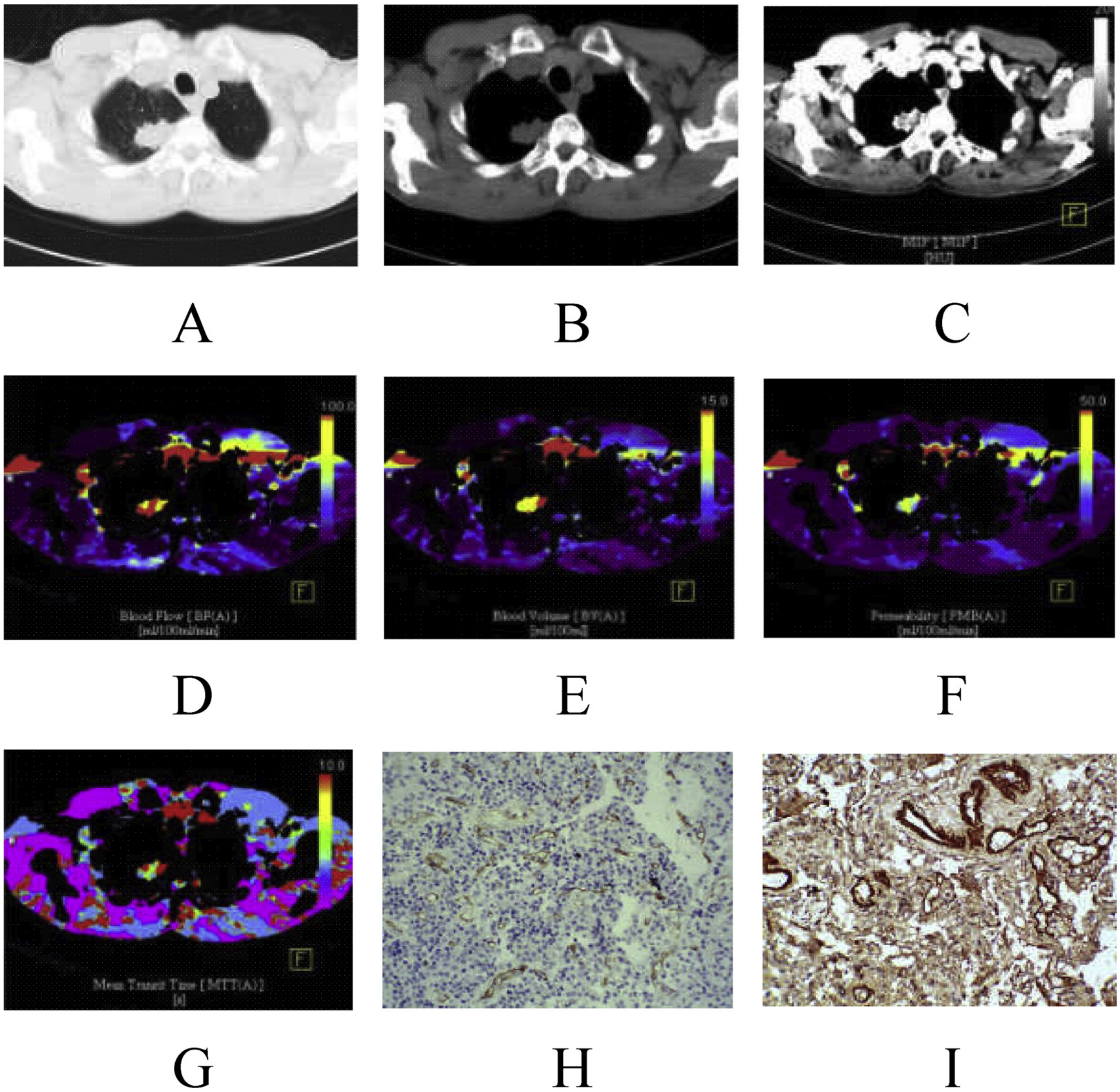

Fig. 2. Inflammatory pseudotumour in a 66-year-old man in the right upper lobe.
Note (1) A-I: The types of images are the same as those shown in Fig. 1.(2) The mean MVD was 122.72 bar/vision, the mean LVN was 10.5 bar/vision, the mean LVA was 10780.59 μm2/vision and the mean LVP was 1897.61 μm/vision. (3) In Figs. 1 and 2, the BF and BV of the two SPNs both had high values, but the PMB value of the SPNs shown in Fig. 1 was higher than that of the SPNs shown in Fig. 2, as indicated by the colour differences.

value of MTT is low. In addition, in our study, no correlation was observed between MTT and MVD or luminal vascular parameters (LVN, LVP and LVA), which was consistent with previous studied [22,23].

Combining BF ≥ 60 ml/100 ml/min, BV ≥ 6.59 ml/100 ml and PMB ≥ 9.9 ml/min/100 ml, the SPNs were considered malignant. Using these parameters, the sensitivity was 82% and the specificity was 62%. The diagnostic specificity did not significantly increase compared with a separate diagnosis, which could be explained by the following reasons: the blood supply greatly varies in malignant SPNs, and the blood supply in certain benign SPNs is also abundant; the proportion of nodules with different properties varies greatly, which can lead to statistical selection bias.

5. Conclusion

In summary, significant differences were observed in the

Table 2
Correlation between the microvascular parameters and CT perfusion parameters.

Parameters	BF		BV		PMB		MTT	
	r	*P*	*r*	*p*	*r*	*p*	*r*	*p*
LVN	0.788	0.000	0.588	0.000	0.374	0.002	−0.140	0.266
LVA	0.672	0.000	0.543	0.000	0.314	0.011	−0.060	0.637
LVP	0.459	0.000	0.457	0.000	0.152	0.277	0.068	0.588
MVD	0.646	0.000	0.487	0.000	0.622	0.000	−0.191	0.127
LVN/MVD	−0.354	0.004	−0.315	0.011	−0.646	0.000	0.092	0.648

Table 3
CT perfusion parameters of the malignant groups and non-malignant groups.

Groups	BF(ml/100 ml/min)	BV(ml/100 ml)	PMB(ml/100 ml/min)	MTT(s)
Malignant groups	104.889 ± 64.549	9.636 ± 4.458	24.649 ± 22.428	7.190 ± 3.790
Non-malignant groups	70.187 ± 75.831	7.316 ± 5.477	12.423 ± 13.071	8.930 ± 5.907
P	0.003	0.048	0.001	0.170

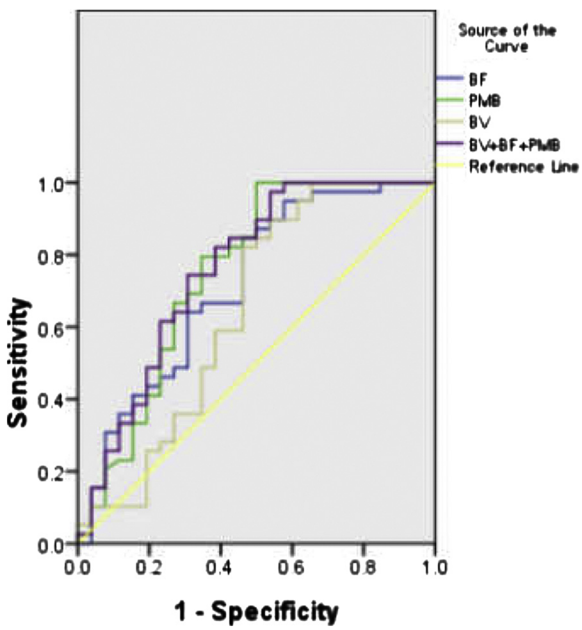

Fig. 3. ROC curve of CT perfusion parameters in diagnosing malignant SPNs.

microvascular composition among the benign, inflammatory and malignant SPNs. CT perfusion parameters were relevant to MVD and luminal vascular parameters, and the correlation between CT perfusion parameters and luminal vascular parameters was stronger than that between CT perfusion parameters and MVD, further confirming that the main indicators reflecting the blood perfusion of SPN are the degree of lumen or maturity of microvessels (e.g. LVN, LVA and LVP), not just the number of microvessels (e.g. MVD). Dual source CT perfusion imaging can be used as an important method to non-invasively evaluate tumour angiogenesis and is conducive to the diagnosis and differential diagnosis of SPNs.

Small sample size and single-center study are the main limitations of this study. Therefore, further work is to expand the sample size of SPN with various properties and conduct multi-center research to improve the diagnostic and differential diagnostic value of CT perfusion imaging for SPN.

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Disclosure

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