SHORT COMMUNICATION

First-pass perfusion imaging of solitary pulmonary nodules with 64-detector row CT: comparison of perfusion parameters of malignant and benign lesions

¹Y LI, MD, PhD, ^{1,2}Z-G YANG, MD, PhD, ¹T-W CHEN, MD, ¹J-Q YU, MD, ¹J-Y SUN, MD and ³H-J CHEN, MD

¹Division of Radiology, ²National Key Laboratory of Biotherapy Center and ³Department of Pathology, West China Hospital, Sichuan University, 37 Guo Xue Xiang, Chengdu, Sichuan 610041, China

ABSTRACT. The purpose of this study was to determine the usefulness of first-pass whole nodule perfusion imaging in the differentiation of benign and malignant solitary pulmonary nodules (SPNs). 77 patients with non-calcified SPNs (46 malignant, 22 benign and 9 active inflammatory) underwent first-pass perfusion imaging with a 64-detector row CT scanner. Perfusion, peak enhancement intensity (PEI), time to peak (TTP) and blood volume (BV) were measured and statistically compared among different groups. Mean perfusion, PEI and BV for benign SPNs were significantly lower than those for malignant nodules ($p < 0.05$) and active infections ($p < 0.05$), but the differences were not statistically significant between malignant tumours and active infections ($p > 0.05$). Receiver operating characteristic (ROC) curve analysis showed that SPNs with perfusion greater than $30.6 \text{ ml min}^{-1} \text{ ml}^{-1}$, PEI higher than 23.3 HU or BV larger than 12.2 ml per 100 g were more likely to be malignant. In conclusion, first-pass perfusion imaging with 64-detector row CT is a feasible way of assessing whole nodule perfusion and helpful in differentiating benign from malignant SPNs.

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The differentiation of solitary pulmonary nodules (SPNs) as benign or malignant remains a diagnostic challenge for thoracic radiology. During the past decade, promising results for more specific differentiation of malignant and benign nodules using dynamic contrast material-enhanced CT have been reported [1–6]. Techniques in these studies rely on single-level acquisition with long time intervals, which were considered to be problematic for quantitative assessment of whole tumour perfusion because the blood flow within tumours is spatially and temporally heterogeneous [7, 8]. Nevertheless, current technological advances in multi-detector row CT (MDCT), specifically sequential volume acquisition and data processing, allow for more accurate evaluation of tissue haemodynamics than that attainable with previous CT techniques. A recent study on MDCT perfusion techniques assessed whole tumour perfusion with the volume coverage of 40 mm in patients with non-small-cell lung carcinoma and achieved good measurement reproducibility [8].

To the best of our knowledge, no data exist on the application of first-pass perfusion CT for the differentiation of benign and malignant SPNs [1–6, 8]. The purpose of our study, therefore, was to determine the utility of

first-pass whole nodule perfusion imaging in the differentiation of benign and malignant SPNs.

Methods and materials

Between August 2006 and May 2007, a total of 93 patients with a newly detected SPN at cross-sectional imaging or conventional radiography (61 men and 32 women; age range 22–79 years; mean age 54.9 years) were recruited prospectively according to the following criteria: presence of SPN 30 mm or less in diameter, without evidence of calcification or fat attenuation, absence of contraindication to the administration of contrast medium and probable ability to co-operate with the procedure. Of these, 77 patients (52 men and 25 women; age range 24–79 years; mean age 55.7 years) with 77 SPNs met the criteria and were classified into the following three groups based on histological findings: (a) malignant SPNs ($n=46$) including 29 adenocarcinomas, 11 squamous cell carcinomas, 3 large-cell carcinomas and 3 small-cell carcinomas; (b) benign SPNs ($n=22$) including 9 inflammatory lesions, 8 inactive tuberculomas, 3 hamartomas and 2 inflammatory pseudotumours; (c) active infections ($n=9$) including 4 active tuberculosis and 5 organising or focal pneumonia.

First-pass perfusion imaging was performed with a 64-detector row CT scanner (Philips Brilliance 64; Philips Medical Systems; the Netherlands). Patients were examined in the supine position with both arms extended

Address correspondence to: Zhi-gang Yang, Department of Radiology, West China Hospital, Sichuan University, 37 Guo Xue Xiang, Chengdu, Sichuan 610041, China. E-mail: yangzg1117@yahoo.com.cn

above the head. A 19-gauge cannula (B. Braun, Melsungen, Germany) was placed into a cubital vein before the examination. A pump injector (Meorao-Stellant; Medrad, Pittsburgh, PA) was used to inject a bolus of 50 ml of iodinated low-osmolar non-ionic contrast material (Ultravist 300, Schering, Berlin Germany) intravenously at the rate of 6–7 ml s⁻¹. Dynamic acquisitions that encompassed the entire nodule commenced 5 s after the start of bolus injection with the following parameters: 120 kV; 100 mAs; rotation time, 0.40 s; table speed 110 mm s⁻¹; collimation, 64 × 0.625 mm; field of view, 350 mm; matrix, 512 × 512. Total duration time varied between patients but was approximately 55 s (range 50–60 s). Patients were reminded to breathe gently during dynamic scans to minimise movement. Images were reconstructed with 3 mm slice thickness and 3 mm slice increment using a standard reconstruction algorithm without edge enhancement at a display window width of 350 Hounsfield units (HU) and a window level of 40 HU.

On completion of CT examination, data were transferred to the Extended Brilliance™ Workstation (Philips Medical Systems) and analysed by a board-certified radiologist (Y Li, with 5 years of experience interpreting perfusion CT images) using commercial perfusion software (Brilliance perfusion 2.1.1). The artery input was determined by placing a circular region of interest (ROI) over the aorta or the left subclavian artery if the aorta was not included in the section. Perfusion parameters of the nodule were measured on a circular or oval ROI around the peripheral margin of SPNs with an electronic cursor and mouse. Large ROI (*i.e.* a ROI larger than 70% of the minimum diameter of the tumour) was chosen to incorporate the solid-appearing part of a tumour, but care was taken to avoid atelectatic lung tissue, cystic necrosis and cavitation. This process was repeated for each contiguous transverse level to ensure that the entire nodule was covered. A global value representing the perfusion of the entire SPN was calculated by taking the mean value of all individual sections of one nodule. The analytical method used in this study was based on the slope model (see Appendix) and dedicated to the first-pass perfusion measurement of the nodule, yielding four major kinetic parameters: (a) perfusion (measured in ml min⁻¹ ml⁻¹); (b) peak enhancement intensity (PEI, measured in HU); (c) time to peak (TTP, measured in seconds); and (d) blood volume (BV, measured in ml per 100 g). Colour parametric and composite maps of these perfusion parameters were generated automatically and recorded for each case.

To minimise the risk of operator-dependent bias, each perfusion measurement was analysed with the observer unaware of the patients' clinical data. To minimise recall bias, the entire processes were repeated 1 month later. Intra-observer reliability of the measurements was tested by using the Bland and Altman methods [9]. When good agreement was achieved between the replicated measurements, average values of the two sets of measurements were chosen to represent the perfusion parameters for each SPN. The Shapiro–Wilk test was used to evaluate the normality of distribution. Because none of the continuous variables was normally distributed, all statistical analyses were performed with non-parametric methods (Kruskal–Wallis test). Receiver operating characteristic (ROC) curve analysis was performed to evaluate the usefulness of perfusion parameters as markers for differentiating malignant from benign nodules.

Results

Repeatability of CT perfusion parameters of SPNs between replicated measurements

Mean values of perfusion, PEI, TTP and BV were 60.9 ± 53.9 (range 0.0–243.0) ml min⁻¹ ml⁻¹, 54.1 ± 50.5 HU (range 0.0–234.4), (range 11–56) 30.0 ± 10.9 s, and (range 0.0–166.4) 29.0 ± 28.7 ml per 100 g, respectively, for the first set of measurements, and (range 0.0–239.4) 59.7 ± 52.3 ml min⁻¹ ml⁻¹, 53.4 ± 48.6 HU (range 0.0–226.7), (range 11–56) 29.9 ± 11.0 s and (range 0.0–160.4) 28.1 ± 26.5 ml per 100 g, respectively, for the second set of measurements. Good agreements were obtained between the replicated measurements in terms of measuring four first-pass perfusion parameters (Table 1).

First-pass perfusion parameters for diagnosis of malignant SPNs

Table 2 summarises first-pass perfusion parameters of SPNs in each group. Images of a malignant and a benign SPN, as well as an SPN with active infection, are shown in Figures 1, 2 and 3, respectively. Perfusion, PEI and BV for benign SPNs were significantly lower than those for malignant and active infectious SPNs (all *p* < 0.05), but the differences in these parameters between the malignant and active infectious nodules were not statistically significant (all *p* > 0.05). Mean TTP was longest for

Table 1. Repeatability for first-pass perfusion, peak enhancement intensity (PEI), time to peak (TTP) and blood volume (BV) measurements

Perfusion parameter	Differences between measurements (mean (SD))	95% CI	95% limits of agreement	ICC (95% CI)
Perfusion (ml min ⁻¹ ml ⁻¹)	1.26 (3.63)	0.43 to 2.09	–5.85 to 8.37	0.9981 (0.9969 to 0.9988)
PEI (HU)	0.68 (3.73)	–0.16 to 1.53	–6.63 to 7.99	0.9979 (0.9967 to 0.9987)
TTP (s)	–0.04 (0.19)	–0.08 to 0.00	–0.41 to 0.33	0.9998 (0.9998 to 0.9999)
BV (ml per 100 g)	0.91 (3.73)	0.06 to 1.76	–6.40 to 8.22	0.9939 (0.9905 to 0.9962)

CI, confidence interval; ICC, intraclass correlation coefficient.

Table 2. Perfusion, peak enhancement intensity (PEI), time to peak (TTP) and blood volume (BV) measurements for solitary pulmonary nodules

Perfusion parameter	Solitary pulmonary nodules			p-Value		
	MNs (n=46)	BN (n=22)	AI (n=9)	MN vs BN	MN vs AI	BN vs AI
Perfusion (ml min ⁻¹ ml ⁻¹)				0.000 ^a	0.375	0.000 ^a
Median	61.5	13.1	76.3			
25th–75th percentile of IQR	38.0–86.2	7.2–22.9	42.0–166.5			
PEI (HU)				0.000 ^a	0.617	0.000 ^a
Median	60.2	11.3	61.8			
25th–75th percentile of IQR	36.5–72.1	6.0–23.5	39.2–156.3			
TTP(s)				0.087	0.163	0.585
Median	32.5	28.0	26.5			
25th–75th percentile of IQR	26.8–37.6	20.0–38.5	19.0–36.5			
BV(ml per 100 g)				0.000 ^a	0.317	0.000 ^a
Median	33.1	3.4	22.5			
25th–75th percentile of IQR	20.4–49.5	0.0–8.7	17.5–36.8			

MN, malignant nodules; BN, benign nodules; AI, active infections; IQR, interquartile range.

^aSignificant difference was found between the two groups by means of the Kruskal–Wallis test.

malignant nodules, followed by benign nodules and active infections, but the differences were not statistically significant (all $p > 0.05$).

To differentiate malignant SPNs from benign SPNs, threshold levels of 30.6 ml min⁻¹ ml⁻¹ for perfusion, 23.3 HU for PEI and 12.2 ml per 100 g for BV were found to be suitable. Areas under the ROC curves were 0.92 (95% CI 0.82–0.97) for perfusion, 0.95 (95% CI 0.86–0.99) for PEI and 0.95 (95% CI 0.87–0.99) for BV. Table 3 summarises the diagnostic characteristics according to the threshold values. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were 91.3%, 86.4%, 93.3%, 82.6% and 88.2%, respectively for perfusion; 93.5%, 81.8%, 91.5%, 85.7% and 88.2%, respectively for PEI; and 93.5%, 90.9%, 95.6%, 87.0% and 92.6%, respectively for BV.

Discussion

In this study, we successfully used first-pass whole nodule perfusion imaging for the characterisation of SPNs. Our study techniques involved a quantitative method based on a whole nodule perfusion measurement and rapid dynamic acquisitions focused on the first pass of contrast material, as this early phase seemed to be very important to the differentiation of malignant from benign SPNs [2, 4, 10]. By using a 64-detector row CT scanner, a 40 mm volume tissue coverage along the z-axis was available, which encompassing the entire nodule. Rapid sequencing of images with a total duration of approximately 55 s following a sharp bolus profile (50 ml, 6–7 ml s⁻¹) was adopted to enable a robust first-pass perfusion analysis [11]. The global perfusion value of the

Figure 1. A 68-year-old male patient with adenocarcinoma (malignant solitary pulmonary nodule). Functional maps of perfusion, peak enhancement intensity (PEI), time to peak (TTP) and blood volume (BV) show that the distribution of perfusion within the tumour is heterogeneous. The colour spectrum indicates the value of the perfusion parameters, ranging from high (red) to low (blue). Values of perfusion, PEI, TTP and BV are 44.8 ml min⁻¹ ml⁻¹, 53.0 HU, 37.0 s and 25.4 ml per 100 g, respectively.

Figure 2. A 28-year-old female patient with tuberculoma (benign solitary pulmonary nodule). Functional maps of perfusion, peak enhancement intensity (PEI), time to peak (TTP) and blood volume (BV) show that enhancement of the nodule are relatively low. Values of perfusion, PEI, TTP and BV are 3.8 ml min⁻¹ ml⁻¹, 4.4 HU, 21.0 s and 0.2 ml per 100 g, respectively.

Figure 3. A 32-year-old male patient with focal organising pneumonia (active infection). Functional maps of perfusion, peak enhancement intensity (PEI), time to peak (TTP) and blood volume (BV) show that enhancement of the nodule are relatively high. Values of perfusion, PEI, TTP and BV are 173.0 ml min⁻¹ ml⁻¹, 208.3 HU, 16.0 s and 38.9 ml per 100 g, respectively.

Table 3. Diagnostic capability of perfusion, peak enhancement intensity (PEI), time to peak (TTP) and blood volume (BV) for differentiation of malignant solitary pulmonary nodules (SPNs) and benign SPNs

Perfusion parameter	Threshold value	Sensitivity (%) mean (range)	Specificity (%) mean (range)	PPV (%)	NPV (%)	Accuracy (%)
Perfusion (ml min ⁻¹ ml ⁻¹)	30.6	91.3 (79.2, 97.5)	86.4 (65.1, 96.9)	93.3	82.6	88.2
PEI (HU)	23.3	93.5 (82.1, 98.6)	81.8 (59.7, 94.7)	91.5	85.7	88.2
BV (ml per 100 g)	12.2	93.5 (82.1, 98.6)	90.9 (70.8, 98.6)	95.6	87.0	92.6

PPV, positive predictive value; NPV, negative predictive value.

entire SPN was calculated by averaging the measured cross-sectional areas with good measurement repeatability. In comparison with previously published techniques to differentiate malignant from benign SPNs [1–6], technique development in the present study contributed to more sophisticated kinetic modelling of SPNs, hence allowing for more accurate and detailed physiological information on the nodule microvasculature.

We found significant differences in PEI between lung carcinoma and tuberculoma, granuloma as well as other benign nodules. This parameter showed high sensitivity and positive predictive value (>90%) for diagnosis of lung cancer and differentiation from benign SPNs other than active infections. However, the cut-off value of PEI in our first-pass perfusion imaging was slightly higher than that reported previously [2–6]. This result might be interpreted by the sharp bolus profile and short acquisition time interval adopted in the present study, because both of them could contribute to higher nodule enhancement. Except for PEI, our results also indicated that perfusion and BV showed high diagnostic value for differentiation of malignant from benign nodules. ROC curve analysis showed that SPNs with perfusion larger than 30.6 ml min⁻¹ ml⁻¹ or BV larger than 12.2 ml per 100 g were more likely to be lung carcinomas. The overall diagnostic accuracy (sensitivity of 91.3%, specificity of 86.4%, PPV of 93.3%, NPV of 82.6% and accuracy of 88.2% for perfusion and sensitivity of 93.5%, specificity of 90.9%, PPV of 95.6%, NPV of 87.0% and accuracy of 92.6% for BV) was also better than those reported previously.

Since previous studies have suggested that the active inflammatory process would sometimes have a faster and/or higher peak enhancement than malignant neoplasms [1–4, 10, 12], we separated the active infection groups from other SPN groups in an effort to test the capability of first-pass CT perfusion imaging in differentiation between malignant SPNs and active infection. Although overlaps between active infection and the malignant SPNs were found when the first-pass kinetic parameters were analysed, we found that some SPNs with active infection in our series (three cases of focal organising pneumonia and one case of active tuberculosis) had even higher perfusion, PEI and BV than the malignant SPNs, and the TTP for active infection was steeper than that of malignant tumour. These findings suggest that initial slope and peak enhancement may be different between malignant and active infection nodules, which might be helpful in distinguishing the active infection from malignant tumours.

Conclusion

First-pass whole nodule perfusion imaging is a technically feasible tool to assess the haemodynamics of SPNs. Perfusion parameters offer utility in distinguishing benign nodules from malignant tumours. Absence of perfusion and relatively low blood volume are strong predictors that an SPN is benign.

References

1. Yamashita K, Matsunobe S, Tsuda T, et al. Solitary pulmonary nodules: preliminary study of evaluation with incremental dynamic CT. *Radiology* 1995;194:399–405.
2. Zhang M, Kono M. Solid pulmonary nodules: evaluation of blood flow patterns with dynamic CT. *Radiology* 1997;205:471–8.
3. Swensen SJ, Brown LR, Colby TV, Weaver AL. Pulmonary nodules: CT evaluation of enhancement with iodinated contrast material. *Radiology* 1995;194:393–8.
4. Swensen SJ, Brown LR, Colby TV, Weaver AL. Lung nodule enhancement at CT: prospective findings. *Radiology* 1996;201:447–55.
5. Swensen SJ, Viggiano RW, Midthun DE, Patz EF Jr, et al. Nodule enhancement at CT: multicenter study. *Radiology* 2000;214:73–80.
6. Yi CA, Lee KS, Kim EA, Han J, Kim H, Kwory OJ, et al. Solitary pulmonary nodules: dynamic enhanced multi-detector row CT study and comparison with vascular endothelial growth factor and microvessel density. *Radiology* 2004;233:191–9.
7. Chaplin DJ, Hill SA. Temporal heterogeneity in micro-regional erythrocyte flux in experimental solid tumours. *Br J Cancer* 1995;71:1210–13.
8. Ng QS, Goh V, Klotz E, Fichte H, Saunders MI, Hoskin PJ, et al. Quantitative assessment of lung cancer perfusion using MDCT: does measurement reproducibility improve with greater tumour volume coverage? *AJR Am J Roentgenol* 2006;187:1079–84.
9. Bland MJ, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;i:307–10.
10. Gückel C, Schnabel K, Deimling M, Steinbrich W. Solitary pulmonary nodules: MR evaluation of enhancement patterns with contrast-enhanced dynamic snapshot gradient-echo imaging. *Radiology* 1996;200:681–6.
11. Miles KA. Ideal contrast medium bolus for perfusion measurement in dynamic CT. *Radiology* 1998;209:583.
12. Kono R, Fujimoto K, Terasaki H, Müller NL, Kato S, Sadohara J, et al. Dynamic MRI of solitary pulmonary nodules: comparison of enhancement patterns of malignant and benign small peripheral lung lesions. *AJR Am J Roentgenol* 2007;188:26–36.

Appendix

The Philips (Best, Netherlands) CT Perfusion package uses the slope method to calculate perfusion. The slope method allows calculation of perfusion from a shorter time series and is analogous to a differentiation with respect to time of the Mullani–Gould Formulation (Equation 1).

$$\frac{F}{V} = \frac{c(t')|_{\max}}{\int_0^{t'} a^*(t) dt} \quad (1)$$

Therefore, perfusion (F/V) can be calculated as the maximum slope of tissue enhancement curve divided by the maximum arterial enhancement.

$$\frac{F}{V} = \frac{\frac{d}{dt}[c(t)]_{\max}}{a(t)_{\max}} \quad (2)$$

The principle advantage of the slope method is that it allows calculation of the perfusion sooner, as the tissue time enhancement curve reaches its peak gradient well before its peak enhancement value. This reduces the chance of the no venous out flow assumption being broken. The peak arterial enhancement and maximum slope in most tissues occur prior to any recirculation thus avoiding the requirement of curve modelling. The earlier time of

perfusion assessment also reduces the likelihood of patient movement and may enable perfusion studies in a single breath hold.

Appendix References

- A1. Gobbel GT, Cann CE, Fike JR. Measurement of regional cerebral blood flow using ultrafast computed tomography. Theoretical aspects. *Stroke* 1991;22:768–71.
- A2. Miles KA, Griffiths MR. Perfusion CT: a worthwhile enhancement? *Br J Radiol* 2003;76(904):220–31.
- A3. Cenic A, Nabavi DG, Craen RA, Gelb AW, Lee TY. A CT method to measure hemodynamics in brain tumors: validation and application of cerebral blood flow maps. *Am J Neuroradiol* 2000;21:462–70.