Clinical Research Paper

Dynamic enhancement patterns of solitary pulmonary nodules at multi-detector row CT and correlation with vascular endothelial growth factor and microvessel density

Nan-Chuan Jiang, Ping Han, Cheng-Kai Zhou, Jin-Long Zheng, He-Shui Shi and Jie Xiao

1Department of Radiology; Union Hospital; Tongji Medical College; Huazhong University of Science and Technology; Wuhan, Hubei P.R. China; 2Siemens Medical Solutions; Shanghai, P.R. China

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Background and Objective: Differential diagnosis of malignant solitary pulmonary nodules (SPNs) from benign ones is difficult based on imaging manifestations. This study was to assess dynamic enhancement patterns of SPNs detected with multi-detector row computed tomography (MDCT), correlate SPN manifestations of MDCT to the expression of vascular endothelial growth factor (VEGF) and microvessel density (MVD), thus to explore the potential value of MDCT imaging in the diagnosis of SPNs.

Methods: Fifty pathologically and one clinically confirmed patients with SPNs (diameter ≤ 4 cm) undergoing MDCT plain and dynamic enhancement scans were enrolled in the study. The entire lung was scanned at 15 s after injection of the contrast agent; dynamic enhancement scans of SPNs were performed at 45 s, 75 s, 135 s, 195 s and 255 s after contrast injection. The enhancement patterns, pre-, peak and net enhancement of SPNs were assessed. Pearson correlation coefficient was used to correlate peak enhancement, net enhancement to the expression of VEGF and MVD.

Results: The peak and net enhancements were significantly higher in malignant nodules (mean attenuation, 69.9 Hu and 32.9 Hu) than in benign nodules (mean attenuation, 51.7 Hu and 17.2 Hu) (p < 0.001). When net enhancement of 20 Hu was set as the cutoff value to differentiate malignant nodules from benign ones, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 96.43%, 69.57%, 79.41%, 94.12% and 84.31%, respectively. The enhancement patterns between malignant and benign SPNs were significantly different. Homogeneous enhancement or heterogeneous tending to homogeneous enhancement appeared mostly in malignant nodules (78.57%). Benign nodules were almost not enhanced (52.17%). Expressions of MVD and VEGF were significantly different between malignant and benign SPNs. VEGF was positively correlated to the peak enhancement value (r = 0.505, p = 0.014) and the net enhancement value (r = 0.565, p = 0.005). Similarly, MVD was also positively correlated to the peak enhancement value (r = 0.819, p < 0.001) and the net enhancement value (r = 0.845, p < 0.001).

Conclusions: Net enhancement value is an important indicator for differential diagnosis of malignant and benign SPNs. Characteristic enhancement patterns are different between malignant and benign SPNs. Peak enhancement and net enhancement values are positively correlated with VEGF and MVD, both of which reflect the extent of angiogenesis in SPNs to some extent.

Solitary pulmonary nodules (SPNs) have been the hot topic in radiological image research. The diagnosis of benignity or malignancy of SPNs is directly related to the treatment planning. Surgical removal is the optimal solution for early stage non-small cell lung cancer (NSCLC). For inflammatory nodules, it is desired to avoid unnecessary surgery.

The degree of SPN enhancement is closely related to the angiogenesis of the nodule. We employed multi-detector row computed tomography (MDCT) for dynamic enhanced scanning on SPNs. In combination with operational pathology, characteristics of benign or malignant SPNs were assessed. We also explored the relationships among dynamic enhancement patterns of SPNs, expression of vascular endothelial growth factor (VEGF) and microvessel density (MVD).

Patients and Methods

Patients. Fifty-one patients with SPNs from May 2003 to January 2006 were included, in which 31 were males and 20 were...
females. The patients were aged between 20 and 80 years (medium age, 50 years). The SPNs were 1 cm to 4 cm in diameter, with an average of 2.65 ± 0.82 cm. Forty-eight cases were confirmed by surgery, two cases were confirmed by pathological examination under CT-guided puncture. The SPN of one case shrank and disappeared after antibiotic treatment. Twenty-eight cases were diagnosed as malignant tumors, among which 13 were squamous cell carcinoma, eight were adenocarcinoma, five were bronchial-aleveolar carcinoma, one was large cell carcinoma and one was leiomyosarcoma. Twenty-three cases were diagnosed as benign nodules, among which four were benign tumors (two hamartomas, one sclerotic hemangiom and one clear cell carcinoma), 10 were tuberculosis, five were inflammatory nodules (one acute inflammatory nodule and four inflammatory pseudocarcinoma), two were pulmonary sequestration and two were pulmonary cysts. Patients were divided into malignant and benign nodule groups. The benign nodule group was composed of benign tumors, tuberculosis, inflammatory nodules, pulmonary sequestration and pulmonary cysts.

MDCT scanning. Lungs were scanned using a 16-slice spiral CT (SOMATOM Sensation 16, Siemens, Germany). Routine scanning of SPNs were firstly performed (120 KV, 125 mAs, 1.5 mm width, spiral interval 1), followed by dynamic enhanced scanning. Using a high-pressure injection apparatus, at a flow rate of 3.2 ml/s, 90 to 120 ml of a nonionic contrast agent (Ultravist, 300 mgI/ml) was injected through the cubital vein. The amount of the contrast agent was calculated based on the body weight (1.5 ml/kg). A total of six groups of scanning were performed. At 15 s, early enhanced scanning of the entire lung was performed. The entire pulmonary nodule was scanned in the other five groups at 45 s, 15 s, early enhanced scanning of the entire lung was performed. The t-test was used to analyze intergroup cases with a regular variance, while the Wilcoxon rank-sum test was used to analyze those with irregular variance. The χ² test was adopted to study the benign and malignant groups in the enhancement pattern. The relationships among the peak enhancement value, net enhancement value, VEGF, and CD31 were compared by Pearson correlation coefficient. The level of statistical significance was set at p < 0.05. All statistical analyses were performed using SPSS 12.0 software. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy for the diagnosis in different regions were calculated, respectively.

Results

Characteristics of enhanced SPN images. The peak enhancement value of malignant nodules (average 69.9 Hu) was significantly higher than that of benign ones (average 51.7 Hu) (p < 0.001). The CT value in plain scan of malignant nodules (average 37.0 Hu) and that of benign nodules (average 34.4 Hu) showed no significant difference (p = 0.179). The increased intensity of malignant nodules (average 32.9 Hu) was significantly higher than that of benign nodules (average 17.2 Hu) during enhanced CT scan in comparison to plain scan (p < 0.001) (Table 1).

The threshold for net enhancement value was set at 20 Hu. In 28 cases of malignant tumors, 27 were accurately diagnosed, with a sensitivity of 96.43%. In 23 cases of benign nodules, 16 were correctly diagnosed, with a specificity of 69.57%. The positive predictive value was 79.41% (27/34), and the negative predictive value was 94.12% (16/17), with an accuracy rate of 84.31% (43/51) (Table 2). One false negative case was leiomyosarcoma whose net enhancement value was 13 Hu. Seven false positive cases were one clear cell carcinoma, one hamartoma, one sclerotic hemangiom, two tuberculosis, one inflammatory pseudotumor and one acute inflammatory nodule.
Dynamic enhancement patterns of SPNs. In 28 cases of malignant nodules, 22 (78.57%) appeared completely homogeneous enhancement or heterogeneous tending to homogeneous enhancement (Fig. 1). Four cases (14.29%) were heterogeneously enhanced, one case (3.57%) showed peripheral enhancement and one case (3.57%) was not enhanced. In 23 cases of benign nodules, 12 (52.17%) were not enhanced, four (17.39%) were homogeneously enhanced and three (13.04%) showed envelope enhancement (Fig. 2). Peripheral enhancement was seen in one case (4.35%) and heterogeneous enhancement in three cases (13.04%). The variation in the enhancement patterns of the two groups had statistical significance when cases with homogeneous enhancement, heterogeneous enhancement and peripheral enhancement were combined, while cases of non-enhancement and envelope enhancement were put together ($x^2 = 21.25, p < 0.001$).

The relationship between dynamic enhancement of SPNs and expressions of VEGF and MVD. Expressions of MVD and VEGF were significantly different between the benign and malignant nodule groups (Table 3). VEGF was positively correlated to the peak enhancement value ($r = 0.505, p = 0.014$) and the net enhancement value ($r = 0.565, p = 0.005$). Similarly, MVD was also positively correlated to the peak enhancement value ($r = 0.819, p < 0.001$) and the net enhancement value ($r = 0.845, p < 0.001$).

Discussion

Selection of the scanning mode. We employed a 16-slice spiral CT to perform dynamic enhanced scan for SPNs. The fast scanning speed and high spatial resolution of the CT machine made it possible to scan the entire lung and nodules, thus to reconstruct thin layers of the nodule. In previous studies, the layer of the nodule was designated, with a thickness of 3 mm–5 mm. This might overlook partial information of the nodule. Additionally, only limited number of layers was selected. Irregular respiration also affects the results greatly, which causes variation in the scanned layer during dynamic enhancement scan. Moreover it is impossible to clarify the conditions of mediastinal lymph nodes and both enlarged pulmonary hilum using such a method. In this study, enhancement scan of the entire lung was performed at 15 s after injection of the contrast agent, in order to understand whether mediastinal lymph nodes and pulmonary hilum were enlarged, as well as to clarify the relationship between nodules and their surrounding blood vessels. One case of pulmonary segestation was confirmed before surgery. Enhancement scan of the entire lung showed that the supplying artery next to the nodule was originated from the junction site of thoracic and abdominal aorta.

The time to reach the peak enhancement scan determines the scan delay time. We scanned every 30 s from 15 to 75 s, and extended the interval to every 60 s afterwards until 255 s. The peak value of most SPNs appeared within three min after starting scanning, and none of the cases reached the peak value at 255 s. In 36 SPNs scanned by enhancement CT, the peak value occurred at 45 s and 75 s in 29 cases (80.56%), at 135 s in 6 cases and at 195 s in one case. Therefore, the best delay time in this study was around 45 s to 135 s.

Significance of the net enhancement value of SPNs in differential diagnosis of benign and malignant nodules. The enhancement degree of malignant nodules was significantly higher than that of benign nodules. The net enhancement value of SPNs is helpful in differentiating benign and malignant nodules. However, because different scanning modes are used, the optimal threshold for net enhancement is not completely consistent. Generally, it is believed that the threshold should be set at 15 Hu or 20 Hu, which helps to achieve better and higher sensitivity, specificity and negative predicative value. Thresholds in this study were set at 15 Hu, 20 Hu, 25 Hu, 30 Hu, 35 Hu and 40 Hu, respectively, in order to calculate the sensitivity, specificity, positive predicative value, negative predicative value and accuracy, separately. We found that when the threshold was set at 20 Hu, higher sensitivity (96.43%),
negative predictive value (94.12%) and accuracy (84.31%) were obtained compared with using other threshold values.

False positive cases in this study were consisted of four inflammatory lesions and three benign tumors. Swensen et al.\(^5\) reveal that the enhancement value of granuloma in the early stage with active inflammation is usually over 15 Hu. The net enhancement values of four out of seven false positive cases, including two tuberculosis, one inflammatory pseudotumor and one acute inflammatory nodule, were larger than 20 Hu. The other three false positive cases were benign tumors, including one clear cell carcinoma, one hamartoma and one sclerotic hemangioma. Partial benign tumor is a major reason causing false positivity.\(^6,7\)

Significance of the enhancement mode for differential diagnosis of benign and malignant nodules. The majority of malignant nodules presented with completely homogeneous enhancement or heterogeneous tending homogeneous enhancement (78.57%). In some malignant nodules, necrotic tissues appeared heterogeneous enhancement and peripheral enhancement. In contrast, the primary manifestation of enhancement images of benign nodules appeared non-enhancement (52.17%). In four cases with homogeneous enhancement or heterogeneous tending homogeneous enhancement, three were benign tumors and one was an acute inflammatory lesion. One case of inflammatory pseudotumor showed peripheral enhancement and two cases of tuberculoma presented with heterogeneous enhancement. Envelope enhancement was only observed in benign lesions: one case of tuberculosis, one case of pulmonary segasturation and one case of pulmonary cysts. These results were generally consistent with those found by Yamashita et al. and Zhang et al.\(^7\) who believe that malignant nodules primarily show complete enhancement or heterogeneous tending to homogeneous enhancement. Yamashita et al.\(^7\) discovered that envelope enhancement appears in some hamartomas and tuberculosis.

Figure 1. Dynamic enhancement patterns of lung squamous carcinoma in the upper left lobe of a 48-year old male patient. [A–G] Dynamic enhancement images show the tendency toward homogeneous enhancement of the nodule. The plain scan value is 34 Hu and the peak enhancement is 61 Hu at 135 s after contrast injection. [H] The lesion size is 2.5 cm x 2.2 cm detected by high resolution CT. (I) The maximum intensity projection image shows multiple vessels in the SPN. (J) A time-density curve of SPN ascends slowly up to the peak at 135 s after contrast injection, and descends slowly afterwards.
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Relationship between the enhancement images and expressions of VEGF and MVD of SPNs. Characteristics of the SPN blood supply is the main factor affecting the enhancement images of SPNs, including host blood vessels, MVD and diffuse of the contrast agent in nodules. We showed that MVD was significantly and positively correlated to the peak enhancement value and the net enhancement value. MVD determines the peak enhancement value and the net enhancement value of benign and malignant nodules. We also found that MVD in malignant nodules was significantly higher than that in benign nodules (p = 0.024). This may be because that more microvessels are formed in malignant than in benign nodules, to supply essential nutrients and oxygen for rapid tumor growth.

VEGF is one of the strongest angiogenesis promoting factors, which has important regulatory functions on angiogenesis and permeability of blood vessels. VEGF is normally highly expressed in tumor cells, yet weakly or not expressed in benign nodules. Because MVD is an index reflecting angiogenesis in tumors, positive correlation between VEGF, the peak enhancement value and the net enhancement value suggests that the elevation of microvessels may be the result of VEGF overexpression.

In summary, the net enhancement value is an important indicator for the diagnosis of benign and malignant SPNs. When the threshold for the net enhancement value is 20 Hu, the sensitivity, accuracy, positive predicative value and negative predicative value for diagnosing benign and malignant nodules are relatively high. The enhancement modes of benign and malignant nodules have characteristic features. The peak enhancement value and the net enhancement value are positively correlated to MVD and VEGF, which could reflect angiogenesis and the growth of SPNs to certain degrees.
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References


