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Application of CT perfusion imaging in NSCLC and its correlation with angiogenesis and lymph node metastasis

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Abstract. – OBJECTIVE: To investigate the application of computed tomography (CT) perfusion imaging in non-small cell lung cancer (NSCLC) and its correlation with angiogenesis and lymph node metastasis.

PATIENTS AND METHODS: A total of 100 patients with NSCLC were selected as the study subjects. They were admitted to our hospital from January 2013 to January 2018. All patients were examined by CT perfusion imaging after admission. The differences and correlations of CT perfusion imaging parameters between patients with different angiogenesis and pathological conditions were analyzed.

RESULTS: There was no significant difference in CT perfusion imaging parameters between patients with different tissue types. Blood flow (BF) in patients with lymph node metastasis was significantly higher than that in patients with non-lymph node metastasis. Blood value (BV) and peak enhancement index (PEI) in patients with lymph node metastasis were lower than those in patients with non-lymph node metastasis. There was no significant difference in mean transit time (MTT) between patients with different lymph node metastasis. The BF of stage I-II patients was significantly higher than that of stage III-IV patients, and there was no significant difference in other indexes ($p < 0.05$). There was significant difference in micro-vessel density (MVD) between patients with different pathological tissues and lymphatic metastasis ($p < 0.05$). There was no significant difference in MVD between patients with different TNM stages ($p > 0.05$). Lymph node metastasis and MVD are negatively correlated with CT perfusion imaging indices BF, BV and PEI, respectively.

CONCLUSIONS: CT perfusion imaging technology can reflect the formation of pulmonary capillaries and the ability of metastasis and dissemination of tumors to a certain extent.

Key Words:
Non-small cell lung cancer (NSCLC), CT perfusion imaging, Lymph node metastasis, Angiogenesis density.

Abbreviations

NSCLC: non-squamous non-small cell lung cancer; BMI: Body Mass Index; KPS: Karnofsky; BF: blood-flow; BV: blood volume; PEI: Peak enhancement image; MTT: mean transit time; MVD: microvessel density.

Introduction

Lung cancer is one of the most common clinical diseases of respiratory tract tumor[1]. Its incidence and mortality rank first in the world in recent years. According to epidemiological statistics[2], non-squamous non-small cell lung cancer (NSCLC) has the highest incidence (85.00%) in all lung cancers. As the industrialization process intensifies, NSCLC is increasing year by year[3], with common clinical symptoms such as chest distended pain, phlegm with blood, low fever, fatigue and weight loss. When disorders of respiratory function are found in the early stage, the disease has already developed. Therefore, it can bring many challenges to the clinical treatment[4]. CT perfusion imaging reflects the vascular formation of patients to some extent. During the course of treatment, the prognosis of patients can also be evaluated by differential analysis of the blood flow patterns. Evaluation of NSCLC preoperative diagnosis in current clinical studies is limited in the determination of case parameters[5]. There are no effective indexes related to tumor biological behavior. This study tried to provide a scientific basis for clinical diagnosis and evaluation of therapeutic effect by analyzing the association between CT perfusion imaging indexes and pathological indexes in patients with NSCLC.

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Patients and Methods

Clinical Data

One hundred patients with NSCLC were selected as the study subjects. They were admitted to our hospital from January 2013 to January 2018. There were 54 males and 46 females, with age range of 45-65 years old and the average age of (57.51±2.37) years old. Their weight was 45-70 kg with the average weight of (61.40±2.37 kg), and BMI index of (25.56±1.29). The average duration of tumor was (2.39±0.89) years, the diameter of lesions was 1.7-7.2 cm with the average diameter of (3.66±1.02) cm. There were 39 patients with squamous cell carcinoma, 37 patients with adenocarcinoma, 24 patients with adenosquamous carcinoma. There were 39 patients with lymph node metastasis, 61 patients without metastasis. Twenty-nine patients were in TNM stage I, fifty-one patients in stage II, eleven patients in stage III, and nine patients in stage IV. None of the patients were lost in the follow-up during the study. All patients signed informed consent, and the study has been approved by the Ethics Committee.

Inclusion criteria: (1) Patients who met the diagnostic criteria for NSCLC[6] and were confirmed by biopsy and histopathology; (2) Patients who were estimated to survive for more than 6 months; (3) Patients with KPS score[7] of more than 70 points; (4) Patients who had no contraindication for radiotherapy drugs used in this study; (5) Patients who had signed the informed consent. Exclusion criteria: (1) Patients with severe heart, liver, and kidney dysfunction; (2) Patients with impaired communication ability; (3) Patients with abnormal blood routine; (4) Patients who did not cooperate with the treatment protocol of this study.

Research Methods

All patients were examined by CT perfusion imaging.

Siemens 64-slice spiral CT (Munich, Germany) was used in this study. The patient took a supine position and accepted breath-holding training before CT perfusion imaging. First, a routine scan was performed on the patient. After the scan, the lesions of the patient were determined. Then, a continuous film scan was performed, with CT perfusion imaging parameters 120 kv and 200 mA. Iodohydrol (Beijing Beilu Pharmaceutical Co., Ltd., SFDA Approval Number H20053800) was used as the contrast agent. It was injected with a high-pressure syringe at the speed of 5 mL/s and the dose of 300 mgI/mL, delayed for 5 s. The scanned image was transferred to the workstation for image processing. The maximum area of the patient's lesions was used as the research object. Aorta was used as a reference vessel. ROI was drawn within 2 cm of the margin of the lesions, as far as possible to choose a large area of ROI depiction and reduce the effect of noise on detection. The blood flow (BF), blood volume (BV), peak enhancement index (PEI) of the aorta, and mean transit time (MTT) at the lesions were analyzed according to the perfusion images of the patient's blood volume.

Observational Indexes

Analysis of CT perfusion imaging parameters in patients with different pathological conditions. By comparing CT perfusion imaging parameters of patients with different tissue types, we analyzed lymphatic metastasis and TNM stage, the differences of CT perfusion imaging parameters of patients with different pathological conditions.

Analysis of CT perfusion imaging parameters in patients with different angiogenesis conditions. Micro-vessel density (MVD) was detected by immunohistochemical SP. CD34 positive criteria: there is a striped or clustered yellow-brown lumen of endothelial cells, with eight red blood cells as one. Weidner technical standards were used for counting capillaries and micro-vessels. The tumor center and surrounding sites were examined under 40× and 100× fold microscopes, respectively. Then, capillaries and micro-vessels were counted under a 200× microscope. The mean value of 6 visual fields was recorded. The microscopic examination was conducted by two specialists. If there were differences over 10%, the examination should be carried out again.

Multivariate analysis of CT perfusion imaging parameters. Logistics regression analysis was used to analyze CT perfusion imaging parameters, pathological status and vascular formation.

Correlation analysis of CT perfusion imaging parameters. Spearman correlation analysis was used to analyze the correlation between CT perfusion imaging parameters and pathological state and vascular formation.

Statistical Analysis

The data of this study were analyzed by SPSS 19.0 (IBM Armonk, NY, USA). The measurement data were expressed as ($\bar{x} \pm s$), the count data were expressed as [(n)]%, and the Chi-square test was used. When $p<0.05$, the difference was considered statistically significant.

Results

CT Perfusion Imaging Parameters in Patients with Different Pathological Conditions

There was no statistical difference between CT perfusion imaging parameters of patients with different tissue types. BF of patients with lymph node metastasis was significantly higher than that of patients with non-lymph node metastasis. BV and PEI of patients with lymph node metastasis were lower than those of patients with non-lymph node metastasis. There was no statistical significance in MTT between patients with different lymph node metastasis. BF of stage I-II patients was significantly higher than that of stage III-IV patients. There was no significant difference in other indexes (p <0.05), as detailed in Table I.

Analysis of CT Perfusion Imaging Parameters in Patients with Different Angiogenesis Conditions

There was significant difference in MVD between patients with different pathological tissues and lymphatic metastasis ($p < 0.05$). While there was no significant difference in MVD between patients in different TNM staging (p>0.05), as detailed in Table II.

Multivariate Analysis of CT Perfusion Imaging Parameters

According to the multivariate analysis of CT perfusion imaging parameters, lymph node metastasis, TNM staging and MVD were taken as independent risk factors of BF. Lymph node metastasis and MVD were taken as independent risk factors of BVF. Lymph node metastasis, TNM staging and MVD were taken as independent risk factors of PEI, with significant difference ($p <$ 0.05), as detailed in Table III.

Correlation Analysis CT Perfusion Imaging Parameters

According to the correlation analysis, lymph node metastasis and MVD were negatively correlated with BF, BV and PEI respectively, with significant difference ($p < 0.05$), as detailed in Table IV.

Discussion

NSCLC is one of the most common respiratory cancer[8], which is also one of the key points in the prevention and treatment of lung cancer. Yabuuchi et al[9] showed that the incidence of NSCLC is related to smoking. In recent years, imaging technology has been constantly developed. It not only has a relatively significant observation of the patient's

Table I. CT Perfusion imaging parameters in patients with different pathological conditions.

Pathological indexes	BF (mL/100 g*min)	BV (mL/100 g)	PEI (HU)	MTT (s)
Type of Tissues				
Squamous cell carcinoma (n=39)	37.25 ± 1.46	7.32 ± 1.19	19.68 ± 1.33	15.25 ± 1.46
Adenocarcinoma (n=37)	39.33 ± 3.19	9.55 ± 1.35	22.78 ± 1.45	16.33 ± 3.19
Adenosquamous carcinoma (n=24)	32.03 ± 1.22	6.33 ± 1.45	20.22 ± 1.18	14.16 ± 1.22
F	0.325	1.669	0.456	0.155
p	0.632	0.221	0.609	0.854
Lymph Node Metastasis				
Yes (n=39)	29.16 ± 3.25	7.35 ± 1.32	16.36 ± 1.57	15.16±3.25
No (n=61)	46.45 ± 1.58	9.31 ± 1.66	24.53 ± 1.45	15.45±1.58
t	30.966	6.219	26.607	0.519
p	0.000	0.000	0.000	0.606
TNM Staging				
Stage I-II (n=80)	48.23 ± 3.26	9.25 ± 2.07	22.19 ± 1.63	13.23 ± 3.26
Stage III-IV (n=20)	27.33 ± 2.16	9.32 ± 1.34	21.68 ± 1.39	14.33 ± 2.16
t	34.541	0.185	1.286	1.818
p	0.000	0.854	0.201	0.076

Table II. Analysis of CT perfusion imaging parameters in patients with different angiogenesis.

Pathological Indexes		MVD (piece/0.723 mm²)
Type of Tissues	Squamous cell carcinoma (n=39)	33.75 ± 1.59
	Adenocarcinoma (n=37)	53.23 ± 3.96
	Adenosquamous carcinoma (n=24)	38.45 ± 1.99
	F	0.445
	p	0.592
Lymph Node Metastasis	Yes (n=39)	54.56 ± 3.75
	No (n=61)	42.45 ± 2.64
	t	17.574
	p	0.000
TNM Staging	Stage I-II (n=80)	50.03 ± 1.22
	Stage III-IV (n=20)	49.16 ± 3.25
	t	1.177
	p	0.253

Table III. Analysis of CT perfusion imaging parameters in patients with different angiogenesis.

Factors	β	S.E.	Wald	*p*	OR	95 CI
BF						
Type of Tissues	1.018	2.361	1.322	0.325	1.019	1.899-1.926
Lymph Node Metastasis	1.062	3.269	1.333	0.002	1.632	1.331-2.320
TNM Staging	0.369	4.139	1.691	0.000	1.089	0.632-2.065
MVD	1.069	4.691	1.336	0.000	1.069	0.032-1.119
BV						
Type of Tissues	1.022	2.361	1.321	0.125	1.022	1.901-1.932
Lymph Node Metastasis	1.0631	3.272	1.333	0.005	1.630	1.339-2.329
TNM Staging	0.370	4.140	1.695	0.231	1.092	1.632-2.075
MVD	0.369	4.552	1.971	0.000	1.225	1.154-1.987
PEI						
Type of Tissues	0.281	4.654	1.398	0.151	1.331	1.443-2.143
Lymph Node Metastasis	1.233	3.221	1.422	0.000	1.443	1.021-2.109
TNM Staging	1.532	3.221	1.541	0.327	1.229	1.332-2.113
MVD	1.336	3.985	1.661	0.000	1.336	1.219-1.669
MTT						
Type of Tissues	0.562	4.441	1.541	0.236	0.369	1.225-1.668
Lymph Node Metastasis	0.558	1.597	1.457	0.614	0.987	1.229-1.887
TNM Staging	1.597	2.697	1.179	0.339	0.691	1.019-1.687
M VD	1.265	4.551	1.971	0.521	0.631	1.397-1.990

Table IV. Correlation analysis of CT perfusion imaging parameters.

Group		BF	BV	PEI	MTT
Type of Tissues	r	0.223	0.671	0.772	1.263
	p	0.561	0.325	0.361	0.328
Lymph Node Metastasis	r	0.981	0.761	0.231	0.175
	p	0.000	0.000	0.000	0.621
TNM Staging	r	1.272	0.778	0.945	1.391
	p	0.000	0.332	0.421	0.192
MVD	r	0.716	0.765	0.670	1.369
	p	0.000	0.000	0.000	1.116

tissue morphology, but also gives positive development of the patient's MVD to a certain extent[10]. CT perfusion imaging technique can clearly show the hemodynamic status of relevant tissues and organs according to dilution principle and central volume law of development tracer. In general, BF is the ratio of BV to MTT of blood[11]. Of which, BF refers to the total amount of blood flowing through the corresponding official cavity per unit time, BV refers to the total amount of blood in the tissue, and MTT reflects the passage time of the contrast machine in the capillaries[12]. After injection of contrast agent, CT perfusion imaging could reflect the patient's blood perfusion indexes by analyzing the time density curve of each pixel in the area of interest from the curve maximum slope and other indexes. In patients with malignant tumor, the lesion structure is much higher than the normal tissue because of the number, size, and openness of capillaries. However, in patients with NSCLC, tissues of lung injure heavily, which causes serious effects on the blood circulation of lung and a higher blood flow signal at the edge of the tumor. While in the central position of the tumor, it mainly shows necrosis of the local tissue[13].

In this study, we analyzed the correlation of the differences of MVD in different tissues, TNM staging and lymph node metastasis with different CT perfusion imaging indexes. Lymph node metastasis and MVD in patients were negatively correlated with BF, BV and PEI of CT perfusion imaging indexes, respectively. According to the analysis on vascular density, adenocarcinoma is the highest, followed by squamous cell carcinoma, and finally adenosquamous carcinoma. However, there was not any statistical significance from CT perfusion indexes of patients. According to the analysis, the blood perfusion at the focal site of lung tumor is not only related to the density and generation of blood vessels at the focal site, but also related to the structure of blood vessels. McGowan et al[14] have reported that the structure of different lesions was related to the tissues of patients. There was a statistically significant difference between the micro-vessels at the lesions in patients with different tissues, however, the vessels were malformed, coarse or even distorted. The absence of basilar membrane of such vessels and nerve endings of smooth muscle resulted in a small amount of perfusion, therefore it had little impact on the local perfusion of patients.

There was significant difference in MVD and CT perfusion indexes among patients with tumor in different stages. According to the analysis, the tumor infiltration degree was relatively small, the diameter of blood vessel formation was relatively low compared with those of patients with tumor in early stage. The malformation of malignant gas and the injury of smooth muscle were significantly lower than those of patients with advanced tumor. At the same time, due to the early stage of tumor, the necrosis rate of local capillaries caused by the body's immune system was relatively low. Therefore, according to the analysis of the vascular density of patients, there was no statistically significant difference between the tumor vascular density of patients with different stages. According to the analysis on the patients' concern situation, there was statistically significant difference between different stages of patients' academic prevalence.

In the analysis of lymph node metastasis in patients, the type of BF of lesions in patients with lymph node metastasis abnormally increased. With the increase of the invasion degree of patients with tumor, the main reason for distant spread is hematogenous dissemination. In the course, there was a certain overlap of BF signals between the cancer tissue of the local lesions and the cancer tissue value of the lymph node. Therefore, the relative increase of the local MVD value and the CT perfusion value could result in the further direct correlation between the hematoma spread of the patient and the tumor lymph node metastasis of the patient[15].

The novelties of this study are to quantify the imaging results of patients and effectively reduce the subjective error of diagnostic physicians. However, there are some limitations in this study. During the sampling of lesions of the patient, accurate sampling could not be conducted according to the actual tumor site of the patient. With the continuous progress of sampling technology, further confirmation is needed in future research. At the same time, the correlation evaluation of the prognosis of tumor patients with therapeutic effect needs to be further analyzed in future studies.

Conclusions

To sum up, lymph node metastasis and MVD were negatively correlated with BF, BV and PEI of CT perfusion imaging indexes respectively. CT perfusion imaging technique can reflect the formation of pulmonary capillaries and the metastasis and dissemination ability of tumor lesions to some extent.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) George RT, Mehra VC, Chen MY, Kitagawa K, Arbab-Zadeh A, Miller JM, Matheson MB, Vavere AL, Kofoed KF, Rochitte CE, Dewey M, Yaw TS, Niinuma H, Brenner W, Cox C, Clouse ME, Lima JA, Di Carli M. Myocardial CT perfusion imaging and SPECT for the diagnosis of coronary artery disease: a head-to-head comparison from the CORE320 multicenter diagnostic performance study. Radiology 2014; 272: 407-16.
2) Yamamoto T, Kent MS, Wisner ER, Johnson LR, Stern JA, Qi L, Fujita Y, Boone JM. Single-energy computed tomography-based pulmonary perfusion imaging: proof-of-principle in a canine model. Med Phys 2016; 43: 3998.
3) Kim SH, Kamaya A, Willmann JK. CT perfusion of the liver: principles and applications in oncology. Radiology 2014; 272: 322-344.
4) Sciagrà R, Lubberink M, Hyafil F, Saraste A, Slart RHJA, Agostini D, Nappi C, Georgoulias P, Bucerius J, Rischpler C, Verberne HJ; Cardiovascular Committee of the European Association of Nuclear Medicine (EANM). EANM procedural guidelines for PET/CT quantitative myocardial perfusion imaging. Eur J Nucl Med Mol Imaging 2020; 444: 1-30.
5) Liu D, Liu J, Wen Z, Li Y, Sun Z, Xu Q, Fan Z. 320-row CT renal perfusion imaging in patients with aortic dissection: A preliminary study. PLoS One 2017; 12: e0171235.
6) Dittrich C, Kosty M, Jezdic S, Pyle D, Berardi R, Bergh J, El-Saghir N, Lotz JP, Österlund P, Pavlidis N, Purkalne G, Awada A, Banerjee S, Bhatia S, Bogaerts J, Buckner J, Cardoso F, Casali P, Chu E, Close JL, Coiffier B, Connolly R, Coupland S, De Petris L, De Santis M, de Vries EG, Dizon DS, Duff J, Duska LR, Eniu A, Ernstoff M, Felip E, Fey MF, Gilbert J, Girard N, Glaudemans AW, Gopalan PK, Grothey A, Hahn SM, Hanna D, Herold C, Herrstedt J, Homicsko K, Jones DV Jr, Jost L, Keilholz U, Khan S, Kiss A, Köhne CH, Kunstfeld R, Lenz HJ, Lichtman S, Licitra L, Lion T, Litière S, Liu L, Loehrer PJ, Markham MJ, Markman B, Mayerhoefer M, Meran JG, Michielin O, Moser EC, Mountzios G, Moynihan T, Nielsen T, Ohe Y, Öberg K, Palumbo A, Peccatori FA, Pfeilstöcker M, Raut C, Remick SC, Robson M, Rutkowski P, Salgado R, Schapira L, Schernhammer E, Schlumberger M, Schmoll HJ, Schnipper L, Sessa C, Shapiro CL, Steele J, Sternberg CN, Stiefel F, Strasser F, Stupp R, Sullivan R, Tabernero J, Travado L, Verheij M, Voest E, Vokes E, Von Roenn J, Weber JS, Wildiers H, Yarden Y. ESMO / ASCO Recommendations for a Global Curriculum in Medical Oncology Edition 2016. ESMO Open 2016; 1: e000097.
7) Badea CT, Johnston SM, Subashi E, Qi Y, Hedlund LW, Johnson GA. Lung perfusion imaging in small animals using 4D micro-CT at heartbeat temporal resolution. Med Phys 2010; 37: 54-62.
8) Lee SH, Rimner A, Gelb E, Deasy JO, Hunt MA, Humm JL, Tyagi N. Correlation Between Tumor Metabolism and Semiquantitative Perfusion MRI Metrics in Non-small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2018; 102: 718-726.
9) Yabuuchi H, Kawanami S, Iwama E, Okamoto I, Kamitani T, Sagiyama K, Yamasaki Y, Honda H. Prediction of Therapeutic Effect of Chemotherapy for NSCLC Using, Dual-Input Perfusion CT Analysis: Comparison among Bevacizumab Treatment, Two-Agent Platinum-based Therapy without Bevacizumab, and Other Non-Bevacizumab, Treatment Groups. Radiology 2018; 286: 685-695.
10) Choi S, Kim K, Kim M. The efficacy of cone beam CT-based liver perfusion imaging for tumor vascularity and treatment response evaluation after TACE for HCC. J Vasc Interv Radiol 2018; 29: S284-S285.
11) Mansueti JR, Maillie S. A Review of Non–Small Cell Lung Cancer Post-Treatment Follow-up Imaging Procedures with PET/CT Scans Versus CT Scans and the Effect on Patient Survival. Int J Radiat Oncol Biol Phys 2017; 98: 231.
12) Li Q, Kim J, Balagurunathan Y, Liu Y, Latifi K, Stringfield O, Garcia A, Moros EG, Dilling TJ, Schabath MB, Ye Z, Gillies RJ. Imaging features from pre-treatment CT scans are associated with clinical outcomes in non-small-cell lung cancer patients treated with stereotactic body radiotherapy. Med Phys 2017; 44: 4341-4349.
13) Laffon E, Marthan R. Performance of 18F-FDG PET/MRI and 18F-FDG PET/CT for T and N staging in patients with non-small-cell lung cancer. Eur J Nucl Med Mol Imaging 2019; 46: 522-523.
14) McGowan DR, Macpherson RE, Hackett SL, Liu D, Gleeson FV, McKenna WG, Higgins GS, Fenwick JD. 18\r, F-fluoromisonidazole uptake in advanced stage non-small cell lung cancer: a voxel-by-voxel PET kinetics study. Med Phys 2017; 44: 4665-4676.
15) Lim JW, Lee H, Her K, Park HW, Shin KE. Myocardial CT perfusion imaging for pre- and postoperative evaluation of myocardial ischemia in a patient with myocardial bridging: a case report. Medicine (Baltimore) 2017; 96: e8277.