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Combination of Fluorine-18 Fluorodeoxyglucose Positron-Emission Tomography/Computed Tomography (^{18}F-FDG PET/CT) and Tumor Markers to Diagnose Lymph Node Metastasis in Non-Small Cell Lung Cancer (NSCLC): A Retrospective and Prospective Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: The early diagnosis of lymph node (LN) metastasis is crucial for patients with non-small cell lung cancer (NSCLC). However, the diagnosis of LN metastasis mainly dependent on ^{18}F-FDG PET/CT (fluorine-18 fluorodeoxyglucose positron-emission tomography/computed tomography) which exhibited high false positive/negative rate.

Material/Methods: In retrospective analysis, 135 patients with NSCLC from February 2014 to March 2017 were enrolled. Based on the pathological examination, 71 patients were distributed to the LN Metastasis Group while 64 patients were distributed to the No LN Metastasis Group. Data from ^{18}F-FDG PET/CT and tumor marker (TM) examination were collected to establish a logistic model. The receiver operating characteristic (ROC) curve analysis set the threshold of diagnostic factors. Finally, the diagnostic values of these factors were verified in a prospective analysis that included 78 patients with NSCLC from July 2017 to April 2019.

Results: In our retrospective analysis, compared with the No LN Metastasis Group, the maximum standardized uptake value (SUVmax)/size of primary lesion, the CT value/SUVmax/short diameter of LN, the level of TM were all significantly different than the LN Metastasis Group (All $P<0.05$). Our logistic model showed that SUVmax of primary lesion (odds ratio [OR]=1.491), short diameter of LN (OR=1.310) and grade of TM (OR=2.927) were significant variables. The ROC curve analysis showed the specificity and sensitivity of our logistic model was 90.6% and 90.1%, respectively. In our prospective analysis, the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of the logistic model were calculated as 85.7%, 90.9%, 87.2%, 96.0%, and 71.4%, respectively.

Conclusions: Our study found that combining ^{18}F-FDG PET/CT data and TM to establish a logistic model performed better in the diagnosis of LN metastasis with low false positive/negative rates in patients with NSCLC.

MeSH Keywords: Carcinoma, Non-Small-Cell Lung • Early Detection of Cancer • Lymphatic Metastasis • Nuclear Medicine

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Background

According to the epidemiological investigation of GLOBOCAN in 2012, lung cancer has become one of the most common cancers, and it accounts for approximately 13% of all newly diagnosed cancers [1]. Lung cancer is also one of the leading causes of cancer-related death [1]. Additionally, lung cancer is also characterized by ineffective treatment and poor prognosis due to its high rate of lymph node (LN) metastasis or hematogenous metastasis.

Based on histological features, non-small cell lung cancer (NSCLC) accounts for over 80% of lung cancers [2]. At present, the treatment method for patients with NSCLC still depends on surgery. Typically, even after radical resection, over 50% of NSCLC will recur or metastasize within 5 year [3]. Thus, preoperative evaluation of LN metastasis is the crucial indicator for cancer staging, requiring individualized systemic therapeutic approaches [4] and assessments of patient prognosis. The early diagnosis of LN metastasis in patients with NSCLC faces huge clinical challenges and requires attention in clinical studies.

^{18}F-FDG PET/CT (fluorine-18 fluorodeoxyglucose positron-emission tomography/computed tomography) is a sensitive imaging method that can identify the anatomical location of lesions and the metabolism alterations of glucose in tissues [5]. ^{18}F-FDG PET/CT is widely used in the staging of primary lung cancers. The FDG metabolism level of LNs can help diagnose LN metastasis. However, the threshold of the maximum standardized uptake value (SUVmax) of LN, which can make a clear distinction of LN metastasis, are still controversial. Additionally, there is a 15% to 20% false positive rate and approximately 20% false negative rate in PET/CT imaging when SUVmax of LN is used for the diagnosis of LN metastasis [6]. Especially for LNs with a diameter less than 1 cm, the false positive rate and false negative rate of PET/CT imaging will be exaggerated. Therefore, in recent years, more studies have used SUVmax of primary lesion as the independent predictor of LN metastasis in lung cancer cases [7,8]. However, the predictor factor for LN metastasis has not been confirmed by consensus and has not been well studied. Large-scale prospective analysis to evaluate the predictive value of factor such as SUVmax, LN diameter and location are still scarce in lung cancer literature.

Additionally, tumor markers (TMs) has been used for the early diagnosis of lung cancers with high accuracy and high sensitivity. Recent studies have highlight TMs as the indicators for evaluating the recurrence and metastasis of NSCLC [3]. Chen et al. reported that the level of carcinoembryonic antigen (CEA) and cytokeratin 19 fragment (CYFRA 21-1) were both significantly elevated in NSCLC with LN metastasis, compared with NSCLC without LN metastasis or benign lesions [9]. This indicates that the level of TMs is associated with the progression of LN metastasis in NSCLC. However, the specificity and sensitivity of TMs are still unclear.

In this study, we first analyzed the ^{18}F-FDG PET/CT parameters and level of TMs among 135 patients with NSCLC admitted to our hospital February 2014 to March 2017. By establishing a logistic regression model, the predictive value of ^{18}F-FDG PET/CT parameters of primary lesion, ^{18}F-FDG PET/CT parameters of LN and level of TM were screened and evaluated. The receiver operating characteristic (ROC) curve analysis was performed to determine the threshold for these factors. Furthermore, we evaluated the specificity and sensitivity of our logistic model in a prospective study in which we recruited 78 patients with NSCLC from July 2017 to April 2019. This study aimed to provide experimental evidences for the application of ^{18}F-FDG PET/CT combined TMs in the early diagnosis of LN metastasis in patients with NSCLC.

Material and Methods

Patients

For the retrospective analysis, 135 patients who were diagnosed with NSCLC at Beijing Chaoyang Hospital from February 2014 to March 2017 were enrolled. All patients received ^{18}F-FDG PET/CT and TM examination (CEA, CYFRA 21-1, neuron-specific enolase [NSE] and carbohydrate antigen 125 [CA125]) before surgery. Inclusion criteria were as follows: 1) patient's body mass index (BMI) was between 18 and 30 kg/m^2; 2) NSCLC diagnosed by pathological examination; 3) patient diagnosed as lung cancers for the first time; 4) patient did not receive radiotherapy, chemotherapy, or other treatment before enrollment; 5) patient received lobectomy and lymph node dissection; 6) LN metastasis in patient was also confirmed by pathological examination; 7) patient completed ^{18}F-FDG PET/CT, TM examination, and surgical operation within 2 weeks; and 8) clinical data of patient was complete. Finally, 71 patients were diagnosed with LN metastasis and 102 LNs were analyzed as the LN Metastasis Group. The rest of the 64 patients who did not have LN metastasis and 105 LNs were analyzed as the No LN Metastasis Group.

For prospective analysis, 78 patients who were diagnosed with NSCLC at Beijing Chaoyang Hospital from July 2017 to April 2019 were enrolled in this study. Inclusion criteria were as follows: 1) patient's BMI index was between 18 and 30 kg/m^2; 2) patient's age was between 40–80 years; 3) patient did not receive radiotherapy, chemotherapy, or other treatment before enrollment; 4) NSCLC was diagnosed by pathological examination; 5) patient received ^{18}F-FDG PET/CT and TM examination (CEA, CYFRA 21-1, NSE, and CA125) and surgery within 2 weeks; 6) patient's clinical data was complete.

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Ethical approval

The retrospective study and prospective study in this article were both approved by the Ethical Committee of Clinical Experiments of Beijing Chaoyang Hospital. All patients enrolled in this study were informed about the contents of this study and signed the informed consent.

^{18}F-FDG PET/CT

^{18}F-FDG PET/CT was performed by using SIEMENS Biograph 64 Truepoint PET/CT imaging system (Japan). The imaging agent was ^{18}F-FDG and the radiochemical purity is ≥95%. Prior to examination, patients fasted for more than 6 hours and fasting blood glucose was controlled below 8 mmol/L. After establishing venous access, ^{18}F-FDG (5.55 MBq/kg) was injected via veins. Then patients were allowed to rest for 60 minutes and drink 300 mL of water. After emptying the bladder of urine, whole body tomography was performed. Patients took the supine position and placed both hands on their head for body image acquisition. PET imaging acquisition was performed after CT scan was completed (120 kV, 0.75 seconds per rotation, pitch of 0.8). Images were collected from the base of the skull to the middle thigh and PET image was 3-dimensional (3D) acquisition mode. The axial field of view of PET/CT was 500 mm and the section thickness was 5 mm. The collection time for body part imaging was approximate 10 minutes (1.5–2 minutes/bed, 7 beds average). After body part imaging was collected, patients were instructed to put down their hands for head image acquisition. Images were collected from the top of the head to the foramen magnum of the skull base. The collection time for body part was approximate 3 minutes (3 minutes/bed, 1 bed in total). The other parameters were the same. The PET data were corrected by CT attenuation using TrueX reconstruction method, 21 subsets, 3 iterations, and high-filtering wave, to obtain PET whole body tomographic reconstruction images.

^{18}F-FDG PET/CT image analysis

^{18}F-FDG PET/CT image analysis was performed by 2 independent radiologists who were unaware of patient's allocation and blinded to the TM results. The final input data were calculated as the mean value from 2 independent radiologists. For measurement of primary lesion, by delineating the 3D region of interest on PET/CT fusion images on software, the SUVmax value was calculated automatically. The size of the primary tumor was measured by the lung window on the CT image, and the maximum cross section (long diameter+short diameter)/2 represents the size of the primary lesion. A primary lesion located in the central 1/3 of the lung field was defined as central type, otherwise lesions were defined as peripheral type. Primary lesions were also divided into solid or non-solid types based on the CT density. For measurement of LNs, the intrapulmonary lymph node area was recorded only when apparent enlargement or abnormal elevation of SUVmax of a LN was observed. Otherwise, only hilar lymph node data were measured. The CT values of LN, SUVmax of LN, and the short diameter of LN were recorded. If the highest short diameter and highest SUVmax were recorded in the same LN, then only that LN was recorded. If not, then 2 LNs with the highest short diameter, highest SUVmax, respectively, were recorded.

TM examination

All blood samples of patients were collected before treatment and analyzed by a fully automated electrochemiluminescence analyzer (Roche, E170). The commercial kit of CEA, CYFRA 21-1, NSE, and CA125 were used. The diagnostic threshold for each TM was 5.0 ng/mL, 3.3 ng/mL, 18.0 ng/mL, and 35.0 U/mL respectively.

TM examination analysis

TM examination analysis was performed by an independent observer, who was unaware of a patient's allocation and was blinded to the ^{18}F-FDG PET/CT results. The grade of TM was marked 0 if any of the CEA, CYFRA 21-1, NSE, or CA125 levels were in the normal range. Grade 1 if any of the TMs were 1-fold higher than normal range. Grade 2 if any of the TMs were 2-fold higher than normal range. Grade 3 if any of TMs were 3-fold (or more) higher than normal range.

Diagnosis of LN metastasis in prospective analysis

The diagnosis of LN metastasis by SUVmax of primary lesion, short diameter of LN, grade of TM, and logistic model were performed by 4 independent observers. Each observer was only aware of 1 parameter and blinded to the other parameters. Additionally, the observers were unaware of a patient's pathological results.

Statistical analysis

The statistical analysis was performed by SPSS 19.0 software. The measurement data were presented as mean±standard deviation and analyzed *t*-test. The enumeration data were presented as frequency and analyzed by χ^2 test or Fisher exact test. The grade data were analyzed by Mann-Whitney test. Binary logistic regression analysis was used to screen the main risk factors affecting LN metastasis and establish a logistic regression model for diagnosis of LN metastasis. The ROC curve was used to analyze the diagnostic efficacy of influential factors. A difference of 2-sided $P<0.05$ was considered as statistically significant.

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Table 1. Clinical characteristics of patients in retrospective analysis.

Variables	Retrospective study				Prospective study
	LN metastasis group	No LN metastasis group	t/χ^2 value	P value	
Number of patients	71	64			78
Age (years)	61.90±10.78	60.25±12.90	0.81	0.42	59.23±12.69
Gender					
Male: Female	48: 23	45: 19	0.12	0.73	50: 28
Smoking history					
Positive: negative	39: 32	40: 24	0.80	0.37	43: 35
Location of primary lesion					
Lesion in right lung	43	31	2.00	0.16	52
Right: superior/middle/inferior lobe	20: 5: 18	14: 3: 14			25: 4: 23
Lesion in left lung	28	33			26
Left: superior/inferior lobe	19: 9	21: 12			19: 7
Pathological type of NSCLC					
Adenocarcinoma	59	50	0.86	0.67	66
Squamous carcinoma	11	12			12
Large cell carcinoma	1	2			0

LN – lymph node; NSCLC – non-small cell lung cancer.

Results

Demographic characteristics of patients

The demographic characteristics of patients in retrospective analysis and prospective study are shown in Table 1. In the retrospective part of this study, a total of 135 patients with NSCLC (based on whether patients have LN metastasis by pathological examination) were included: 71 patients in the LN Metastasis Group and the rest of the 64 patients were in the No LN Metastasis Group. There were no significant differences of age (61.90±10.78 versus 60.25±12.90, *P*=0.42), gender (*P*=0.73), smoking history (*P*=0.37), location of primary lesion (*P*=0.16), or pathological type of NSCLC (*P*=0.67) between the LN Metastasis Group and No LN Metastasis Group.

^{18}F-FDG PET/CT of primary lesion and LN in patients

We statistically analyzed the ^{18}F-FDG PET/CT parameters of the primary lesion and LN between the LN Metastasis Group and the No LN Metastasis Group. As shown in Table 2, SUVmax and size of primary lesion were significantly higher in the LN Metastasis Group compared with those in the No LN Metastasis Group (14.00±5.75 versus 5.03±3.29, *P*<0.01; 28.02±13.28 versus 20.62±7.29, *P*<0.01). However, results also showed that there were no significant differences in location type (*P*=0.06) or internal characteristics of tumors (*P*=0.16) between the LN Metastasis Group and the No LN Metastasis Group.

Additionally, the ^{18}F-FDG PET/CT parameters of LNs between the LN Metastasis Group and the No LN Metastasis Group showed that compared with the No LN Metastasis Group, the CT value (43.14±13.01 versus 55.56±17.36, *P*<0.01) was significantly lower while SUVmax (7.85±versus 4.35 versus 4.21±3.28, *P*<0.01), and short diameter of LN (14.34±5.70 versus 8.18±2.68, *P*<0.01) were all significantly higher in the LN Metastasis Group (Table 2).

TM examination of patients

As shown in Table 3, the TM analysis were also significantly different between the LN Metastasis Group and the No LN Metastasis Group. The grade distribution of TMs between the 2 groups was distinct (*P*=0.02): 31% of patients (22 out of 71 patients) in the LN Metastasis Group compared to 56% of patients (36 out of 64 patients) expressed TMs at the normal range in the No Metastasis Group. It is noteworthy that when the grade of the TMs reached 2, 92% of patients (24 out of

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Table 2. ^{18}F-FDG PET/CT parameters of primary tumor and LN in patients.

Variables	LN metastasis group	No LN netastasis group	t/χ^2 value	P-value
SUVmax of primary lesion	14.00±5.75	5.03±3.29	10.96	<0.01
Size of primary lesion (mm)	28.02±13.28	20.62±7.29	3.95	<0.01
Location type				
Peripheral	46	51	3.70	0.06
Central	25	13		
Internal characteristics of tumor				
Solid	61	49	1.95	0.16
Non-Solid	10	15		
CT value of LN (HU)	43.14±13.01	55.56±17.36	4.97	<0.01
SUVmax of LN	7.85±4.35	4.21±3.28	5.44	<0.01
Short diameter of LN (mm)	14.34±5.70	8.18±2.68	7.89	<0.01

^{18}F-FDG PET/CT – fluorine-18 fluorodeoxyglucose positron-emission tomography/computed tomography; LN – lymph node; SUV – standardized uptake value; CT – computed tomography.

Table 3. Level of TM in patients.

Variables	LN metastasis group	No LN metastasis group	t/Z value	P-value
Grade of TM				
0	22	36	4.13	0.02
1	25	26		
2	12	2		
3	12	0		
Level of CEA (ng/mL)	8.68±8.61	3.75±2.09	4.46	<0.01
Level of CYFRA 21-1 (ng/mL)	5.47±5.27	2.71±1.66	4.01	<0.01
Level of NSE (ng/mL)	22.94±15.93	16.84±6.78	2.84	0.01
Level of CA125 (U/mL)	51.42±36.60	31.97±18.26	3.84	<0.01

TM – tumor marker; LN – lymph node; CEA – carcinoembryonic antigen; CYFRA 21-1 – cytokeratin 19 fragment; NSE – neuron-specific enolase; CA125 – carbohydrate antigen 125.

26 patients) developed LN metastasis. When the grade of TM reached 3, all grade-3 patients (12 out of 12 patients) developed LN metastasis. Additionally, the level of CEA, CYFRA 21-1, NSE, and CA125 were all significantly higher in the LN Metastasis Group compared with those in No LN Metastasis Group (CEA: 8.68±8.61 versus 3.75±2.09, P<0.01; CYFRA 21-1: 5.47±5.27 versus 2.71±1.66, P<0.01; NSE: 22.94±15.93 versus 16.84±6.78, P=0.01; CA125: 51.42±36.60 versus 31.97±18.26, P<0.01).

Logistic analysis of risk factors for LN metastasis

We constructed the logistic correlation model by inputting patient's data for age, gender, smoking history, location of primary lesion, pathological type, SUVmax of primary lesion, size of primary lesion, location type, internal characteristics of tumor, CT value of LN, SUVmax of LN, short diameter of LN, and grade of TM. Results of the logistic correlation analysis showed that the statistically significant variables were SUVmax of primary lesion (P<0.001), short diameter of LN (P=0.001),

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Table 4. Logistic analysis of risk factors in LN metastasis.

Variables	Regression coefficient (β)	Wald value	P-value	OR
SUVmax of primary lesion	0.350	23.391	<0.001	1.419 (1.231–1.635)
Short diameter of LN (mm)	0.270	10.226	0.001	1.310 (1.110–1.546)
Grade of TM	1.074	7.295	0.007	2.927 (1.343–6.380)
Constant	–6.698	35.449	<0.001	

LN – lymph node; SUV – standardized uptake value; OR – odds ratio.

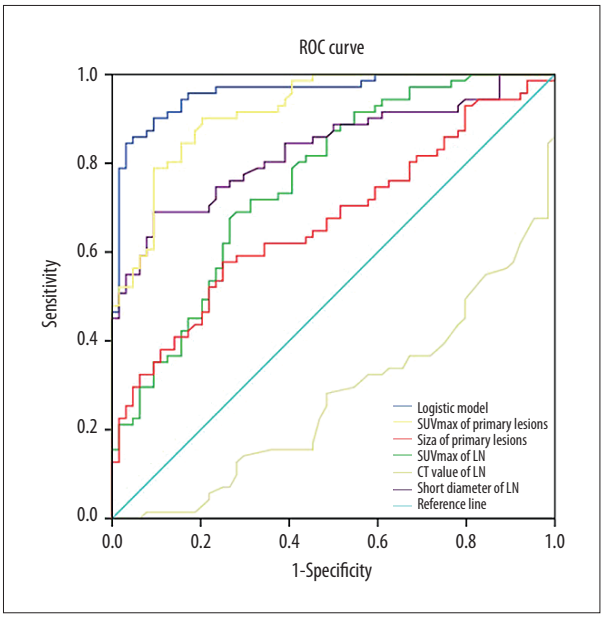

Figure 1. ROC curve of diagnostic factors in LN metastasis. ROC – receiver operating characteristic; LN – lymph node.

and grade of TM (*P*=0.007). The odds ratio (OR) of SUVmax of primary lesion, short diameter of LN, and grade of TM were 1.419, 1.310, and 2.927, respectively and the grade of TM was the most influential factor in assessing LN metastasis in patients with NSCLC. We established the equation for our logistic model: y=–6.698+0.350* (SUVmax of primary lesion)+0.270* (short diameter of LN)+1.074* (grade of TM). The predictive value P=e^y/(1+e^y) and e was the natural logarithm. If *P*>0.5, LN metastasis was diagnosed by our logistic model. If *P*<0.5, LN was diagnosed as non-metastatic (Table 4).

ROC curve analysis of diagnostic factors in LN metastasis

We constructed ROC curves to evaluate the diagnostic effects of factors including the logistic model, SUVmax of primary lesion, size of primary lesion, SUVmax of LN, CT value of LN, and short diameter of LN. As shown in Figure 1, because the area under curve (AUC) for CT value of LN was below the reference line, this factor was irrelevant and removed. Among the included factors, the AUC of our logistic model was the highest (0.961±0.016) and the specificity, sensitivity reached 90.6% and 90.1%, respectively (Table 5). Additionally, SUVmax of primary lesion and short diameter of LN also displayed notable diagnostic efficacy. The threshold of SUVmax of the primary lesion was 9.53 and the specificity, sensitivity was 90.6% and 78.9%, respectively. The threshold of short diameter of the LN was 11.40 and the specificity, sensitivity was 90.6% and 69.0%, respectively.

Logistic model better diagnosed LN metastasis in prospective analysis

After performing the retrospective analysis, we recruited 78 patients with NSCLC for a prospective analysis. The demographic

Table 5. ROC curve analysis.

Factors	AUC	Threshold	Specificity	Sensitivity
Logistic model	0.961±0.016	0.56	90.6	90.1
SUVmax of primary lesion	0.920±0.022	9.53	90.6	78.9
Size of primary lesion	0.669±0.046	24.58	75.0	57.7
SUVmax of LN	0.759±0.041	5.38	73.4	67.6
Short diameter of LN	0.832±0.035	11.40	90.6	69.0

ROC – receiver operating characteristic; AUC – area under the curve; SUVmax – maximum standardized uptake value; LN – lymph node.

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Table 6. Diagnosis of LN metastasis by short diameter of LN, SUVmax of primary lesion, TM and logistic model in prospective study.

Short diameter of LN	Pathological diagnosis		Total
	LN metastasis	No LN metastasis	
LN metastasis	31	3	34
No LN metastasis	25	19	44
Total	56	22	78
SUVmax of primary lesion	**Pathological diagnosis**		**Total**
	LN metastasis	**No LN metastasis**	
LN metastasis	37	4	41
No LN metastasis	19	18	37
Total	56	22	78
TM	**Pathological diagnosis**		**Total**
	LN metastasis	**No LN metastasis**	
LN metastasis	28	6	34
No LN metastasis	28	16	44
Total	56	22	78
Logistic model	**Pathological diagnosis**		**Total**
	LN metastasis	**No LN metastasis**	
LN metastasis	48	2	50
No LN metastasis	8	20	28
Total	56	22	78

LN – lymph node; SUV – standardized uptake value; TM – tumor marker.

Table 7. Diagnostic efficacy of factors in prospective study.

Variables	Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value
SUVmax of primary lesion	0.661	0.818	0.705	0.902	0.486
Short diameter of LN	0.554	0.864	0.641	0.912	0.432
TM	0.500	0.727	0.564	0.824	0.364
Logistic model	0.857	0.909	0.872	0.960	0.714

LN – lymph node; SUV – standardized uptake value; TM – tumor marker.

characteristics of the enrolled patients are listed in Table 1. Among 78 patients, 56 patients were diagnosed with LN metastasis while 22 patients were diagnosed with no LN metastasis by pathological examination.

Firstly, based on the threshold of SUVmax of the primary lesion (9.53 from ROC curve) 41 patients were diagnosed with LN metastasis while 37 patients were diagnosed with no LN metastasis by SUVmax of primary lesion. Among the 41 patients with LN metastasis, 37 patients were truly positive while 4 cases were falsely positive. Among the 37 patients with no LN metastasis, 18 patients were truly negative while 4 cases were falsely negative. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of SUVmax of primary lesion were calculated as 66.1%, 81.8%, 70.5%, 90.2%, and 48.6%, respectively (Tables 6, 7).

Based on the threshold of short diameter of LN (11.40 from ROC curve), 34 patients were diagnosed with LN metastasis while 44 patients were diagnosed with no LN metastasis by

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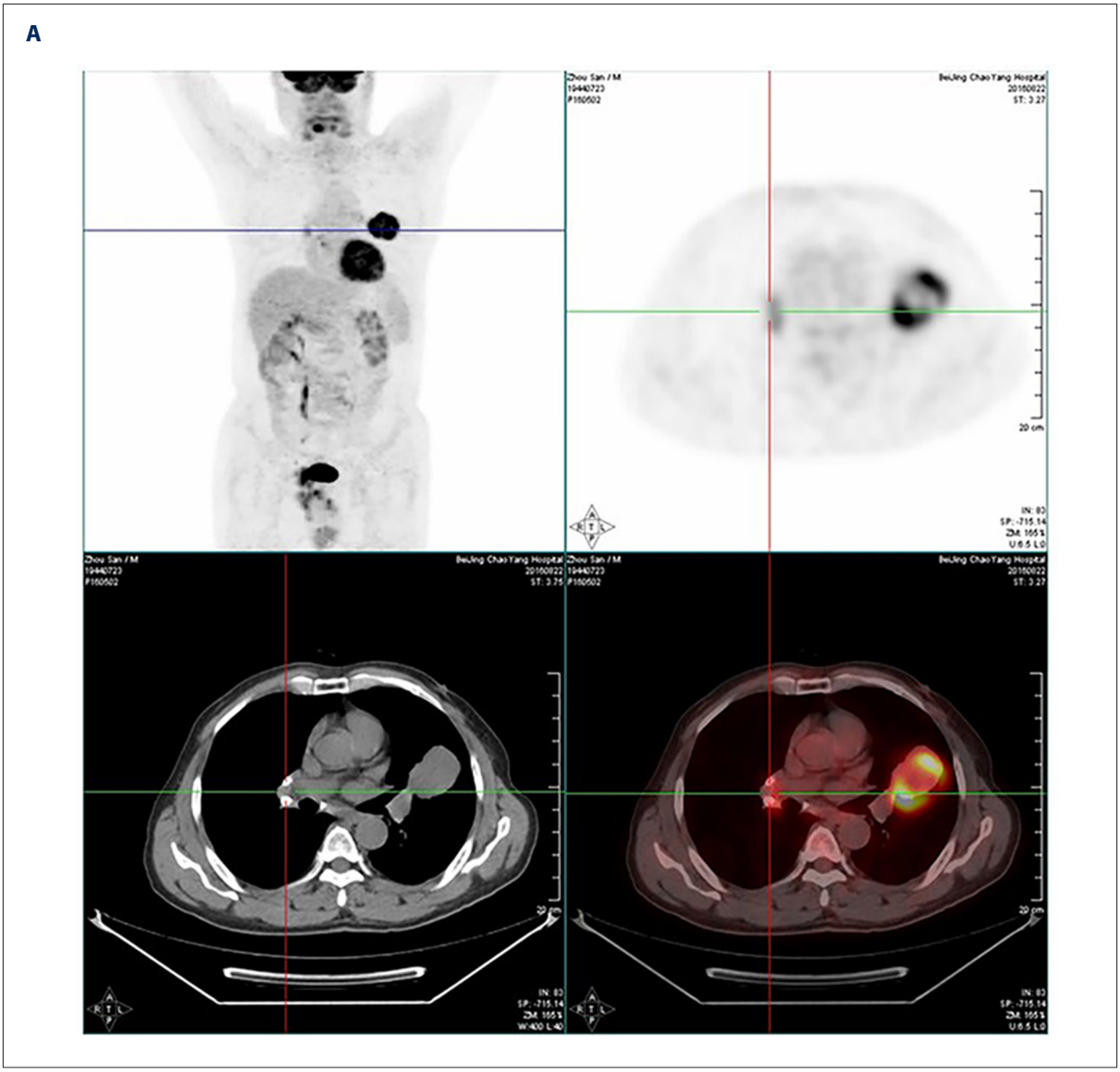
short diameter of LN. Among the 34 patients with LN metastasis, 31 patients were truly positive while 3 cases were falsely positive. Among the 44 patients with no LN metastasis, 19 patients were truly negative while 25 cases were falsely negative. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of short diameter of LN were calculated as 55.4%, 86.4%, 64.1%, 91.2%, and 43.2%, respectively (Tables 6, 7).

As aforementioned in previous results, when the grade of TM reached 2, over 90% of grade-2 patients developed LN metastasis. Thus grade 2 of TM was set as the threshold of TM for diagnosis of LN metastasis. Results showed that 34 patients were diagnosed with LN metastasis while 44 patients were diagnosed with no LN metastasis by TM. Among the 34 patients with LN metastasis, 28 patients were truly positive while 6 cases were falsely positive. Among the 44 patients with no LN metastasis, 16 patients were truly negative while 28 cases were falsely negative. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of TM were calculated as 50.0%, 72.7%, 56.4%, 82.4% and 36.4%, respectively (Tables 6, 7).

Finally, we used our logistic model to diagnose LN metastasis. There were 50 patients diagnosed with LN metastasis while 28 patients were diagnosed with no LN metastasis by our logistic model. Figure 2 shows 2 typical cases: 1 case was NSCLC with LN metastasis and the other case was NSCLC without LN metastasis, and the ^{18}F-FDG PET/CT data for these 2 cases are shown in Figure 2. The diagnosis of these 2 cases using our



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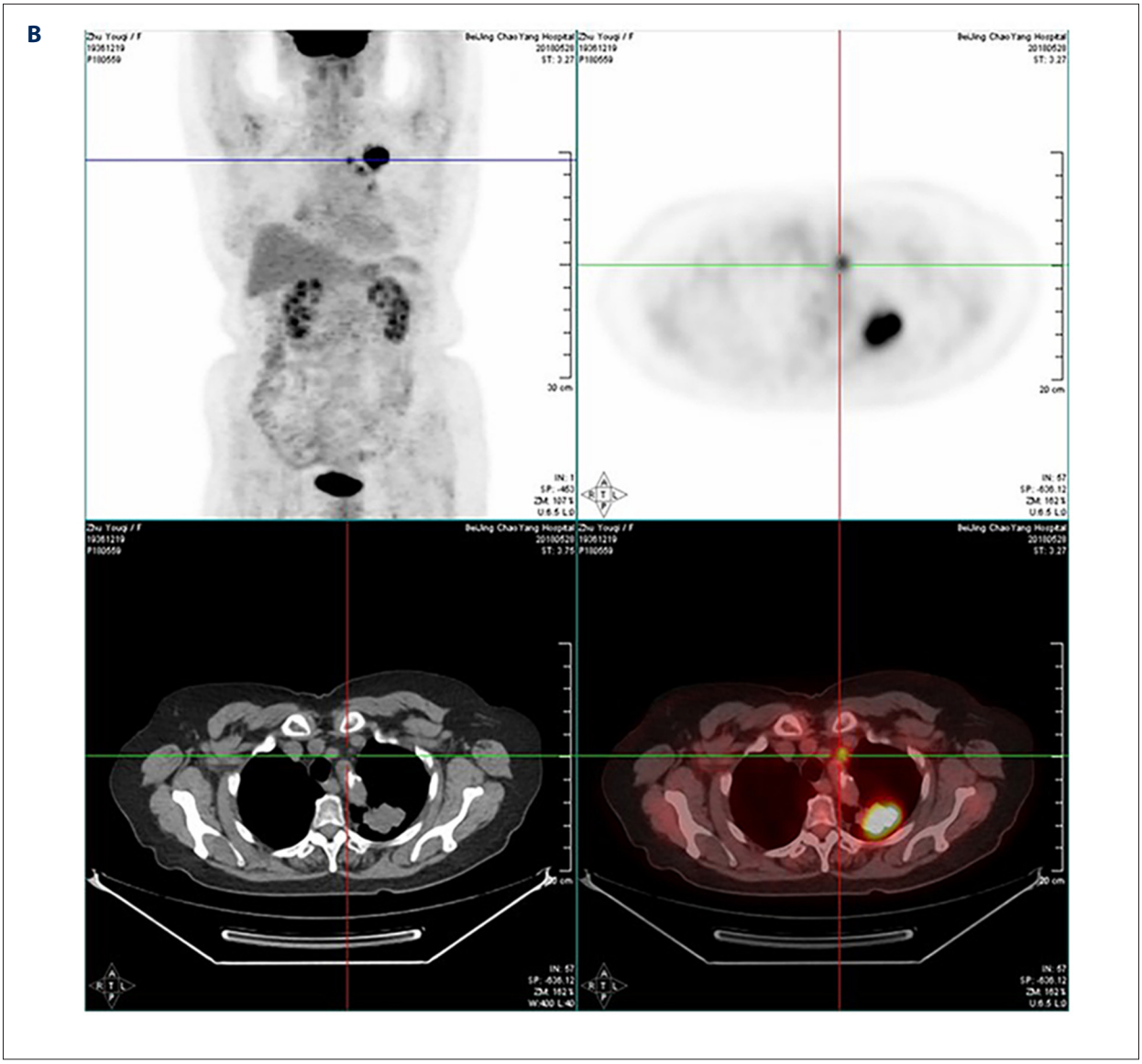

Figure 2. (**A**) ^{18}F-FDG PET/CT from a male patient, 72 years old, adenocarcinoma in the upper left lobe, size of primary lesion: 64×42 mm, SUVmax of primary lesion: 8.3, SUVmax and short diameter of left hilar lymph node were 2.3 and 9.1, respectively. CEA was 7.2 ng/mL, the other TMs were in the normal range. Using our logistic model, y=–0.262, *P*<0.5, the patient was diagnosed as non-metastasis of LN, which was consistent with pathological examination. (**B**) ^{18}F-FDG PET/CT from a female patient, 80 years old, adenocarcinoma in the upper left lobe, size of primary lesion: 25×41 mm, SUVmax of primary lesion: 14.6, SUVmax and short diameter of left hilar lymph node were 6.4 and 10.0, respectively. CEA was 11.3 ng/mL, CYFRA 21-1 was 5.6 ng/mL, CA125 was 44 U/mL, NSE was in the normal range. Using our logistic model, y=3.26, *P*>0.5, the patient was diagnosed as metastasis of LN, which was consistent with pathological examination. ^{18}F-FDG PET/CT – fluorine-18 fluorodeoxyglucose positron-emission tomography/computed tomography; SUV – standard uptake value; CEA – carcinoembryonic antigen; TM – tumor marker; LN – lymph node; CYFRA 21-1 – cytokeratin 19 fragment; CA125 – carbohydrate antigen 125; NSE – neuron-specific enolase.

logistic model are also elucidated. Finally, among the 50 patients with LN metastasis, 48 patients were truly positive while 2 cases were falsely positive. Among the 28 patients with no LN metastasis, 20 patients were truly negative while 8 cases were falsely negative. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of our logistic model were calculated as 85.7%, 90.9%, 87.2%, 96.0%, and 71.4%, respectively. These results indicated that our logistic model performed better than other factors in the diagnosis of LN metastasis in patients with NSCLC (Tables 6, 7).

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Discussion

The early diagnosis of LN metastasis is one of the most crucial indicators for staging, making treatment planning, and assessing the prognosis of NSCLC. At present, the early diagnosis of LN metastasis in patients with NSCLC still depends on imagological examination, especially conventional CT methods. However, CT examination only provides anatomical or morphological information for LNs. Therefore, when the short diameter of a LN ≥10 mm by CT examination, the LN is diagnosed as metastatic in a clinic setting. In our study, we found that compared with the No LN Metastasis Group, the short diameter of LN was significantly increased in LN Metastasis Group (14.34±5.70). The threshold for the short diameter of LN was 11.40 by ROC curve analysis, which was similar with the clinical standard. The sensitivity and specificity of the short diameter of LN in the diagnosis of the LN Metastasis Group was only 55.4% and 86.4%, respectively. This result was consistent with previous studies. Gould et al. reported the sensitivity of CT examination in the diagnosis of LN metastasis was 44–63% while the specificity was 43–79% [10]. The low sensitivity and specificity of CT examination indicates a huge need for improvements in the diagnostic method of LN metastasis in patients with NSCLC.

In recent years, the application of ^{18}F-FDG PET/CT in the diagnosis of cancer recurrence or metastasis has attracted huge attentions [11]. ^{18}F-FDG PET/CT combines functional metabolic imaging with morphological imaging to provide the anatomical information and also the metabolic situations of glucose in lesions [12]. Numerous studies have typically proven that SUVmax of 2.5 is the effective threshold in the diagnosis of malignant and benign lesions. However, in the diagnosis of metastatic and nonmetastatic LNs, SUVmax of 2.5 was not appropriate and the threshold of SUVmax of LN is still controversial. Hellwing et al. reported that the elevated SUVmax (≥4.5) of LNs was more specific to LN metastasis [13]. Ayesha et al. analyzed the FDG imaging of 1252 LNs and found that SUVmax of 5.3 was an excellent threshold in the diagnosis of LN metastasis. The diagnosis accuracy even reached 92.0% [14]. In our study, compared with the No LN Metastasis Group, the SUVmax of LN was significantly increased in the LN Metastasis Group (7.85±4.35). The threshold of SUVmax of LN was set as 5.38 by ROC curve analysis, which was similar with the Ayesha et al. study values. However, the sensitivity and specificity of SUVmax of LN in the diagnosis of LNs was only 73.4% and 67.6%, respectively. Additionally, in small LNs with diameters less than 10 mm, the diagnostic accuracy of SUVmax of LN declined drastically. This indicates that SUVmax of LN was not a reliable indicator for the diagnosis of LN metastasis.

In our study, compared with No LN Metastasis Group, the CT value of LN was also significantly lower in the LN Metastasis Group (43.14±13.01). The ROC curve analysis indicated that the AUC of the CT value of LN was less than 0.5. The CT value of a LN was considered an irrelevant factor in the diagnosis of LN metastasis. However, in clinical practice, some researchers have highlighted that the extremely high CT value of a LN always indicated that the LN was nonmetastatic. They considered that the high CT value of a LN was induced by previous tuberculosis infection or LN calcification [15,16].

Previous results have indicated that diagnostic efficacy is limited when only considering ^{18}F-FDG PET/CT data of LNs. Thus, in recent years, researchers have looked to assess the diagnostic efficacy of ^{18}F-FDG PET/CT data of primary lesions. In our study, compared with the No LN Metastasis Group, the SUVmax of a primary lesion was significantly higher in the LN Metastasis Group (14.00±5.75). The ROC curve analysis suggested 9.53 as the threshold for SUVmax of a primary lesion. In our retrospective analysis, the sensitivity and specificity of SUVmax of a primary lesion in the diagnosis of LN was 66.1% and 81.8%, respectively. This result was consistent with a previous report. Miyasaka et al. reported that with the increase of SUVmax of primary lesion, the incidence of LN metastasis increased. When the SUVmax of a primary lesion reached 10, 41% of patients developed occult LN metastasis [17]. The SUVmax of a primary lesion was an important indicator for LN metastasis. However, its diagnostic efficacy was not strong enough.

Compared with the No LN Metastasis Group, the size of primary lesion was also significantly higher in the LN Metastasis Group (28.02±13.28). The ROC curve analysis suggested 34.58 as the threshold of size of primary lesion. Its sensitivity and specificity were only 75.0% and 57.7%, respectively. This indicated that the size of the primary lesion was associated with LN metastasis. However, as the metastasis also occurred in the early stage of NSCLC, it is not appropriate to be considered as a diagnostic factor.

TMs are specific markers, produced by malignant tumors or by tumor-stimulated normal cells, which reflect tumor growth and progression. In clinical settings, the combination of markers CAE, CYFRA 21-1, NSE, and CA125 have been used for the early diagnosis of NSCLC [18,19]. Our results showed that compared with the No LN Metastasis Group, the grade of TM was significantly elevated in the LN Metastasis Group. The expression level of CAE, CYFRA 21-1, NSE, and CA125 were all significantly increased in patients with LN metastasis. However, the sensitivity, specificity, and accuracy of TM only reached 50.0% and 72.7%, respectively. This indicated that the application of TM alone exhibited high false positive and negative rate. Huang et al. reported that TM combined imagological examination could overcome the deficiency of a single

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detection, avoid misdiagnosis, and increase the positive detection of hepatocellular carcinoma [20]. In our study, by combining TM with ^{18}F-FDG PET/CT data, we established a logistic model for predicting LN metastasis in NSCLC. The threshold of our logistic model was 0.56. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of our logistic model was calculated as 85.7%, 90.9%, 87.2%, 96.0%, and 71.4%, respectively, in our prospective study. This indicated that our logistic model displayed excellent diagnostic values of LN metastasis in patients with NSCLC. This result was consistent with the Mu et al. study that reported that the combination of ^{18}F-FDG PET/CT and TM exhibited high accuracy in diagnosing the recurrence and metastasis of NSCLC [3]. However, Mu et al. [3] failed to clarify the threshold of parameters and the study findings have not been verified in large sample prospective studies.

For further study, we will try to evaluate the efficiency and accuracy of our logistic model in diagnosing LN metastasis in NSCLC patients with different histological types or with different tumor stages in large sample, double blind, high quality clinical trials. Thus, we aim to provided evidence for the combined application of ^{18}F-FDG PET/CT and TM in diagnosing LN metastasis in patients with NSCLC in clinical settings.

Conclusions

In this study, we found SUVmax/size of primary lesion, CT value/SUVmax/short diameter of LN, and level of TM were all significantly different in patients with LN metastasis compared with patients without LN metastasis. By establishing a logistic correlation model, we screened out 3 significant variables: SUVmax of primary lesion, short diameter of LN, and grade of TM. Our ROC curve analysis showed the AUC of our logistic model was highest with specificity of 90.6% and sensitivity of 90.1%. Furthermore, the diagnostic efficacy of our logistic model was verified by our prospective study: sensitivity of 85.7%, specificity of 90.9%, accuracy of 87.2%, positive predictive value of 96.0%, and negative predictive value of 71.4%. These results indicate the combination of ^{18}F-FDG PET/CT and TMs can better diagnosis LN metastasis in patients with NSCLC.

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