ORIGINAL ARTICLE

Primary tumor PET/CT [18F]FDG uptake is an independent predictive factor for regional lymph node metastasis in patients with non-small cell lung cancer

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Abstract

Aim: To investigate the correlation between [18F]fluorodeoxyglucose (FDG) uptake in a primary tumor and pathologic N stages, and to further analyze the possible risk factors contributing to the regional lymph node metastasis. **Patients and methods:** Eighty patients with non-small cell lung cancer (NSCLC) who underwent positron emission tomography/computed tomography were enrolled in the study. The FDG uptake in the primary tumor was compared for the different N staging groups and further correlation was performed. The degree of FDG uptake in the primary tumor and other possible variables related to the incidence of lymph node metastasis were examined by univariate and logistic multivariate analysis. FDG uptake was quantitated using the maximum standardized uptake value (SUV_{max}). **Results:** Statistically significant differences were found in the SUV_{max} of the primary tumors among different N staging groups ($F = 4.124$, $P = 0.023$), and the correlation between them was also statistically significant ($r = 0.438$, $P = 0.000$). Univariate analysis showed that blood tumor markers, primary tumor size, histologic grade, and SUV_{max} of the primary tumor were significantly associated with lymph node involvement. Logistic multivariate analysis showed that blood tumor makers and SUV_{max} of primary tumor might be considered as significant predictive factors for lymph node metastasis in patients with NSCLC. **Conclusion:** Our results show that there is a significant relationship between the SUV_{max} of the primary tumor and the pathologic N stage of NSCLC. FDG uptake by the primary tumor may be an independent predictor of regional lymph node metastasis in patients with NSCLC.

Keywords: *Non-small cell lung cancer; FDG; PET/CT; standardized uptake value; staging; lymph node metastasis; risk factor.*

Introduction

Lung cancer is the leading cause of cancer-related death in the world, and non-small cell lung cancer (NSCLC) accounts for 75–80% of cases[1]. The molecular and quantitative imaging technique, positron emission tomography (PET)/computed tomography (CT) has proven especially useful in lung cancer diagnosis and staging[2], and the positron-emitting radiopharmaceutical [18F]fluorodeoxyglucose (FDG) is the most widely used agent for oncologic PET/CT imaging[3,4]. Studies have shown that FDG uptake reflects the metabolic activity of patients with primary NSCLC, and as such appears to have a prognostic role, especially after surgical resection[5–8]. The standardized uptake value (SUV) is a quantified index of FDG uptake. Patients with NSCLC who had a lower SUV had better therapeutic and prognostic outcomes[9]. Given that TNM stage is the most significant prognostic factor of NSCLC, especially the nodal stage (N stage)[10], we investigated the correlation between FDG uptake of the primary tumor and pathologic N stage.

Over the past decade, FDG-PET/CT has demonstrated more accurate non-invasive nodal staging than traditional

imaging, such as CT, in lung cancer; however, the sensitivity of PET/CT remains relatively low[11–14], which has resulted in many nodal micro-metastasis going undetected. Moreover, non-specific inflammatory and granulomatous diseases can lead to FDG uptake and false-positive results[15–17]. Mediastinoscopy was long considered the gold standard of N staging of lung cancer before surgery; however, this was also a traumatic procedure, which was restricted by accessibility to the region and depended on the presence of N_2/N_3 disease[18]. In order to provide more information for clinical use to predict lymph node metastasis of NSCLC, we analyzed the possible risk factors for regional lymph node metastasis and determined whether the quantitative degree of FDG uptake by the primary tumor is an independent predictor for nodal metastasis in NSCLC. This approach might also represent a new and non-invasive way to evaluate and predict the nodal status of patients with NSCLC.

Materials and methods

Patient enrollment

Our institutional review board approved this study and written informed consent was obtained from all patients. Eighty consecutive patients with NSCLC (52 men and 28 women; mean age, 58 years; range, 35–84 years) who were candidates for surgical resection from October 2006 to March 2009 were enrolled in the study. Then they all underwent curative surgical resection after FDG-PET/CT scan. Seventy patients underwent a whole-body scan and 10 patients had a thoracic scan only. All the patients received no chemotherapy or radiation prior to surgery. The median time between the PET/CT scan and surgery was 6.5 days. Seventy-one patients were positive for a blood tumor marker (TM) prior to surgery. The TMs measured were carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), carbohydrate antigen 125 (CA125), cytokeratin 19 fragment (CK19/cyfra21-1), and squamous cell carcinoma (SCC) antigen. The corresponding diagnostic threshold for each was 5.0 ng/ml, 18.0 ng/ml, 35.0 U/ml, 3.3 ng/ml, and 1.5 ng/ml, respectively.

PET/CT image acquisition

All patients fasted for at least 6 h before the PET/CT examination. After confirmation of a normal blood glucose level ($\leq$144 mg/dl or 8 mmol/l) in a peripheral fingertip blood sample, the patients were administered an intravenous injection of FDG at 3.70–4.44 MBq/kg and were then rested for approximately 60 min before undergoing the body scan, as recommended for tumor PET imaging[2,19]. Image acquisition was performed with an integrated PET/CT device (GE Discovery ST 16). The whole-body scan was performed from the head to the root of the thigh, and the thoracic scan was performed from the super clavicle to the adrenal gland. The CT scan

was performed with section thickness of 3.75 mm using a standardized protocol that involved 120 kV, 150 mA, and 0.8 s per tube rotation. No intravenous contrast material was administered. Immediately after CT, PET was performed in an identical transverse field of view with a section thickness of 3.27 mm, and using 3 min per table position and three-dimensional acquisitions. Patients were allowed normal shallow respiration during the image acquisition procedure. Coregistered images were displayed using software (Xeleris), which allowed image integration and analysis.

PET/CT image analysis and surgical staging

Two chest radiologists with PET/CT diagnostic experience prospectively evaluated the integrated PET/CT images. For determination of the SUV, a cylindrical region of interest (ROI) was manually placed over the tumor site on the hottest trans-axial slice. The maximum SUV (SUV_{max}) within the ROI was used as the reference measurement. The primary tumor was classified according to location: central or peripheral; additional classification included 3 types based on the CT density findings: solid, mixed gross glass opacity (mGGO) or pure gross glass opacity (pGGO).

Lung resection, including lobectomy and pneumonectomy with mediastinal lymph node dissection, was performed on all patients. The dissected lymph nodes were identified as to station, according to the lymph node map proposed by Mountain et al.[20]. The pathologist then evaluated the nodes as numbered in the surgical field. Final pathologic N stage was assigned on the basis of image analysis using the American Joint Committee on Cancer (AJCC) staging system (7th edition)[21].

Statistical analysis

The distribution (normal or non-normal) of quantitative data was assessed using the Kolmogorov–Smirnov) test. Normal distribution data was presented as $\bar{x} \pm s$ and compared by t test. Abnormal distribution data was presented as $M \pm Q$ and compared by Mann–Whitney U test. Comparisons between multiple different groups were performed with the ANOVA or Kruskal–Wallis test. When significant differences were found, further evaluation of the correlation was tested with the Spearman rank non-parametric correlation test. The possible risk factors for regional lymph node metastasis were analyzed by logistic univariate and multivariate analysis. Odds ratio (OR) and its 95% confidence interval (CI) were used to estimate the correlation strength between the risk factors and nodal metastasis. The threshold of primary tumor SUV_{max} was chosen by the receiver operating curve (ROC) curve. Statistically significant differences were determined with $P < 0.05$. All analyses were performed using the Stata statistical software (version 11.0, StataCorp, College Station, TX).

Table 1   **Correlations between SUV_{max} of the primary lung tumor, N stage and lymph node metastasis**

Stage (group)	n	SUV_{max} of the primary tumor	ANOVA/t test		Spearman rank test	
			F (t)	P	r	P
N stage						
N_0	49	5.75 ± 4.76	3.462	0.036*	0.439	0.000
N_1	11	8.07 ± 5.05				
N_2	20	8.66 ± 3.43				
LNM						
N_0	49	5.75 ± 4.76	-2.623	0.010#	0.416	0.000
$N_{1,2}$	31	8.45 ± 4.01				

LNM, lymph node metastasis. $P < 0.05$ indicates significant difference.
*ANOVA.
#t test.

Results

Pathological staging and PET/CT results

Among the 80 NSCLC cases, 49 were N_0 stage, 11 were N_1 stage, and 20 were N_2 stage, according to the pathologic results. The SUV_{max} of the primary tumor in patients with N_0, N_1, N_2 and $N_{1,2}$ (N_1 and N_2) staging were 5.75 ± 4.76, 8.07 ± 5.05, 8.66 ± 3.43 and 8.45 ± 4.01, respectively.

Correlation between FDG uptake of the primary tumor, N staging and regional nodal metastasis

As shown in Table 1, a statistically significant difference was found in the SUV_{max} of the primary tumor among N staging groups ($F = 4.124$, $P = 0.023$), and the correlation between SUV_{max} and N stage showed a statistically significant difference ($r = 0.438$, $P = 0.000$). Statistically significant differences were also found in SUV_{max} between N_0 and $N_{1,2}$ groups ($t = -2.623$, $P = 0.010$), and the correlation between SUV_{max} and nodal status ($r = 0.416$, $P = 0.000$).

Risk factors for regional lymph nodal metastasis

We also evaluated the possible risk factors that might affect nodal metastasis. We showed that the levels of blood TMs, primary tumor size, histologic differentiation, and SUV_{max} of the primary tumor were significantly associated with lymph node involvement by univariate analysis (Table 2). Multivariate logistic analysis indicated that the SUV_{max} of the primary tumor and levels of blood TM had significant predictive roles for lymph nodal metastasis in patients with NSCLC (Table 2). The detailed predictive roles combining the SUV_{max} of the primary tumor and blood TM are shown in Table 3.

Discussion

In this study, we evaluated the relationship between primary NSCLC FDG uptake and N stage. In addition, we determined whether tumor FDG uptake could predict the N status of patients with lung cancer. Our study demonstrated a correlation between primary NSCLC FDG uptake quantified by SUV_{max} and pathologic N stage. The SUV_{max} of the primary tumor showed a statistically significant difference between the group of patients without lymphatic involvement (N_0) and the patients with tumor cells detected in the lymph nodes ($N_{1,2}$); moreover, correlation between the SUV_{max} of the primary tumor and nodal status was also found. Thus, the greater the tumor FDG uptake, the higher the malignant grade. FDG was mainly taken up by tumor cells because cancer tissue consumes a large amount of glucose as an energy source[22]. Some previous studies have also shown that tumor FDG uptake could be affected by cell differentiation, proliferative rate potential, microvessel density, and hypoxia, which are all consistent with the biological behavior of malignant cells[23–25]. The detailed mechanism, however, needs to be further determined. Nonetheless, the findings from our study demonstrate that FDG uptake can reflect the potential metastasis of NSCLC.

As a quantified index of FDG uptake, SUV can be determined by either SUV_{mean} or SUV_{max}. The reasons we choose to use SUV_{max} in this study were as follows: (1) the metabolic activity of glucose in tumor tissue is heterogeneous; thus, the most active area of metabolism measured as SUV_{max} could largely represent the malignant behavior of the tumor. (2) SUV_{mean} can be easily affected by necrotic and cystic areas. (3) SUV_{max} is less variable and subjective, but more reproducible, than SUV_{mean}[26]. (4) SUV_{max} is more commonly used in current clinical practice.

Several studies have shown that FDG-PET/CT was superior to CT for mediastinal nodal staging; however, the sensitivity of PET/CT remained low[11–14]. The lack of sufficient FDG uptake in lymph nodes with micrometastasis can result in a false-negative interpretation[27].

Table 2 **Univariate and multivariate analyses of potential risk factors for LNM**

Variables	LNM		Univariate analysis		Multivariate analysis	
	+	−	OR (95%CI)	P	adjusted OR (95%CI)[a]	P
Age						
≤60 years	12	25	Ref		Ref	
>60 years	19	24	1.65 (0.66–4.12)	0.282	1.20 (0.33–4.32)	0.782
Gender						
Female	10	18	Ref		Ref	
Male	21	31	1.22 (0.47–3.16)	0.683	0.53 (0.14–2.06)	0.366
Smoking						
No	13	26	Ref		Ref	
Yes	18	23	1.57 (0.63–3.88)	0.333	1.39 (0.25–7.62)	0.704
Blood TM						
Normal	6	27	Ref		Ref	
Increased	22	17	5.82 (1.96–17.28)	0.001	5.63 (1.39–22.80)	0.016
Location						
Peripheral	27	46	Ref		Ref	
Central	4	3	3.28 (0.87–12.34)	0.068	1.26 (0.22–7.07)	0.789
Primary tumor size						
≤3.0 cm	10	33	Ref		Ref	
3.1–5.0 cm	13	12	3.58 (1.24–10.28)	0.018	1.38 (0.28–6.94)	0.693
>5.0 cm	8	4	6.60 (1.64–26.59)	0.008	1.41 (0.21–9.73)	0.724
Pathologic type						
Adenocarcinoma	20	36	Ref		Ref	
Non-adenocarcinoma	11	13	1.52 (0.58–4.02)	0.395	0.76 (0.17–3.33)	0.716
Histologic differentiation						
High	2	11	Ref		Ref	
Moderate	13	23	3.11 (0.60–16.24)	0.179	5.58 (0.45–68.90)	0.179
Poor	16	15	5.87 (1.11–30.95)	0.037	10.65 (0.82–138.21)	0.071
CT density						
Solid	29	38	Ref		Ref	
mGGO and pGGO	2	11	0.24 (0.05–1.16)	0.076	1.81 (0.22–14.70)	0.579
SUV_{max} of primary tumor						
<5.4	5	29	Ref		Ref	
≥5.4	26	20	7.54 (2.48–22.97)	0.001	6.39 (1.28–31.89)	0.024

LNM, lymph node metastasis; OR, odds ratio; 95% CI, 95% confidence interval. $P < 0.05$ indicates significant difference.
[a]Adjusted for age, gender, blood TM, primary tumor size, histologic differentiation and SUV_{max} of the primary tumor.

In order to predict nodal metastasis in at-risk patients with NSCLC, we assessed the possible risk factors of nodal metastasis and analyzes the contributions of each of the clinical, pathologic and imaging features. By univariate analysis, we demonstrated that primary tumor size, blood TM, histologic differentiation and SUV_{max} of the primary tumor were risk factors (OR > 1, $P < 0.05$) for lymph node involvement. In other words, patients with larger tumor size, higher blood TM level, poorer histologic differentiation, or higher SUV_{max} of the primary tumor may be more likely to experience nodal metastasis. Our results are consistent with other reports[28–30]. Furthermore, we analyzed these factors by logistic multivariate analysis to assess the joint effects and interactions of the variables on lymph node involvement. Our results show that only blood TM and SUV_{max} of the primary tumor retained statistical significance, whereas tumor size and histologic differentiation had no significant difference on multivariate analysis; we believe that their effects were substituted by the enrolled index.

A TM found in the blood or other body fluid can either be the product of the cancer cells themselves or produced by the body in response to the cancer or other concomitant conditions. The blood TMs selected in our research represent those commonly used in clinical practice for lung cancer screening, diagnosis, and detection. Our results suggest that the levels of blood TM were also associated with regional nodal metastases and might be used as important predictive factors.

Through univariate and multivariate analyses, we found that SUV_{max} of the primary tumor showed statistical significance, suggesting that the FDG uptake in the primary tumor was an independent predictor for N status of patients with NSCLC. In this study, the degree of SUV_{max} was classified in 2 levels according to the threshold of 5.4 (the cutoff value of ROC curves of primary tumor SUV_{max} for lymph nodal metastases). The probability of nodal metastasis for the 2 levels was 14.7% (5/34) and 56.5% (26/46), respectively. When the SUV_{max} of the primary tumor exceeded 5.4, the risk of nodal metastasis increased. We further utilized the SUV_{max} of the primary tumor and blood TM jointly to

Table 3   **Predictive significance of combined SUV$_{max}$ of the primary tumor and blood TM for LNM in patients with NSCLC**

SUV$_{max}$ of primary tumor	Blood TM	LNM		OR (95%CI)	P
		+	−		
−	−	1	19	Ref	
+	−	5	8	11.88 (1.20–118.50)	0.035
−	+	3	7	8.14 (0.72–91.89)	0.090
+	+	19	10	36.10 (4.20–310.45)	0.001

LNM, lymph node metastasis. OR, odds ratio; 95% CI, 95% confidence interval. $P < 0.05$ indicates statistically significant difference. SUV$_{max}$ of the primary tumor: −, <5.4; +, ≥5.4. Blood TM: −, normal; +, increased.
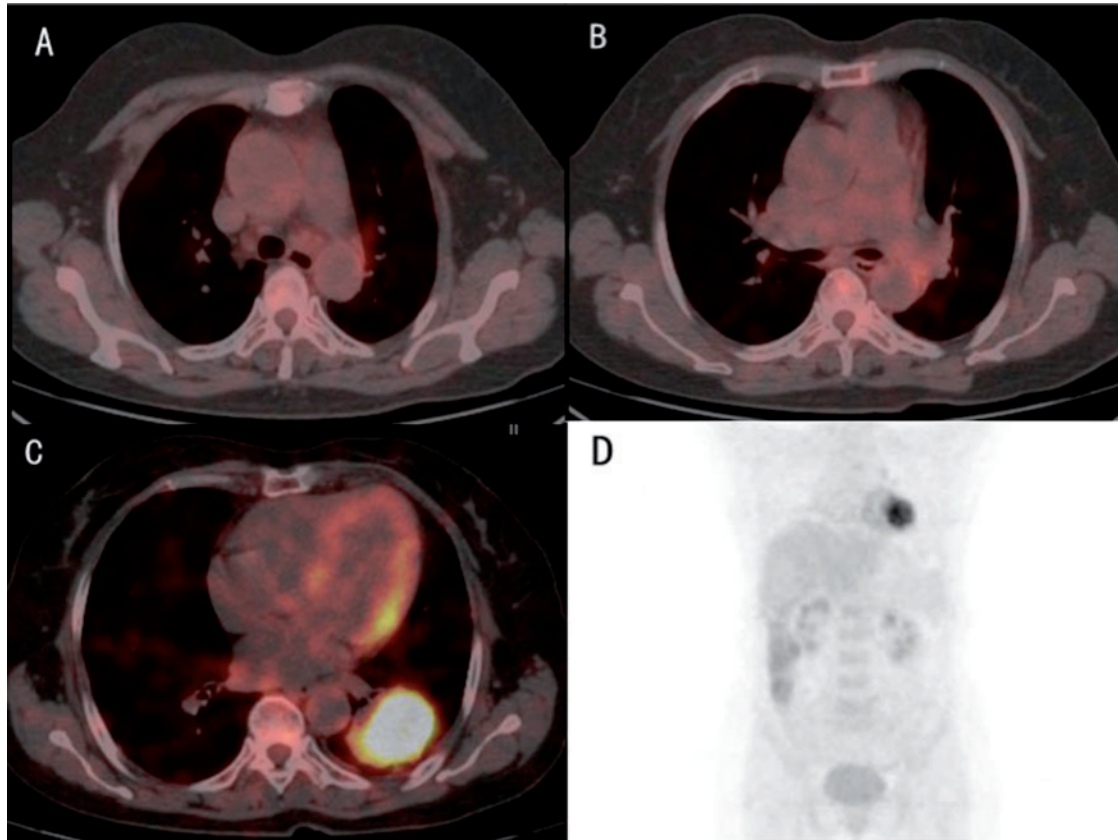

Figure 1   **A 67-year-old woman, with blood CEA of 14.95 ng/ml, was diagnosed with poorly differentiated adenocarcinoma in the inferior lobe of the left lung. Three different slices of integrated FDG-PET/CT images (A–C) and maximum intensity projection showed an SUV$_{max}$ of the primary tumor of 9.4. Although there was no obvious mediastinal lymph nodal metastasis on imaging, the high SUV$_{max}$ of the primary tumor and CEA level indicated that the patient might be at risk for lymph nodal metastasis. Pathologic results after surgery showed micro-metastases in subaortic and subcarinal lymph nodes (N2).**

predict lymph node metastasis in NSCLC. The results showed that whenever the SUV$_{max}$ of the primary tumor and blood TM were both positive, the risk of nodal metastasis increased over 30-fold (36.10) compared with patients with both factors negative. This result may provide a non-invasive way to predict the high-risk population for lymph node metastasis in patients with NSCLC.

Primary tumor FDG uptake has high affinity for cells undergoing nodal metastasis, although it cannot substitute for the benefit of immediate imaging of the mediastinum. This suggests that evaluation of FDG uptake may be a useful tool to help plan the appropriate surgical treatment. Studies have reported that lymph node metastasis was found in about 20% of clinical stage IA ($T_1N_0M_0$) pulmonary adenocarcinomas, and that a

higher local recurrence rate after limited resection, such as a wedge resection or a segmentectomy, was even observed in those with pathologically confirmed negative surgical margins[31,32]. These findings might be due to micro-metastasis in lymph nodes or the spread of tumor cells into lymphatic vessels beyond the primary tumor, even at the N_0 stage. Therefore, we should maintain a positive attitude toward lobectomy or major lung resection with systematic dissection of hilar or mediastinal lymph nodes for patients with NSCLC presenting with higher FDG uptake in the primary tumor, even when the preoperative nodal imaging is negative. On the other hand, limited resection might be performed successfully in stage IA patients whose primary cancer showed lower FDG uptake.

This study had several limitations. First, to ensure thoroughness of surgical staging, all the patients with NSCLC underwent curative surgical resection, which resulted in no N3 patients being included in our study. Second, despite the fact that the area of GGO on thin-section CT images and tumor location have been reported as predictors of lymph node metastasis[28,33,34], the population of patients in our study with GGO, especially with pGGO (only one case), and central location of the tumor was relatively small, which may have influenced our statistical results. Thus, future studies with large sample populations are needed to confirm our findings.

Collectively, our results show that there are significant relationships between the SUV_{max} of the primary tumor and pathologic N stage of NSCLC. FDG uptake by the primary tumor may be an independent predictor of regional lymph node metastasis in patients with NSCLC. SUV_{max} is readily amenable to clinical use due to its non-invasive nature and convenience.

Conflict of interest

The authors have no conflicts of interest.

Acknowledgments

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