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Original Article

Pre-radiotherapy assessment of non-small cell lung cancer with ^{18}F-FLT PET/CT or ^{18}F-FDG PET/CT

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Abstract: Purpose: To evaluate the pre-radiotherapy assessment of ^{18}F-FDG PET/CT in patients with non-small cell lung cancer (NSCLC) in comparison wiht ^{18}F-FLT PET/CT. Methods and materials: A total of fourteen patients were enrolled and underwent both ^{18}F-FDG and ^{18}F-FLT PET/CT. For visualized primary tumors, the maximum and mean standardized uptake value (SUVmax and SUVmean) was calculated. Nodal stages and metastasis were determined by using the American Joint Committee on Cancer (AJCC) staging system. Target volumes were delineated using both ^{18}F-FDG and ^{18}F-FLT PET/CT. In addition, we compared the simulation plans using the optimal threshold of ^{18}F-FDG and ^{18}F-FLT PET/CT. The radiation dose was prescribed as 60 Gy in 30 fractions with a precise radiotherapy technique. Results: ^{18}F-FLT PET/CT instead of ^{18}F-FDG PET/CT detected the lymph node and metastasis in the mediastinal regions of two patients and bone metastasis in another two patients. The SUVmax and SUVmean of ^{18}F-FDG was significantly higher than ^{18}F-FLT (8.12 vs 4.96, 7.05 vs 3.51; $P < 0.01$, respectively). Target volumes of ^{18}F-FLT PET/CT including gross tumor volume (GTV), clinical target volume (CTV) and planning target volume (PTV) (29.31 vs 38.03 cm^3, 166.47 vs 189.28 cm^3, 233.71 vs 269.94 cm^3; $P < 0.05$, respectively) were smaller than ^{18}F-FDG PET/CT. ^{18}F-FLT PET/CT-based radiotherapy treatment planning had the lower radiation dose to the normal lungs, esophagus and heart than ^{18}F-FDG PET/CT. Conclusion: ^{18}F-FLT PET/CT showed better accuracy for TNM staging than ^{18}F-FDG PET/CT. ^{18}F-FLT PET/CT could more precisely delineate GTV, CTV and PTV than ^{18}F-FDG PET/CT. Moreover, ^{18}F-FLT PET/CT-based radiotherapy treatment planning could provide more protective benefits to the normal lungs, esophagus and heart than ^{18}F-FDG PET/CT.

Keywords: Lung cancer, pre-radiotherapy, ^{18}F-FLT PET/CT, ^{18}F-FDG PET/CT, non-small cell

Introduction

Lung cancer is still the leading cause of cancer-related mortality worldwide resulting in more than 1 million deaths annually [1]. Non-small cell lung cancers (NSCLC) accounts for about 85% of lung cancers [2]. Unfortunately, despite advancements in this field, including the systemic chemotherapy and molecularly targeted therapy, treatment outcomes have not improved obviously over the last 30 years. For patients with early stage NSCLC who are not candidates for surgery due to medical comorbid illness, radiotherapy, often combined with chemotherapy [3], is the best choice for local tumor treatment and control [4]. Too much radiation dose is harmful to normal tissue and would decrease its benefit to improvement of survival. Therefore, it has become increasingly important to improve the accuracy of the target volume definition, together with development in intensity-modulated and image-guided radiotherapy, which could avoid unnecessary radiation of normal tissues and help avoid geographic misses [5, 6].

It has been reported that using computed tomography (CT) to delineate the target volume would lead to large differences among different observers [7]. Some researchers suggested that ^{18}F-fluorodeoxyglucose-positron emission tomography/CT (^{18}F-FDG PET/CT) information reduces this variation [8]. However, FDG is not a tumor-specific tracer, and false positive findings can occur in inflammatory lesions [9-11]. To overcome the drawbacks of ^{18}F-FDG, alterna-

tive radiotracers that are more closely related to cell proliferation have been investigated. Recently, a thymidine analog 3'-deoxy-3'-18F-fluorothymidine (^{18}F-FLT) was introduced as a stable cell proliferation imaging agent, which could improve the specificity and accuracy of the assessment of primary and regional lymph node metastasis [12-14].

Since the greater accuracy in the detection of the gross tumor volume (GTV) of NSCLC than possible using morphologic imaging modalities, ^{18}F-FDG PET/CT can be incorporated into radiotherapy planning to improve target volume delineation and change the treatment plan [15-18]. But few studies have compared the results of ^{18}F-FDG and ^{18}F-FLT PET/CT in delineating the GTV in NSCLC. Herein we performed this study to compare the ^{18}F-FDG and ^{18}F-FLT PET/CT parameters simulated in the treatment planning system. The treatment planning parameters included the GTV, clinical target volume (CTV) and planning target volume (PTV). We also assessed the organs at risk (OARs) evaluation index, such as volume of bilateral lung receiving ≥ 20 or 30 Gy, volume of heart receiving ≥ 40 Gy (V40) and volume of esophagus receiving ≥ 40 Gy (V40). Moreover, we evaluated whether ^{18}F-FLT uptake reflects proliferative activity as indicated by the Ki-67 index in NSCLC, in comparison with ^{18}F-FDG.

Materials and methods

Patient selection and histopathologic analysis

From June 2008 to February 2011, the patients were consecutively included, who referred to our hospital for treatment of NSCLC. Diagnosis was confirmed by CT and pathological biopsy. Patients with inadequate liver and kidney functions and severe complications were excluded.

The stage of regional lymph node involvement (N stage) was determined for all patients on the basis of findings at tumor resection with mediastinal lymph node dissection. Distant metastasis stage (M stage) was determined by means of biopsy or radiologic follow-up. Apart from assessment of tumor stage, PET/CT images were evaluated for additional clinically important findings. Tumor staging was based on the AJCC staging system for the classification of lung cancer.

^{18}F-FDG and ^{18}F-FLT PET/CT imaging

PET/CT studies were performed using a Discovery STE PET/CT system (GE Medical Systems, Milwaukee, WI). Both FDG and FLT were automatically synthesized using the same type of cyclotron (MiniTrace, GE Healthcare, Milwaukee, WI) and synthesizer (TracerLab FxFN, GE Healthcare, Milwaukee, WI). The raw materials and agents for synthesis were purchased from the same supplier. The products had to meet certain criteria (e.g., the radiochemical yield had to be > 10% and the radiochemical purity had to be > 95%) to be used for imaging. All ^{18}F-FDG and ^{18}F-FLT PET/CT scans were performed according to clinical protocol. Patient preparation included 6 hours without caloric intake or insulin administration and to rest for 15 minutes before the administration of radioactive tracer. Image acquisition was started 1 h after intravenous injection of ^{18}F-FDG (3.7 MBq/kg) or ^{18}F-FLT (3.7 MBq/kg). The CT scan was performed in whole-body mode and was performed immediately before the PET scan using a multidetector spiral CT scanner (4.25 mm slice thickness). A whole-body PET scan was performed, covering an area identical to that covered by the CT scan. The acquisition time was 3 min per bed position with eight bed positions. The images were reconstructed using an iterative reconstruction technique and were read from workstation (Xeleris, GE Healthcare, Milwaukee, WI) computer monitors. Two experienced nuclear medicine radiologists reviewed PET/CT images at the workstation. Any difference of opinion was resolved by consensus. The tumor maximal standardized uptake value (SUVmax) was measured. The mediastinal lesions were assigned according to the Mountain and Dresler classification of regional lymph nodes. Tumor staging with PET/CT was also based on the AJCC staging system for the classification of lung cancer.

GTV delineation

The GTV included the primary GTV (GTVp) and nodal GTV (GTVn). The GTVp and GTVn were delineated by seven different methods using ^{18}F-FLT PET/CT: visual interpretation, SUV 1.4 and ^{18}F-FDG PET/CT: visual interpretation, SUV of > 2.5 and uptake equal to or greater than that of the mediastinum score as previous research had suggested [19, 20]. Positive results with PET/CT were defined as true-positive results when confirmed by histologically

Table 1. Patients' characterstics and staging results

Patients no.	Gender	Age	Histology	Tumor Location	Staging				FDG PET/CT		FLT PET/CT	
					CT	FDG PET/CT	FLT PET/CT	Pathological Biopsy	SUV-max	SUV mean	SUV-max	SUV mean
1	M	48	AC	Right lower lobe	T3 N1 M0	T+ N1 M0	T+ N1 M0	T3 N1 M0	8.15	7.67	4.03	3.21
2	M	65	AC	Left lower lobe	T3 N0 M0	T+ N1 M0	T+ N0 M0	T3 N0 M0	7.48	6.81	4.65	3.38
3	M	58	AC	Right upper lobe	T3 N1 M0	T+ N1 M0	T+ N1 M0	T3 N1 M0	7.24	6.43	4.86	3.57
4	M	59	SCC	Right middle lobe	T3 N0 M1	T+ N0 M1	T+ N0 M1	T4 N0 M1	6.99	6.01	4.04	2.88
5	M	71	AC	Right lower lobe	T4 N1 M1	T+ N1 M1	T+ N1 M1	T4 N1 M1	11.09	9.20	6.62	4.99
6	F	53	SCC	Left upper lobe	T3 N1 M0	T+ N1 M0	T+ N1 M1	T3 N1 M1	8.43	7.26	5.49	4.35
7	F	60	AC	Right upper lobe	T2 N1 M0	T+ N1 M0	T+ N1 M1	T3 N1 M1	7.66	6.83	4.81	3.37
8	M	62	AC	Left upper lobe	T3 N0 M0	T+ N0 M0	T+ N1 M0	T4 N1 M0	8.12	7.04	5.70	3.64
9	M	45	AC	Right lower lobe	T4 N1 M0	T+ N1 M0	T+ N1 M0	T4 N1 Mx	10.27	8.79	6.01	4.23
10	M	61	SCC	Left upper lobe	Tx N0 M0	T+ N0 M0	T+ N0 M0	T3 N0 M0	5.98	4.63	3.32	2.01
11	F	63	AC	Right lower lobe	T4 N0 M1	T+ N0 M1	T+ N0 M1	T4 N0 M0	6.64	5.84	4.27	3.02
12	M	52	AC	Right upper lobe	T3 N0 M0	T+ N0 M0	T+ N0 M0	T3 N0 M0	6.89	5.99	4.11	2.87
13	M	79	AC	Right upper lobe	T3 N1 M0	T+ N0 M0	T+ N1 M0	T3 N1 M0	9.45	7.90	5.53	4.15
14	F	67	AC	Left upper lobe	T2 N0 M0	T+ N0 M0	T+ N0 M0	T3 N0 M0	9.23	8.31	5.98	3.51

No.: number; M: male; F: female; AC: adenocarcinoma; SCC: squamous cell carcinoma.

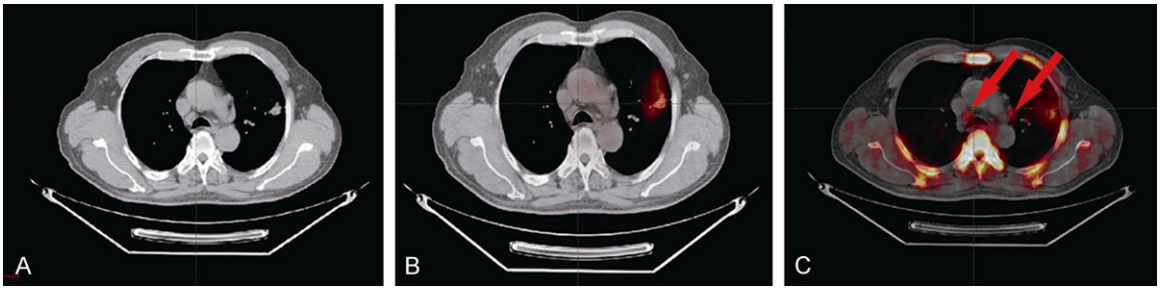

Figure 1. ^{18}F-FDG PET/CT showed no uptake in the mediastinal region, whereas ^{18}F-FLT PET/CT showed the mediastinal lymph node metastasis. Pathologic examination proved the metastasis. A-C showed CT, ^{18}F-FDG and ^{18}F-FLT PET/CT imaging of patient 13, respectively.

examination as lymph node metastasis and as false-positive results when histologically examination of the resected nodal group revealed no evidence of metastasis.

Conformal radiotherapy simulation

^{18}F-FDG and ^{18}F-FLT PET/CT and CT data for all patients were transmitted to Eclipse treatment planning system by network for simulation purposes. The conformal primary CTV and PTV was created using the method, which was reported by Han et al. [19]. The radiation dose was prescribed as 60 Gy in 30 fractions with conformal or intensity-modulated radiotherapy. The precise dose contribution was under the normal tissue tolerance. Radiotherapy was delivered with the same dose given to the same target volume using the seven-field intensity modulated radiotherapy arrangement endeavoring to meet the following treatment planning goals: > 90% of the PTV covered by the prescription isodose line, volume of bilateral lung receiving ≥ 20 Gy of < 30% (V20, V30), heart V40, esophagus V40, and global hotspot of < 15%. We compared the parameters of treatment planning according to the optimal threshold of FLT and FDG PET/CT simulation.

Ki-67 immunohistochemistry

Formalin-fixed, paraffin-embedded sections (2.5 μm) of resected specimens from lung cancer were taken for immunohistochemical staining. For morphology, slides were routinely stained with hematoxylin and eosin. For immunohistochemistry, slides were pretreated for 30 min in Tris buffer (pH 9.5) at 98°C. Staining was performed using the labelled streptavidin biotinylated antibody (LSAB) method with an autostaining system (Ventana Benchmark System, Ventana Medical Systems, Tucson, AZ) accord-

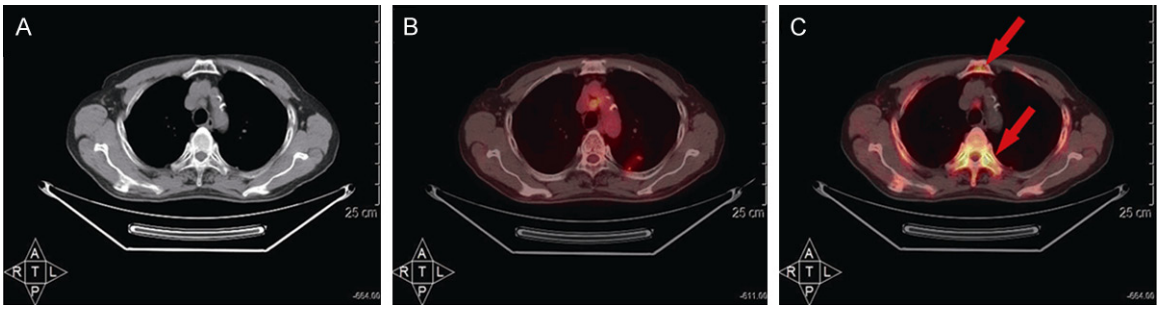

Figure 2. ^{18}F-FDG PET/CT showed no uptake in the bone. However, ^{18}F-FLT PET/CT showed uptake in the sternum and vertebra. Pathologic examination revealed cellular reactivity in sternum and vertebra. A-C showed CT, ^{18}F-FDG and ^{18}F-FLT PET/CT imaging of patient 6, respectively.

Table 2. Overall values of measured dose-volume histogram-based parameters for NSCLC patients

	^{18}F-FDG PET/CT (Mean ± SD)	^{18}F-FLT PET/CT (Mean ± SD)	*p*
GTV (cm^3)	38.03±22.05	29.31±19.45	0.015
CTV (cm^3)	189.28±66.73	166.47±50.83	0.023
PTV (cm^3)	269.94±85.26	233.71±69.22	0.014
Total lung			
V20	31.34±35.76	28.95±24.06	0.034
V30	11.52±9.08	8.13±5.10	0.019
Heart			
V40	22.35±19.73	14.60±10.91	0.027
Esophagus			
V40	19.80±13.25	13.29±9.71	0.018

Abbreviations: GTV = gross tumor volume; CTV = clinical target volume; PTV = planning target volume; V20, V30, V40 = volume receiving ≥ 20, ≥ 30, ≥ 40 Gy, respectively.

ing to the manufacturer's protocol. MIB-1 antibody (Dako, Glostrup, Denmark) was used as the primary antibody in a 1:100 dilution. The MIB-1 score was estimated by counting the percentage of MIB-1 positive cell nuclei per 1,000 tumor cells in the region of the tumor with the greatest density of staining, which, in most instances, corresponds to areas with the highest mitotic activity. The pathologist was unaware of the results of the PET/CT images.

Statistical analysis

Data were expressed as mean ± SD. The Mann-Whitney U test or the Kruskal-Wallis test was used to evaluate differences in pathological factors among groups. Spearman's rank correlation was used to evaluate the relationship between two quantitative variables. The Mann-Whitney U or Wilcoxon signed-ranks test was used to evaluate the differences between two quantitative variables. The χ^2 test was used to explore the associations between FDG or FLT PET/CT N stage and surgical N stage. Two-tailed *p* values < 0.05 were considered significant. All statistical analyses were performed by SPSS version 17.0 (Chicago, Illinois, USA).

Results

Patients

A total of 14 patients (10 men, 4 women; mean ± SD age 60.2 ± 9.0 years, range 45-79 years) with histologically confirmed NSCLC were enrolled in this study. All patients had CT of the chest, ^{18}F-FDG and ^{18}F-FLT PET/CT imaging between June 2008 and February 2011. None of the patients had had prior surgery, radiotherapy or chemotherapy. All patients gave written consent to participate in the study, which was approved by our hospital ethical committee.

Staging of NSCLC with FDG PET/CT and FLT PET/CT

Pathology for assessment of lymph nodes was available in all patients. ^{18}F-FDG PET/CT and ^{18}F-FLT PET/CT were comparable with regard to the detection of regional lymph nodes. Both ^{18}F-FDG PET/CT and ^{18}F-FLT PET/CT correctly detected regional lymph node metastases in 6 of 14 patients (**Table 1**).

In two patients (No. 8, 13), ^{18}F-FDG PET/CT showed no uptake in the mediastinal region, whereas both ^{18}F-FLT PET/CT and pathological biopsy showed the lymph node metastasis.

Figure 1 shows CT, ^{18}F-FDG and ^{18}F-FLT PET/CT imaging of patient 13. In patient 6 and 7, ^{18}F-FDG PET/CT also showed no uptake in the

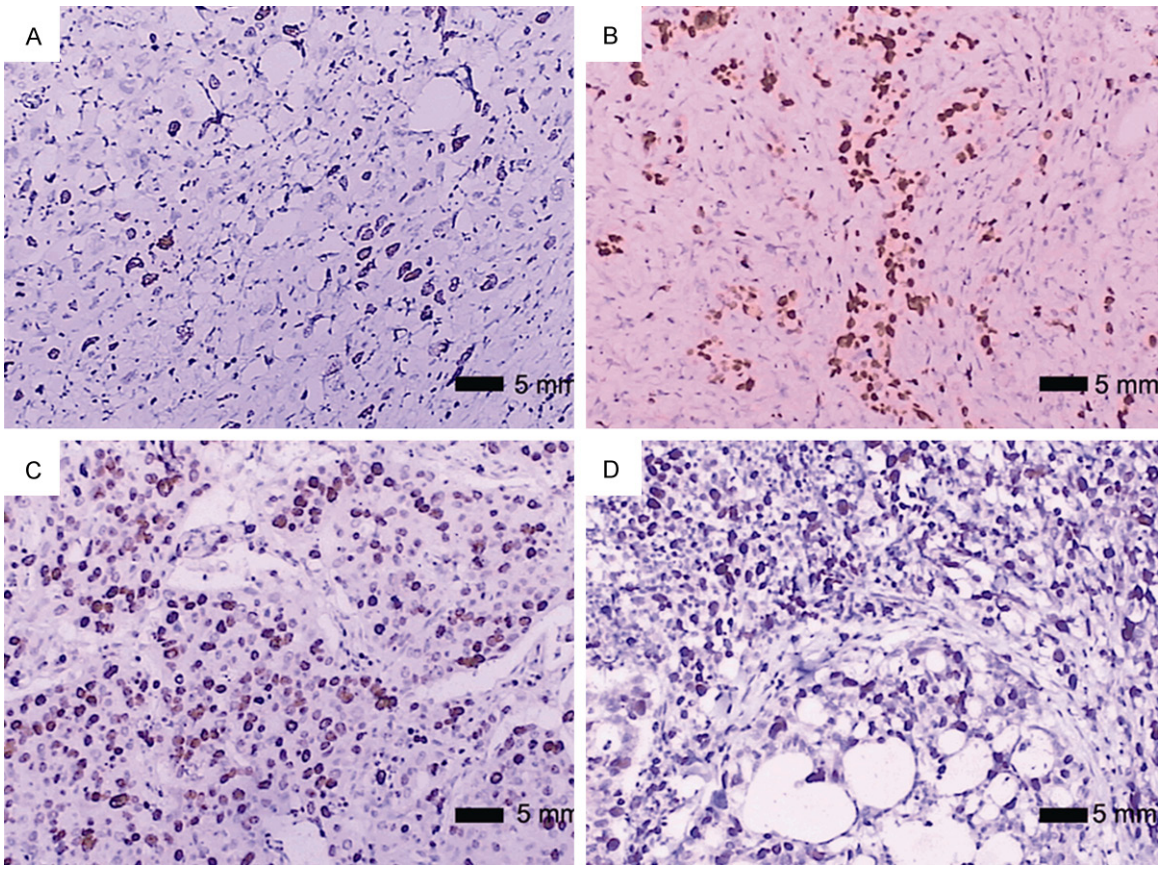

Figure 3. Ki-67 positive cells in different NSCLC patients. The positive rate of (A-D) is 10%, 30%, 50% and 80%.

bone. However, ^{18}F-FLT PET/CT showed uptake in the sternum and vertebra. Pathologic examination revealed cellular reactivity in the sternum and vertebra in these patients.

Figure 2 shows CT, ^{18}F-FDG and ^{18}F-FLT PET/CT imaging of patient 6. In patient 2, ^{18}F-FDG PET/CT showed false-positive uptake in the mediastinal region, whereas all other staging modalities, including 18F-FLT PET, did not show any abnormality.

The median SUVmax and median SUVmean for ^{18}F-FDG were 8.12 and 7.05 and for ^{18}F-FLT were 4.96 and 3.51. Uptake of ^{18}F-FDG was significantly higher than ^{18}F-FLT, whether expressed in SUVmax ($P < 0.01$) or SUVmean ($P < 0.01$).

Outcome of radiotherapy simulation

The GTV include the GTVp and GTVn. The primary PTV (PTVp) plus the nodal PTV (PTVn) equaled the PTV. A total of 29 groups or 164 nodes were dissected in the 8 patients; 73 nodes in 7 patients proved to be positive for malignancy on pathologic examination. Then, we compared the two radiotherapy simulation plans using the ^{18}F-FDG and ^{18}F-FLT PET/CT optimal threshold contouring target volumes in the Eclipse treatment planning system (**Table 2**).

In **Table 2**, we also list the parameters of ^{18}F-FDG and ^{18}F-FLT PET/CT planning. The difference in the volume of bilateral lung receiving ≥ 20 and ≥ 30 Gy, V40 of the heart and esophagus between ^{18}F-FDG and ^{18}F-FLT were significantly different.

Ki-67 immunohistochemistry

Ki-67 immunohistochemical staining was evaluated for all specimens obtained at surgical resection (**Figure 3**).

All NSCLC specimens contained Ki-67-positive cells. Stained nuclei belonged mainly to epithelial cells, and a very small portion to inflammatory cells [1.7 ± 1.9 (mean ± SD)]. The mean (± SD) proliferation fraction was 43.5 ± 19.2% (range 6.2-80.9%). Pearson's correlation analysis indicated a significant correlation between

FLT SUV and the Ki-67 index ($r = 0.8677$, $P < 0.01$). A significant correlation was also observed between the Ki-67 index and FDG SUV ($r = 0.8085$, $P < 0.01$).

Discussion

Radiotherapy is the best choice for local treatment and control for patients with early stage NSCLC, who cannot accept surgery due to various reasons. Since the overdose radiation is harmful to the normal tissue and even reduces the survival benefit, the precise conformal radiotherapy is consequently becoming more and more important to improve survival benefit and decrease the damage to normal organs. Some publications have reported ^{18}F-FDG PET/CT can be incorporated into radiotherapy planning to improve target volume delineation and change the treatment plan [21-23]. However, ^{18}F-FDG is limited in distinguishing the proliferation of tumor cells from inflammatory tissue. ^{18}F-FLT was introduced as a stable cell proliferation imaging agent. Thus, ^{18}F-FLT PET/CT could improve the specificity and accuracy of the assessment of primary and regional lymph node metastasis.

In our studies, we compared the ^{18}F-FLT PET/CT in pre-radiotherapy assessment, including staging of NSCLC, delineation of target volume and OARs evaluation index, with ^{18}F-FDG PET/CT. ^{18}F-FDG PET/CT showed no uptake in the mediastinal region in two patients, whereas both ^{18}F-FLT PET/CT and pathological biopsy showed the lymph node metastasis. In another patient with bone metastasis, ^{18}F-FDG PET/CT also indicated no uptake but ^{18}F-FLT PET/CT suggested uptakes in the sternum and vertebra. Pathologic examination proved the metastasis in these patients. These results lead to the change of N and M staging and also changed the treatment planning. The present study demonstrated that ^{18}F-FLT PET/CT had good specificity (93%), accuracy (85%; ^{18}F-FDG PET/CT had 78 and 74%, respectively) and moderate positive predictive value (67%; ^{18}F-FDG PET/CT had 36%) on a per-patient basis for N staging. Nevertheless, other studies reported ^{18}F-FLT PET/CT had low sensitivity for N staging assessment (33-56%) [24-27]. The opposite findings may be related to proliferation of lymphocytes and nonspecific increase in the accumulation of ^{18}F-FLT due to increased perfusion and vascular permeability [28]. Whether the ^{18}F-FLT PET/CT has the diagnostic accuracy for N staging is still need more research on uptake mechanism of ^{18}F-FLT and larger patient populations trials.

To determine whether ^{18}F-FLT PET/CT can be used directly in radiation planning, we also used ^{18}F-FDG and ^{18}F-FLT PET/CT images for simulation. Han et al. studied the margins in radiotherapy planning for 22 patients with esophageal squamous cell carcinoma [19]. They set a 3-cm margin in the craniocaudal direction (following the course of the esophagus) beyond ^{18}F-FLT or ^{18}F-FDG PET/CT using the optimal threshold-defined GTV and a 1-cm margin in the lateral and anteroposterior directions of the CT-defined GTVp. The CTVp was then expanded in the craniocaudal direction by 1 cm and in the anteroposterior and lateral directions by 0.5 cm to create the PTVp. The CTVn included the ^{18}F-FLT or ^{18}F-FDG PET/CT-defined GTVn and a 1-cm margin in all of directions beyond the GTVn, as well as the prophylactic nodal irradiation region, such as the celiac nodes for lower thoracic tumors and supraclavicular nodes for upper thoracic carcinomas. The CTVn was expanded in all directions by 0.5 cm to create the PTVn. The PTV consisted of the PTVp and PTVn in the treatment planning system. They found that dual tracer PET/CT-based planning can meet the target dose-painting requirement, and ^{18}F-FLT PET/CT-based treatment planning brought potential benefits to some OARs such as the lungs and heart. Button et al. studied the margins in radiotherapy planning for 145 patients with esophageal carcinoma by detailing the patterns of recurrence after definitive chemo-radiotherapy [29]. The delineation of target volume is almost same to Han et al. but the margin in the craniocaudal direction is 2-cm. They found that a 96% locoregional relapse rate occurred within the radiotherapy field. Considering these studies, we used the Han's method to delineate the target volume. As the data in **Table 2** show, significant differences were found in GTV, CTV, and PTV. The different shape of extended margins perhaps caused the difference in GTV, CTV, and PTV between ^{18}F-FLT and ^{18}F-FDG PET/CT. Most of the OARs in simulation treatment planning received acceptable dose according to the limitations set. The significant differences were also found in the proportion of the bilateral lung volume receiving ≥ 20 Gy, V40 of heart and esophagus, which indicated that ^{18}F-FLT PET/CT-based

treatment planning could bring potential benefits to these OARs on some aspects.

Our study also showed a significant correlation ($r = 0.8677$, $P < 0.01$) between ^{18}F-FLT uptakes and Ki-67 proliferative index. This correlation coefficient was better than that obtained with ^{18}F-FDG ($r = 0.8085$, $P < 0.01$). This result suggested that ^{18}F-FLT PET/CT may be used as a non-invasive method of quantitating cellular proliferation in NSCLC. The correlation between ^{18}F-FLT uptakes and its proliferation rate has important clinical implications for PET imaging. However, when we compared the ^{18}F-FDG SUV with ^{18}F-FLT, we found both SUVmax and SUVmean of ^{18}F-FDG were significantly higher than ^{18}F-FLT. Therefore, our data in a relatively small patient population do not support a clear-cut conclusion about correlation between ^{18}F-FDG or ^{18}F-FLT uptake and proliferation. Larger patient populations need to be examined to determine their relationship.

The major limitation of our study was that the number of included patients is too small. In order to get the complete clinical information, including patients' image data and surgical specimens, we just enrolled 14 patients. However, we still found ^{18}F-FLT PET/CT showed better pre-radiotherapy assessment than ^{18}F-FDG PET/CT such as staging and GTV delineation, which is similar to Han et al. study. These results should be confirmed in the large and rigorous prospective studies.

Conclusion

Our study demonstrated that ^{18}F-FLT PET/CT showed better accuracy for TNM staging than ^{18}F-FDG PET/CT. ^{18}F-FLT PET/CT could more precisely delineate GTV, CTV and PTV than ^{18}F-FDG PET/CT. Moreover, ^{18}F-FLT PET/CT-based radiotherapy treatment planning could provide protective benefits to the normal lungs, esophagus and heart than ^{18}F-FDG PET/CT. These results could help us to design the better treatment planning for patients with early stage NSCLC who are not candidates for surgery.

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Disclosure of conflict of interest

None.

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