Mismatched intratumoral distribution of [^{18}F] fluorodeoxyglucose and 3'-deoxy-3'-[^{18}F] fluorothymidine in patients with lung cancer

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Abstract. In a mouse model of human lung cancer, intratumoral distribution between 3'-deoxy-3'-[^{18}F] fluorothymidine (^{18}F -FLT) and [^{18}F] fluorodeoxyglucose (^{18}F -FDG) was mutually exclusive. ^{18}F -FLT primarily accumulated in proliferating cancer cells, whereas ^{18}F -FDG accumulated in hypoxic cancer cells. The aim of the present study was to evaluate these preclinical findings in patients with lung cancer. A total of 55 patients with solitary pulmonary lesion were included in the present study. Patients underwent ^{18}F -FLT positron emission tomography-computed tomography (PET/CT) and ^{18}F -FDG PET/CT scan with a 3-day interval. The final diagnosis was based on histological examination. Among the 55 cases, a total of 24 cases were confirmed as malignant lesions. Mismatched ^{18}F -FLT- and ^{18}F -FDG-accumulated regions were observed in 19 cases (79%) and matched in 5 (21%). Among the 31 benign lesions, ^{18}F -FLT and ^{18}F -FDG were mismatched in 12 cases (39%) and matched in 19 (61%). The difference in intratumoral distribution of ^{18}F -FLT and ^{18}F -FDG between malignant and benign lesions was statistically significant ($P < 0.05$). The results of the present study indicate that a mismatch in intratumoral distribution of ^{18}F -FLT and ^{18}F -FDG may be a feature of patients with lung cancer. Increased ^{18}F -FDG accumulation may serve as an indicator of tumor hypoxia, whereas regions with increased ^{18}F -FLT uptake may be associated with an increased rate of cancer cell proliferation in patients with lung cancer.

Introduction

Positron emission tomography (PET) is widely used for cancer detection, staging and monitoring the response to therapy.

[^{18}F] fluorodeoxyglucose (^{18}F -FDG) and 3'-deoxy-3'-[^{18}F] fluorothymidine (^{18}F -FLT) are commonly used PET tracers for imaging glucose metabolism and cell proliferation, respectively (1-12). In a mouse model of human lung cancer, it has been previously demonstrated that intratumoral distribution between ^{18}F -FLT and ^{18}F -FDG was mutually exclusive. ^{18}F -FLT accumulated primarily in proliferating cancer cells, whereas ^{18}F -FDG accumulated in hypoxic cancer cells that are less proliferative (13-16). To the best of our knowledge, intratumoral distribution of ^{18}F -FLT and ^{18}F -FDG in patients with lung cancer has not been previously reported.

Differential diagnosis of malignant pulmonary lesions may be challenging. Computed tomography (CT) is the method of choice for the diagnosis of pulmonary lesions. PET/CT imaging reflects the biological and metabolic aspects of pulmonary lesions (17). ^{18}F -FDG PET/CT has been widely used for the diagnosis of pulmonary lesions; however, false-negative as well as false-positive results are frequently observed (17,18). ^{18}F -FLT is a positron radioactive tracer that reflects cancer cell proliferation. Therefore, ^{18}F -FLT may be a useful tool for the diagnosis of pulmonary lesions (19).

In the present study, it was hypothesized that the mutually exclusive distribution pattern between ^{18}F -FLT and ^{18}F -FDG described in animal tumor models may apply to patients with lung malignancies as well. To examine this hypothesis, patients with pulmonary lesions that initially underwent a ^{18}F -FDG PET/CT scan and subsequently a ^{18}F -FLT PET/CT scan were studied.

Materials and methods

Patients. The present study was approved by the Institutional Review Boards of the Inner Mongolia Medical University (Hohhot, China) and the Soochow Medical University (Jiangsu, China). Written informed consent was obtained from all patients prior to participation. The Institutional Review Board of the University of Louisville (Louisville, KY, USA) approved data transfer and use. From June 2013 to August 2015, a total of 55 patients (Table I) with pretreated lung lesions were recruited to the present study (31 males and 24 females; age range, 17-68 years). Histological examination

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Table I. Patients' clinical data and PET/CT results.

Patient no.	Age/sex	SUV _{max} FDG/FLT	Pathological diagnosis	FDG/FLT PET/CT SUV _{max}
1	55/F	5.3/2.7	Adenocarcinoma	Mismatch
2	48/F	3.5/1.4	Tuberculoma	Match
3	61/F	4.2/2.1	Squamous carcinoma	Match
4	65/F	2.8/1.1	Tuberculoma	Mismatch
5	59/F	2.3/1.0	Organizing pneumonia	Match
6	63/F	5.8/2.1	Adenocarcinoma	Mismatch
7	60/F	2.3/1.2	Tuberculoma	Mismatch
8	62/F	4.8/2.2	Adenocarcinoma	Mismatch
9	64/F	3.2/2.0	Adenocarcinoma	Mismatch
10	64/F	1.6/0.9	Tuberculoma	Mismatch
11	67/F	1.9/0.9	Hamartoma	Match
12	49/F	2.1/1.5	Tuberculoma	Match
13	57/F	3.8/2.8	Adenocarcinoma	Mismatch
14	59/F	4.1/2.6	Adenocarcinoma	Mismatch
15	47/F	2.0/1.4	Tuberculoma	Match
16	49/M	2.6/1.6	Tuberculoma	Mismatch
17	53/M	3.7/2.4	Adenocarcinoma	Mismatch
18	60/M	7.9/2.8	Squamous carcinoma	Match
19	65/M	1.5/0.9	Organizing pneumonia	Match
20	67/M	3.5/2.0	Inflammatory pseudotumor	Mismatch
21	57/M	6.8/2.4	Squamous carcinoma	Match
22	60/M	3.7/2.6	Squamous carcinoma	Match
23	58/M	4.2/2.0	Squamous carcinoma	Mismatch
24	62/M	3.6/2.5	Adenocarcinoma	Mismatch
25	63/M	3.4/2.6	Adenocarcinoma	Mismatch
26	66/M	1.8/1.0	Inflammatory pseudotumor	Mismatch
27	45/M	1.6/1.3	Tuberculoma	Mismatch
28	59/M	2.6/1.2	Tuberculoma	Match
29	17/M	2.9/1.5	Tuberculoma	Match
30	48/M	3.0/1.8	Squamous carcinoma	Mismatch
31	62/M	1.1/1.0	Tuberculoma	Match
32	62/M	2.4/1.6	Tuberculoma	Match
33	62/M	2.1/0.8	Organizing pneumonia	Mismatch
34	50/M	3.1/0.9	Tuberculoma	Match
35	52/M	1.5/1.0	Hamartoma	Match
36	57/M	3.6/2.2	Adenocarcinoma	Mismatch
37	54/M	3.2/1.9	Adenocarcinoma	Mismatch
38	52/M	1.6/0.7	Tuberculoma	Match
39	44/M	1.0/0.7	Hamartoma	Mismatch
40	49/M	5.4/1.8	Squamous carcinoma	Mismatch
41	62/M	1.5/0.7	Tuberculoma	Match
42	68/M	3.5/2.0	Adenocarcinoma	Mismatch
43	47/F	4.1/1.1	Tuberculoma	Match
44	49/M	3.1/1.4	Tuberculoma	Match
45	58/M	6.8/2.4	Squamous carcinoma	Mismatch
46	60/M	2.6/1.1	Tuberculoma	Mismatch
47	67/M	8.2/3.5	Adenocarcinoma	Mismatch
48	55/F	3.2/1.8	Adenocarcinoma	Match
49	48/F	1.5/1.0	Organizing pneumonia	Mismatch
50	61/F	5.8/2.5	Adenocarcinoma	Mismatch
51	65/F	2.7/2.1	Adenocarcinoma	Mismatch
52	59/F	1.9/0.8	Inflammatory pseudotumor	Match

Table I. Continued.

Patient no.	Age/sex	SUV _{max} FDG/FLT	Pathological diagnosis	FDG/FLT PET/CT SUV _{max}
53	63/F	1.6/0.8	Hamartoma	Mismatch
54	60/F	1.8/1.1	Inflammatory pseudotumor	Match
55	62/F	1.5/0.9	Hamartoma	Match

PET/CT, positron emission tomography-computed tomography; FLT, 3'-deoxy-3'-[¹⁸F]fluorothymidine; FDG, [¹⁸F]fluorodeoxyglucose; SUV_{max}, maximal standardized uptake value; F, female; M, male.

of the lesions was performed in every patient. The diameter of the lesions ranged between 8 and 50 mm.

Radiopharmaceuticals. [¹⁸F] fluoride was generated in-house using a cyclotron. ¹⁸F-FDG and ¹⁸F-FLT were synthesized automatically using FX-FN conventional modules at the PET/CT facility of the Inner Mongolia Medical University (Hohhot, China). ¹⁸F-FDG and ¹⁸F-FLT were pyrogen-free and qualified for clinical use, with radiochemical purity >98%.

PET/CT imaging protocol. PET/CT images were obtained using a GE Discovery ST PET/CT scanner. Prior to ¹⁸F-FDG PET scanning, patients were instructed to fast for >6 h and their blood glucose levels were determined to be <6 mmol/L. Whole body ¹⁸F-FDG PET/CT scans were performed 1 h after intravenous administration of 3.7 MBq/kg ¹⁸F-FDG. Subsequently, 3 days after ¹⁸F-FDG imaging, local thoracic ¹⁸F-FLT PET/CT scans were performed, 1 h after the injection of ¹⁸F-FLT (3.7 MBq/kg). Spiral CT scans (voltage, 120 kV; current, 160-220 mA) were conducted for attenuation correction and anatomy referral.

A board of three certified physicians in nuclear medicine assessed the PET/CT images. Visual analysis to score lesion radioactivity uptake of each tracer was performed (20). The maximal standardized uptake value (SUV_{max}) was used to spatially compare the intralesional distribution of ¹⁸F-FDG and ¹⁸F-FLT.

Histological examination of the lesions was performed for all patients by board-certified pathologists at the Department of Pathology (Affiliated Hospital of Inner Mongolian Medical University). Routine hematoxylin and eosin (H&E) staining was performed. Briefly, slides containing 5 μm paraffin sections were placed on a slide holder, deparaffinized and rehydrated. Sections were treated with hematoxylin solution, dipped 8-12 times in acid ethanol to destain, and stained for 30 sec with eosin. H&E stain imaging was developed with a light microscope at x100 magnification.

Statistical analysis. SPSS software (version 17.0; SPSS, Inc., Chicago, IL, USA) was used to analyze the data using a χ^2 test. P<0.05 was considered to indicate a statistically significant difference.

Results

The clinical information and PET/CT results of the patient cohort are summarized in Table I. Among the 55 cases,

24 lesions were confirmed as primary lung malignancies (16 cases with adenocarcinoma, 8 cases with squamous cell carcinoma) and 31 lesions were benign (18 cases with tuberculosis, 5 with hamartoma, 4 with inflammatory pseudo-tumor and 4 with organizing pneumonia).

Spatial intratumoral distribution of ¹⁸F-FLT and ¹⁸F-FDG mismatched in 19/24 malignant lesions (79%) and matched in 5 (21%). Fig. 1 presents an apparent mismatch in intratumoral distribution of ¹⁸F-FLT and ¹⁸F-FDG in a 67-year-old male patient with pretreated lung adenocarcinoma. Increased ¹⁸F-FDG uptake combined with decreased ¹⁸F-FLT accumulation in a patient with squamous carcinoma is presented in Fig. 2. Intratumoral distribution of ¹⁸F-FLT and ¹⁸F-FDG in lung malignancies was identified to be mainly heterogeneous and mutually excluded.

Regarding the 31 benign lesions, intralesional mismatched distribution of ¹⁸F-FLT and ¹⁸F-FDG was observed in 12 cases (39%). Fig. 3 presents scan images of mismatched ¹⁸F-FLT and ¹⁸F-FDG intralesional distribution in a 49-year-old male patient with lung tuberculoma. Matched intralesional distribution of ¹⁸F-FLT and ¹⁸F-FDG was observed in 19/31 benign lesions (61%). An indicative example of a patient with an inflammatory pseudotumor demonstrating negative ¹⁸F-FLT and positive ¹⁸F-FDG PET scans is presented in Fig. 4.

These results indicate that mismatched intralesional accumulation of ¹⁸F-FLT and ¹⁸F-FDG was more frequently observed in malignant compared with benign lung lesions. The difference in intralesional distribution of ¹⁸F-FLT and ¹⁸F-FDG between malignant and benign lesions was statistically significant (P<0.05).

Discussion

It has previously been reported based on studies using mouse non-small cell lung cancer models that ¹⁸F-FDG accumulates in hypoxic regions, whereas ¹⁸F-FLT accumulates in well-oxygenated proliferating cells. Additionally, it has been demonstrated that the intratumoral distribution of ¹⁸F-FDG and ¹⁸F-FLT is mutually exclusive (13,14). In the present study, the association between ¹⁸F-FDG and ¹⁸F-FLT uptake was further elucidated in patients with lung cancer.

In the present study, it was demonstrated that intratumoral ¹⁸F-FDG and ¹⁸F-FLT accumulation is mutually exclusive. It was observed that regions with increased ¹⁸F-FDG accumulation were mainly associated with decreased ¹⁸F-FLT uptake. This is consistent with previous preclinical results in mouse lung cancer models (13-16). Intratumoral heterogeneity of

Figure 1. Scan images of a 67-year-old male patient with pretreated adenocarcinoma (39x23 mm) in the right middle lobe of the lung. An ^{18}F -FLT PET/CT scan was performed 3 days after an ^{18}F -FDG scan. (A) ^{18}F -FDG PET/CT scan image. (B) ^{18}F -FLT PET/CT scan image. (C) CT scan providing additional anatomical information. (D) Enlarged ^{18}F -FDG scan image of the area indicated by the arrow. (E) Enlarged ^{18}F -FLT scan image of the area indicated by the arrow. (F) Hematoxylin and eosin staining indicated lung adenocarcinoma. PET/CT, positron emission tomography-computed tomography; ^{18}F -FLT, 3'-deoxy-3'- [^{18}F] fluorothymidine; ^{18}F -FDG, [^{18}F] fluorodeoxyglucose; R, right.

Figure 2. Scan images of a 49-year-old male patient with pretreated squamous carcinoma (30x17 mm) in the left upper lobe in the lung. An ^{18}F -FLT PET/CT scan was performed 3 days after an ^{18}F -FDG scan. (A) ^{18}F -FDG PET/CT scan image. (B) ^{18}F -FLT PET/CT scan image. (C) CT scan providing additional anatomical information. (D) Enlarged ^{18}F -FDG scan image of the area indicated by the arrow. (E) Enlarged ^{18}F -FLT scan image of the area indicated by the arrow. (F) Hematoxylin and eosin staining indicated squamous carcinoma. PET/CT, positron emission tomography-computed tomography; ^{18}F -FLT, 3'-deoxy-3'- [^{18}F] fluorothymidine; ^{18}F -FDG, [^{18}F] fluorodeoxyglucose; R, right.

^{18}F -FDG and ^{18}F -FLT accumulation reflected the heterogeneous distribution of hypoxic (increased ^{18}F -FDG uptake) and highly proliferative (increased ^{18}F -FLT uptake) cancer cells; in agreement with previously reported preclinical results (13-16).

^{18}F -FDG PET/CT is widely used in clinical practice for the detection of malignancies. However, it is not a cancer-specific tracer as it accumulates in hypoxic tissues regardless of malignant phenotype (10,13,15). Even though benign lesions present mainly low ^{18}F -FDG uptake, in certain cases increased ^{18}F -FDG

accumulation is observed in inflammatory diseases including tuberculosis. Activated macrophages and other inflammatory cells may result in enhanced ^{18}F -FDG accumulation in benign conditions including pneumonia, bronchiectasis, pulmonary tuberculosis, fungal infections, sarcoidosis, histoplasmosis and granuloma (21,22). Macrophages and other inflammatory cells, frequently observed in necrotic regions of inflammatory lesions, accumulate increased levels of ^{18}F -FDG possibly due to the hypoxic microenvironment (23).

Figure 3. Scan images of a 49-year-old male patient with untreated tuberculoma (13x18 mm) in the right upper lobe in the lung. An ^{18}F -FLT PET/CT scan was performed 3 days after an ^{18}F -FDG scan. (A) ^{18}F -FDG PET/CT scan image. (B) ^{18}F -FLT PET/CT scan image. (C) CT scan providing additional anatomical information. (D) Enlarged ^{18}F -FDG scan image of the area indicated by the arrow. (E) Enlarged ^{18}F -FLT scan image of the area indicated by the arrow. (F) Hematoxylin and eosin staining indicated tuberculoma. PET/CT, positron emission tomography-computed tomography; ^{18}F -FLT, 3'-deoxy-3'-[^{18}F] fluorothymidine; ^{18}F -FDG, [^{18}F] fluorodeoxyglucose; R, right.

Figure 4. Scan images of a 59-year-old female patient with inflammatory pseudotumor (50x40 mm) in the right upper lobe in the lung. An ^{18}F -FLT PET/CT scan was performed 2 days after an ^{18}F -FDG scan. (A) ^{18}F -FDG PET/CT scan image. (B) ^{18}F -FLT PET/CT scan image. (C) CT scan providing additional anatomical information. (D) Enlarged ^{18}F -FDG scan image of the area indicated by the arrow. (E) Enlarged ^{18}F -FLT scan image of the area indicated by the arrow. (F) Hematoxylin and eosin staining indicated inflammatory pseudotumor. PET/CT, positron emission tomography-computed tomography; ^{18}F -FLT, 3'-deoxy-3'-[^{18}F] fluorothymidine; ^{18}F -FDG, [^{18}F] fluorodeoxyglucose; R, right.

In the present study, ^{18}F -FDG and ^{18}F -FLT PET/CT scan uptake, performed with a 3-day interval, were compared in patients with lung lesions. A mismatch in the intralesional ^{18}F -FLT and ^{18}F -FDG accumulation was observed particularly in lung malignancies compared with benign lesions (Table I). Therefore, on the basis of the results of the present study, it is suggested that this mismatch may serve as an indicator of lung malignancy.

In well-differentiated slow-growing tumors, including bronchiole alveolar carcinomas, false-negative ^{18}F -FDG PET results have been reported (20,24). This may be attributed to the absence of hypoxic microenvironment of slow-growing malignancies⁴⁴ ^{18}F -FDG is mainly considered as a hypoxia-specific rather than a tumor avid tracer (13,15,16). This explains why ^{18}F -FDG exhibited relatively low specificity in distinguishing malignant from benign lesions.

It has been demonstrated that the combination of ^{18}F -FLT and ^{18}F -FDG, either as separate PET scans performed on subsequent days or as one scan using a ^{18}F -FLT and ^{18}F -FDG cocktail, may be superior to an ^{18}F -FDG scan for accurate disease detection (14). ^{18}F -FDG mainly accumulates in hypoxic regions, whereas ^{18}F -FLT accumulates in highly proliferating cells (6,7,13,14). The use of ^{18}F -FLT and ^{18}F -FDG cocktail PET may have an advantage compared with individual tracer PET. A clinical trial for ^{18}F -FLT and ^{18}F -FDG cocktail PET scanning for cancer detection and management is currently underway (25).

The results of the present study demonstrate that mismatched intratumoral distribution of ^{18}F -FLT and ^{18}F -FDG is a common feature of patients with lung cancer and may serve as an indicator of lung malignancy.

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