SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 14: 5279-5284, 2017

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

XIANGCHENG WANG[1,2], YULIN HE[1], WEINA ZHOU[1], XIA BAI[1], YIWEI WU[2], XUEMEI WANG[1] and XIAO-FENG LI[3,4]

[1]Department of Nuclear Medicine, Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia 010050; [2]Department of Nuclear Medicine, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215000, P.R. China; [3]Department of Diagnostic Radiology, University of Louisville School of Medicine, Louisville, KY 40202, USA; [4]PET/CT/MRI Center, The Fourth Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang 150028, P.R. China

Received July 19, 2016; Accepted July 14, 2017

DOI: 10.3892/ol.2017.6840

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

Correspondence to: Dr Yiwei Wu, Department of Nuclear Medicine, The First Affiliated Hospital of Soochow University, 188 Shixin Street, Suzhou, Jiangsu 215000, P.R. China
E-mail: wuyiwei3988@gmail.com

Key words: lung cancer, [^{18}F] fluorodeoxyglucose, 3'-deoxy-3'-[^{18}F] fluorothymidine, positron emission tomography-computed tomography

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'-[^{18}F]fluorothymidine; FDG, [^{18}F]fluorodeoxyglucose; SUV_{max}, maximal standardized update 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. [^{18}F] fluoride was generated in-house using a cyclotron. ^{18}F-FDG and ^{18}F-FLT were synthesized automatically using FX-FN conventional modules at the PET/CT facility of the Inner Mongolia Medical University (Hohhot, China). ^{18}F-FDG and ^{18}F-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* ^{18}F-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 ^{18}F-FDG PET/CT scans were performed 1 h after intravenous administration of 3.7 MBq/kg ^{18}F-FDG. Subsequently, 3 days after ^{18}F-FDG imaging, local thoracic ^{18}F-FLT PET/CT scans were performed, 1 h after the injection of ^{18}F-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 ^{18}F-FDG and ^{18}F-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 ^{18}F-FLT and ^{18}F-FDG mismatched in 19/24 malignant lesions (79%) and matched in 5 (21%). Fig. 1 presents an apparent mismatch in intratumoral distribution of ^{18}F-FLT and ^{18}F-FDG in a 67-year-old male patient with pretreated lung adenocarcinoma. Increased ^{18}F-FDG uptake combined with decreased ^{18}F-FLT accumulation in a patient with squamous carcinoma is presented in Fig. 2. Intratumoral distribution of ^{18}F-FLT and ^{18}F-FDG in lung malignancies was identified to be mainly heterogeneous and mutually excluded.

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

These results indicate that mismatched intralesional accumulation of ^{18}F-FLT and ^{18}F-FDG was more frequently observed in malignant compared with benign lung lesions. The difference in intralesional distribution of ^{18}F-FLT and ^{18}F-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 ^{18}F-FDG accumulates in hypoxic regions, whereas ^{18}F-FLT accumulates in well-oxygenated proliferating cells. Additionally, it has been demonstrated that the intratumoral distribution of ^{18}F-FDG and ^{18}F-FLT is mutually exclusive (13,14). In the present study, the association between ^{18}F-FDG and ^{18}F-FLT uptake was further elucidated in patients with lung cancer.

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

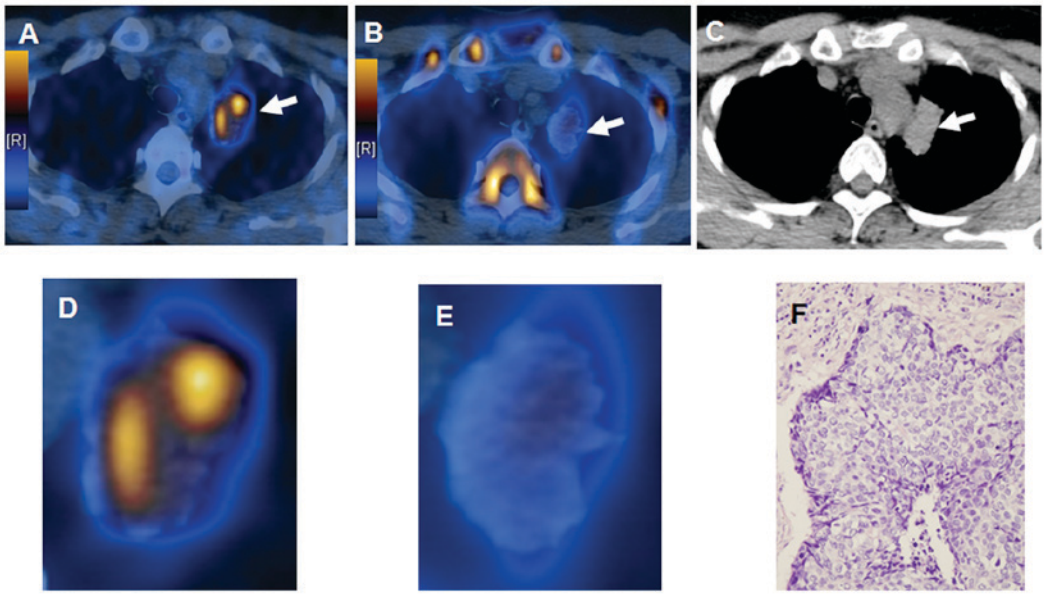

Figure 1. Scan images of a 67-year-old male patient with pretreated adenocarcinoma (39x23 mm) in the right middle lobe of the lung. An ^{18}F-FLT PET/CT scan was performed 3 days after an ^{18}F-FDG scan. (A) ^{18}F-FDG PET/CT scan image. (B) ^{18}F-FLT PET/CT scan image. (C) CT scan providing additional 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.

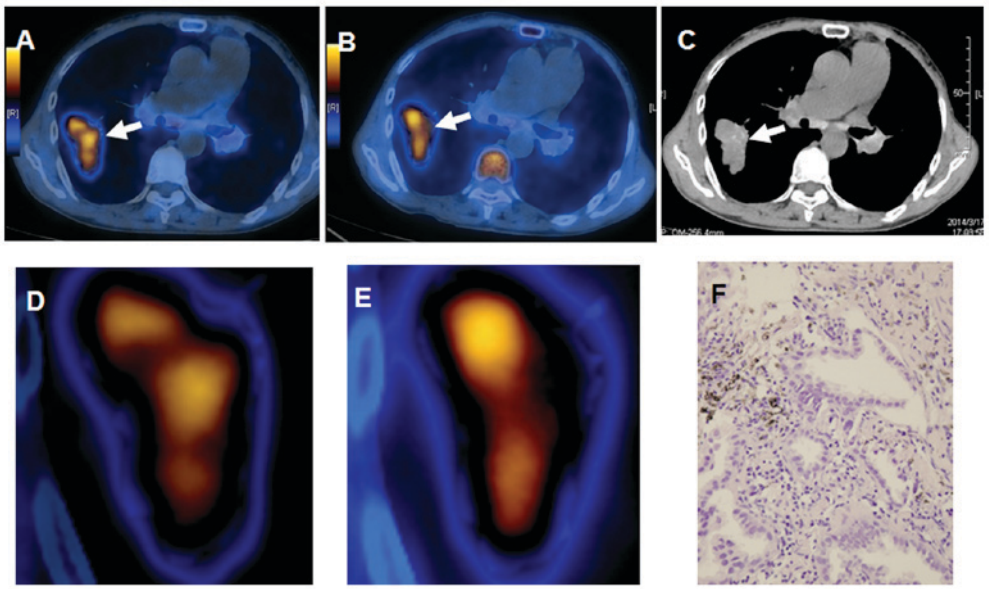

Figure 2. Scan images of a 49-year-old male patient with pretreated squamous carcinoma (30x17 mm) in the left upper lobe in the lung. An ^{18}F-FLT PET/CT scan was performed 3 days after an ^{18}F-FDG scan. (A) ^{18}F-FDG PET/CT scan image. (B) ^{18}F-FLT PET/CT scan image. (C) CT scan providing additional 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).

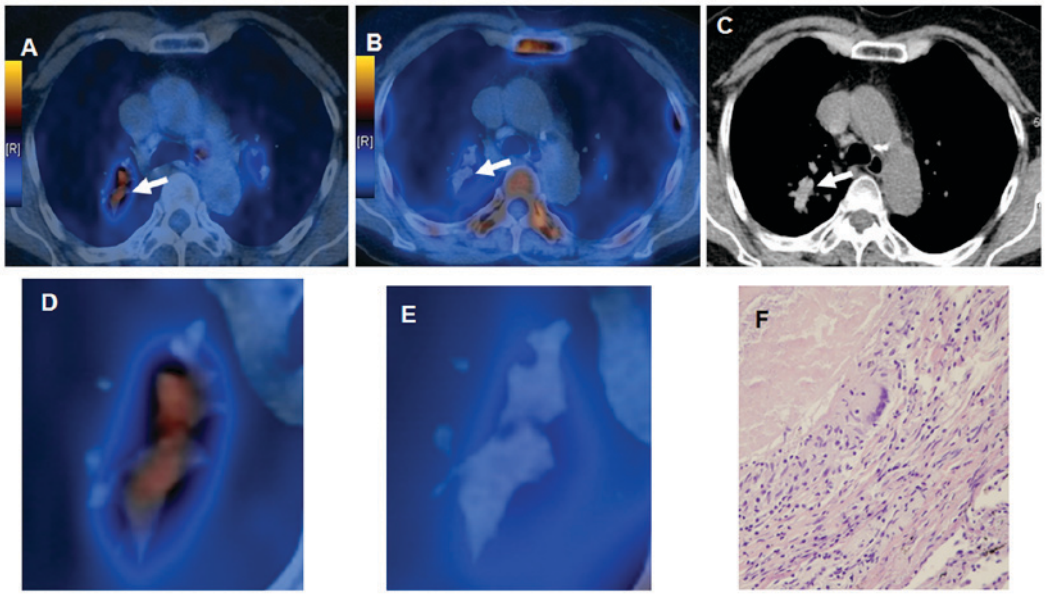

Figure 3. Scan images of a 49-year-old male patient with untreated tuberculoma (13x18 mm) in the right upper lobe in the lung. An ^{18}F-FLT PET/CT scan was performed 3 days after an ^{18}F-FDG scan. (A) ^{18}F-FDG PET/CT scan image. (B) ^{18}F-FLT PET/CT scan image. (C) CT scan providing additional 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] fluoro-thymidine; ^{18}F-FDG, [^{18}F] fluorodeoxyglucose; R, right.

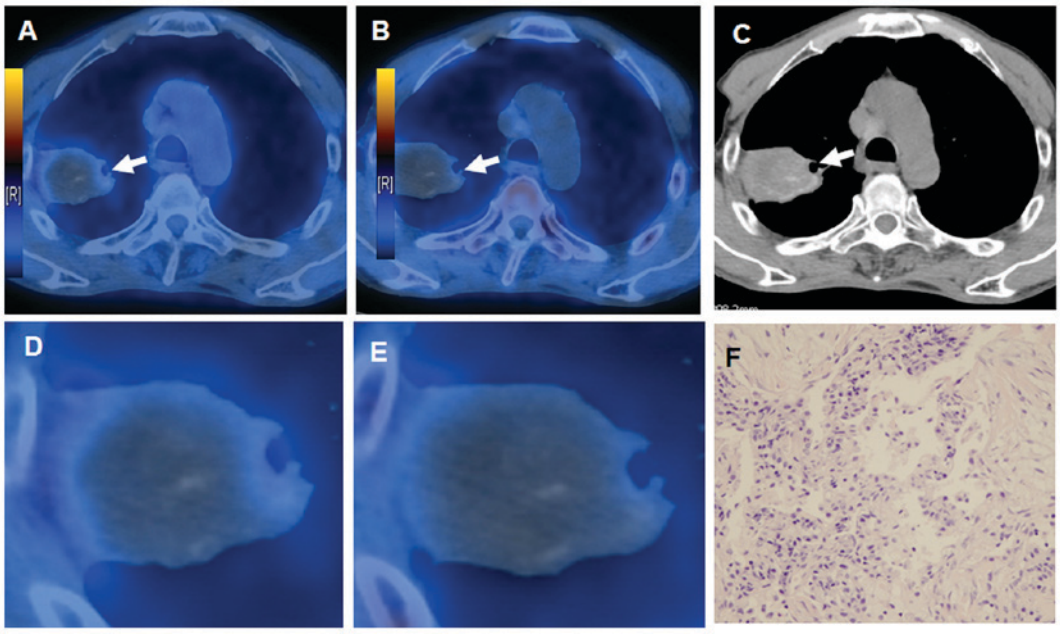

Figure 4. Scan images of a 59-year-old female patient with inflammatory pseudotumor (50x40 mm) in the right upper lobe in the lung. An ^{18}F-FLT PET/CT scan was performed 2 days after an ^{18}F-FDG scan. (A) ^{18}F-FDG PET/CT scan image. (B) ^{18}F-FLT PET/CT scan image. (C) CT scan providing additional 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 to the absence of hypoxic microenvironment of slow-growing malignancies“^{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.

Acknowledgements

The authors would like to thank Dr Cheng Wang, Mr. Baoliang Bao and Dr Chunmei Wang (Department of Nuclear Medicine, Affiliated Hospital of Inner Mongolian Medical University, Hohhot, China) for their technical assistance. The present study was supported by the Natural Science Foundation of Inner Mongolia (grant no. 2013MS1188), the Scientific Research Project of the Affiliated Hospital of Inner Mongolian Medical University (grant no. 2014NYFYYB008), the Inner Mongolian Major Basic Science Research Program (grant no. 201503001) and the Inner Mongolian Science and Technology Innovation Project (grant no. 2015cztcxyd03). Part of the present study was presented at The Society of Nuclear Medicine and Molecular Imaging 2015 Annual Meeting (Baltimore, MD, USA; 4-10 June 2015) (26).

References

1. Herrmann K, Erkan M, Dobritz M, Schuster T, Siveke JT, Beer AJ, Wester HJ, Schmid RM, Friess H, Schwaiger M, *et al*: Comparison of 3'-deoxy-3'-[18F]fluorothymidine positron emission tomography (FLT PET) and FDG PET/CT for the detection and characterization of pancreatic tumours. Eur J Nucl Med Mol Imaging 39: 846-851, 2012.
2. Nakajo M, Nakajo M, Kajiya Y, Jinguji M, Mori S, Aridome K, Suenaga T and Tanaka S: High FDG and low FLT Uptake in a thyroid papillary carcinoma incidentally discovered by FDG PET/CT. Clin Nucl Med 37: 607-608, 2012.
3. Zander T, Scheffler M, Nogova L, Kobe C, Engel-Riedel W, Hellmich M, Papachristou I, Toepelt K, Draube A, Heukamp L, *et al*: Early prediction of nonprogression in advanced non-small-cell lung cancer treated with erlotinib by using [(18)F] fluorodeoxyglucose and [(18)F]fluorothymidine positron emission tomography. J Clin Oncol 29: 1701-1708, 2011.
4. Frings V, de Langen AJ, Smit EF, van Velden FH, Hoekstra OS, van Tinteren H and Boellaard R: Repeatability of metabolically active volume measurements with 18F-FDG and 18F-FLT PET in non-small cell lung cancer. J Nucl Med 51: 1870-1877, 2010.
5. Yang W, Zhang Y, Fu Z, Yu J, Sun X, Mu D and Han A: Imaging of proliferation with 18F-FLT PET/CT versus 18F-FDG PET/CT in non-small-cell lung cancer. Eur J Nucl Med Mol Imaging 37: 1291-1299, 2010.
6. Yamamoto Y, Nishiyama Y, Ishikawa S, Nakano J, Chang SS, Bandoh S, Kanaji N, Haba R, Kushida Y and Ohkawa M: Correlation of 18F-FLT and 18F-FDG uptake on PET with Ki-67 immunohistochemistry in non-small cell lung cancer. Eur J Nucl Med Mol Imaging 34: 1610-1616, 2007.
7. Buck AK, Halter G, Schirrmeister H, Kotzerke J, Wurziger I, Glatting G, Mattfeldt T, Neumaier B, Reske SN and Hetzel M: Imaging proliferation in lung tumors with PET: 18F-FLT versus 18F-FDG. J Nucl Med 44: 1426-1431, 2003.
8. Burgman P, O'Donoghue JA, Humm JL and Ling CC: Hypoxia-induced increase in FDG uptake in MCF7 cells. J Nucl Med 42: 170-175, 2001.
9. Pugachev A, Ruan S, Carlin S, Larson SM, Campa J, Ling CC and Humm JL: Dependence of FDG uptake on tumor microenvironment. Int J Radiat Oncol Biol Phys 62: 545-553, 2005.
10. Li XF, Ma Y, Sun X, Humm JL, Ling CC and O'Donoghue JA: High 18F-FDG uptake in microscopic peritoneal tumors requires physiologic hypoxia. J Nucl Med 51: 632-638, 2010.
11. Dence CS, Ponde DE, Welch MJ and Lewis JS: Autoradiographic and small-animal PET comparisons between (18)F-FMISO, (18) F-FDG, (18)F-FLT and the hypoxic selective (64)Cu-ATSM in a rodent model of cancer. Nucl Med Biol 35: 713-720, 2008.
12. Mudd SR, Holich KD, Voorbach MJ, Cole TB, Reuter DR, Tapang P, Bukofzer G, Chakravartty A, Donawho CK, Palma JP, *et al*: Pharmacodynamic evaluation of irinotecan therapy by FDG and FLT PET/CT imaging in a colorectal cancer xenograft model. Mol Imaging Biol 14: 617-624, 2012.
13. Huang T, Civelek AC, Li J, Jiang H, Ng CK, Postel GC, Shen B and Li XF: Tumor microenvironment-dependent 18F-FDG, 18F-fluorothymidine, and 18F-misonidazole uptake: A pilot study in mouse models of human non-small cell lung cancer. J Nucl Med 53: 1262-1268, 2012.
14. Li XF, Huang T, Jiang H, Wang X, Shen B, Wang X, Ng CK, Postel GC and Civelek AC: Combined injection of (18) F-fluorodeoxyglucose and 3'-Deoxy-3'-[(18)F]fluorothymidine PET achieves more complete identification of viable lung cancer cells in mice and patients than individual radiopharmaceutical: A proof-of-concept study. Transl Oncol 6: 775-783, 2013.
15. Li XF, Du Y, Ma Y, Postel GC and Civelek AC: (18) F-fluorodeoxyglucose uptake and tumor hypoxia: Revisit (18) F-fluorodeoxyglucose in oncology application. Transl Oncol 7: 240-247, 2014.
16. Zhang G, Li J, Wang X, Ma Y, Yin X, Wang F, Zheng H, Duan X, Postel GC and Li XF: The reverse Warburg effect and 18F-FDG uptake in non-small cell lung cancer A549 in mice: A pilot study. J Nucl Med 56: 607-612, 2015.
17. Bunyaviroch T and Coleman RE: PET evaluation of lung cancer. J Nucl Med 47: 451-469, 2006.
18. Graves EE, Maity A and Le QT: The tumor microenvironment in non-small-cell lung cancer. Semin Radiat Oncol 20: 156-163, 2010.
19. Vesselle H, Grierson J, Muzi M, Pugsley JM, Schmidt RA, Rabinowitz P, Peterson LM, Vallières E and Wood DE: In vivo validation of 3'deoxy-3'-[(18)F]fluorothymidine ([(18)F]FLT) as a proliferation imaging tracer in humans: Correlation of [(18)F] FLT uptake by positron emission tomography with Ki-67 immunohistochemistry and flow cytometry in human lung tumors. Clin Cancer Res 8: 3315-3323, 2002.
20. Tian J, Yang X, Yu L, Chen P, Xin J, Ma L, Feng H, Tan Y, Zhao Z and Wu W: A multicenter clinical trial on the diagnostic value of dual-tracer PET/CT in pulmonary lesions using 3'-deoxy-3'-18F-fluorothymidine and 18F-FDG. J Nucl Med 49: 186-194, 2008.
21. van Waarde A, Cobben DC, Suurmeijer AJ, Maas B, Vaalburg W, de Vries EF, Jager PL, Hoekstra HJ and Elsinga PH: Selectivity of 18F-FLT and 18F-FDG for differentiating tumor from inflammation in a rodent model. J Nucl Med 45: 695-700, 2004.
22. Grierson JR and Shields AF: Radiosynthesis of 3'-deoxy-3'-[(18) F]fluorothymidine: [(18)F]FLT for imaging of cellular proliferation in vivo. Nucl Med Biol 27: 143-156, 2000.
23. Tarkin JM, Joshi FR and Rudd JH: PET imaging of inflammation in atherosclerosis. Nat Rev Cardiol 11: 443-457, 2014.
24. Higashi K, Ueda Y, Seki H, Yuasa K, Oguchi M, Noguchi T, Taniguchi M, Tonami H, Okimura T and Yamamoto I: Fluorine-18-FDG PET imaging is negative in bronchioloalveolar lung carcinoma. J Nucl Med 39: 1016-1020, 1998.
25. Kurdziel K, Ravizzini G, Croft B, Tatum J, Choyke P and Kobayashi H: The evolving role of nuclear molecular imaging in cancer. Expert Opin Med Diagn 2: 829-842, 2008.
26. Wang X, Wang X, Zhao Z and Li XF: The mismatched intratumoral distribution of ^{18}F-FLT and ^{18}F-FDG may be a better indicator of malignancy: A PET/CT study in patients with solitary pulmonary nodule. J Nucl Med 56 (Suppl 3): S124, 2015.