[^{18}F] 3-deoxy-3'-fluorothymidine positron emission tomography: Alternative or diagnostic adjunct to 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography in the workup of suspicious central focal lesions?

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Background: 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography has been established as a standard diagnostic imaging method in the preoperative workup of suspicious pulmonary focal lesions, showing a sensitivity of more than 90% and a specificity of about 80%. Determination of malignant pulmonary lesions with FDG positron emission tomography depends on the assessment of glucose metabolism. However, false-positive findings can occur in inflammatory processes, such as sarcoidosis or pneumonia. The thymidine analogue 3-deoxy-3[^{18}F]-fluorothymidine (FLT) is a new positron emission tomography tracer that more specifically targets proliferative activity of malignant lesions. The objective of this study was to determine whether FLT positron emission tomography, in comparison with FDG positron emission tomography, provides additional information in the preoperative workup of central pulmonary focal lesions.

Methods: In this prospective study FLT and FDG positron emission tomography examinations were performed as a part of the preoperative workup in 20 patients with histologically confirmed bronchial carcinoma, 7 patients with benign lesions, and 1 patient with an atypical carcinoid. Results were compared with final pathologic findings.

Results: For staging of the primary tumor, FLT positron emission tomography revealed a sensitivity of 86% and a specificity of 100% compared with a sensitivity of 95% and a specificity of 73% for FDG positron emission tomography. For N staging, the sensitivity of FLT positron emission tomography was 57% and the specificity was 100%, and for FDG positron emission tomography, the sensitivity was 86% and the specificity was 100%, respectively.

Conclusions: Our preliminary findings indicate specific FLT uptake in malignant lesions. The number of false-positive findings in FDG positron emission tomography might be reduced with FLT positron emission tomography. Therefore positron emission tomography imaging with FLT represents a useful supplement to FDG in assessing the malignancy of central pulmonary focal lesions.

Exact preoperative staging in patients with bronchial carcinoma is of crucial importance in determining appropriate therapeutic management, especially when central focal lesions are present. The potential role of 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in the diagnostic workup of bronchial carcinoma has been investigated in numerous studies beginning in the 1990's. Determination of malignant lesions with FDG-PET is based on glucose metabolism. This also explains the lack of specificity because FDG-PET shows increased activity in inflammatory processes, sarcoidosis, or muscle activity.[1-14]

Shields and coworkers[15,16] have developed the new PET tracer 3-deoxy-3[^{18}F]-fluorothymidine (FLT) for noninvasive detection of tumor proliferation.

A study by Rasey and coworkers[17] using cultured A549 human lung carcinoma cells showed that FLT uptake correlated positively with cell growth and thymidine kinase 1 activity in the cytosol. In a first clinical trial, Buck and associates[18] demonstrated specific FLT uptake in malignant pulmonary nodules in a series of 30 patients with unclear pulmonary nodules. None of 8 benign lesions demonstrated visible FLT uptake.

The objective of the present study was to investigate the diagnostic accuracy of FLT-PET and whether the strategy of specific imaging of proliferation can provide additional information during the preoperative diagnostic workup.

Patients and Methods

In this prospective study 28 patients (21 men and 7 women) were included (mean age, 63.4 years; range, 41-78 years). Only those patients with findings of a central focal lesion on spiral computed tomography (CT) were included in this study.

Patient Selection

In this prospective study FLT-PET was performed as part of the preoperative workup in 20 patients with histologically confirmed bronchial carcinoma, 7 patients with benign lesions, and 1 patient with atypical carcinoid. For staging, patients also underwent FDG-PET, CT scanning of the thorax, bronchoscopy with biopsy for confirmation of the diagnosis, and upper abdominal ultrasonography and whole-body bone scanning for detection of possible distant metastases. Patients in whom the findings on CT, FDG-PET, or both were consistent with stage N3 disease also underwent diagnostic mediastinoscopy. Depending on the results of staging, patients then underwent either chemotherapy or surgical management. Staging was conducted in accordance with internationally accepted staging guidelines. Surgical therapy with curative intention was performed in patients staged at International Union Against Cancer stages I to IIIa. Mediastinal lymph node dissection was performed according to the mapping scheme published by Naruke and coworkers.[19] The study was approved by our institutional ethics commission, and all patients provided informed written consent.

Synthesis of [^{18}F]FLT

The detailed protocol of the synthesis of FLT was described elsewhere.[18,20] Briefly, benzoyl-protected anhydrothymidine was used for FLT synthesis. Radiosynthesis was carried out in a PET tracer synthesizer from a nuclear interface. After nucleophilic introduction of [^{18}F] fluoride accompanied by anhydro-ring opening, deprotection of the benzylated intermediate was performed by using 1% NaOH solution. [^{18}F]FLT was purified by means of preparative high-performance liquid chromatography.

Positron Emission Tomography

Both PET examinations were performed on consecutive days within 2 weeks before resective surgery or core biopsy. PET was performed with a high-resolution full-ring scanner (ECAT Exact or ECAT HR+, Siemens/CTI), which produces 47 or 63 contiguous slices per bed position. The axial field of view is 15.5 cm per bed position. Five bed positions were measured in each patient, covering a total field of view of 77.5 cm. The emission scan included the thorax and abdomen in all patients. Patients fasted for at least 6 hours before undergoing PET. Static emission scans were performed 45 minutes after injection of 265 to 370 MBq of [^{18}F]FLT (mean, 334 MBq) and 345 to 550 MBq of [^{18}F]FDG (mean, 391 MBq), respectively. The acquisition time was 8 minutes per bed position. Three-minute transmission scans with a germanium-68/gallium-68 ring source were performed for attenuation correction after tracer application. Images were reconstructed by using an iterative reconstruction algorithm described by Schmidlin.[21]

All images were evaluated by 2 experienced nuclear medicine physicians. For calculation of standardized uptake value, circular regions of interest were drawn containing the area with focally increased pulmonary FLT and FDG uptake.

Analysis of Data

The results of thorax CT scanning, FDG-PET, and FLT-PET were compared with histologic findings, with subsequent determination of the specificity (TN/[TN + FP]), sensitivity (TP/[TP + FN]) and accuracy ([TP + TN]/[TP + TN + FP + FN]; TN = true negative, TP = true positive, FP = false positive, and FN = false negative).

Results

Surgical resection was performed within a time interval of 14 days in 22 patients. In the remaining patients diagnostic staging and histologic confirmation of malignancy was performed by means of mediastinoscopy, bronchoscopy, or both.

Twenty-one patients had malignant lesions, and 7 patients had benign lesions. Lesions included 5 nondifferentiated non–small cell bronchial carcinomas (Figure 1), 5 adenocarcinomas, 2 large cell bronchial carcinomas, 7 squamous cell carcinomas, 1 small cell bronchial carcinoma, 1 atypical carcinoid, 1 lipoma with inflammatory margin, 1 case of tuberculosis (Figure 2), 1 bronchopulmonary chondroma, 1 instance of an anthracotic lymph node, 1 cholesterol granuloma, and 2 cases of chronic, nonspecific bron-

chitis (Table 1). Twelve patients with malignant tumors had involvement of the lymph nodes.

Imaging of the Primary Tumor With FLT-PET and FDG-PET

FLT-PET showed visible tracer uptake in 18 of 21 malignant primary tumors. Therefore SUV values for FLT were not calculated in the 3 negative lesions.

Mean [^{18}F]FLT uptake in all patients was 2.0 (median, 1.7; SD, 2.1; range, negative to 5.6). In patients with bronchial carcinomas, mean FLT uptake was 2.9 (median, 3.0; SD, 3.1; range, negative to 10.4). FLT-PET results were false-negative in patient 7 with a highly differentiated adenocarcinoma and in patient 11 with a histologically confirmed carcinoma in situ (non–small cell bronchial carcinoma). A third malignant primary tumor (patient 28) representing an atypical carcinoid also exhibited no visible FLT uptake. False-positive findings were not returned in all patients with benign lesions. This results in an overall sensitivity of 86%, a specificity of 100%, and an accuracy of 90% for staging of the primary tumor.

Twenty of 21 malignant lesions exhibited focal accumulation of FDG, resulting in a sensitivity of 95% for determination of the malignant primary tumor. Mean FDG uptake in all lesions was 3.9 (median, 3.0; SD, 4.6; range, negative to 10.6). In the malignant lesions mean FDG uptake was 6.9 (median, 5.9; SD, 7.2; range, negative to 22.7). FDG-PET returned false-negative findings in patient 11 with a carcinoma in situ that were also negative on FLT-PET. Of 7 patients with benign lesions, 2 exhibited tumoral FDG uptake (Figure 3).

Lymph Node Status

FLT-PET staging results with regard to patient lymph node status were true negative in 16 patients, false negative in 5 patients, and true positive in 7 patients. Thus the sensitivity of FLT-PET for detecting malignant lymph nodes was 57%, with a specificity of 100% and an accuracy of 82%. In comparison, findings of FDG-PET were true positive in 10 patients, true negative in 16 patients, and false negative in 2 patients. On the basis of these findings, the sensitivity of FDG-PET for determination of patients' lymph node status is 86%, with a specificity of 100% and an accuracy of 93% (Figure 4).

Discussion

In a meta-analysis of 15 studies including a total of 1144 patients, determination of the malignant primary tumor with FDG-PET was associated with a sensitivity of 96% and a specificity of 80%. The performance of FDG-PET in N staging (20 studies, 1292 patients; sensitivity, 88%; specificity, 92%; accuracy, 91%) was superior to that of CT (19 studies, 1268 patients; sensitivity, 65%; specificity, 76%; accuracy, 73%).[6,22-24]

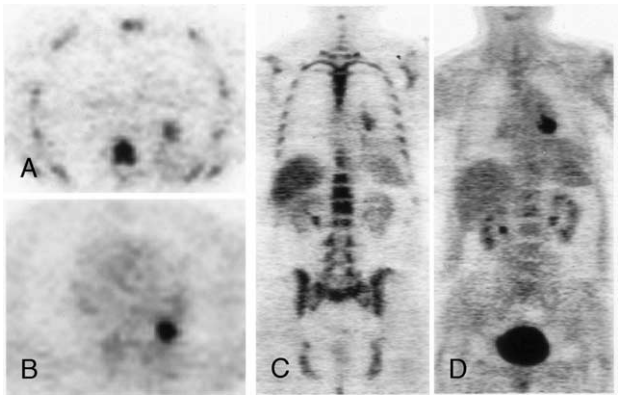

Figure 1. A, FLT-PET (transaxial section) of patient 2 with a non–small cell bronchial carcinoma in the left upper lobe (T2 N0 M0). Tumoral FLT uptake indicates moderate proliferative activity. B, Corresponding transaxial section of FDG-PET with intense tracer uptake. C, Coronal section of FLT-PET demonstrating uptake of the primary tumor and physiologic uptake in the proliferating bone marrow of the spine, pelvis, ribs, and scapula. Accumulation in the liver is related to FLT glucoronization. D, Corresponding FDG-PET section, physiologic accumulation in the bladder caused by renal excretion of FDG.

Numerous studies have investigated the role of FDG-PET in the diagnosis of central bronchial carcinoma. In a meta-analysis published by Hellwig and colleagues,[6] a sensitivity of 96% and a specificity of 80% was described for functional imaging with PET. FDG, however, is not a selective tracer. An increased uptake is observed in both malignant tissue and inflammatory lesions.[7,25] In the search for a more selective tracer for PET imaging identifying cellular proliferation, Shields and coworkers[16] reported initial findings regarding the use of the thymidine analog FLT in a pilot study. FLT was first evaluated as a chemotherapeutic agent for the treatment of leukemia.[26] Researchers soon discovered its exceptional anti-HIV activity.[27] Toxicity observed during phase II clinical trials with FLT deterred investigation of the drug administered at pharmacologic doses.[28] The successful labeling of FLT with ^{18}F led to a novel proposal to use [^{18}F]FLT as a radiopharmaceutical for monitoring HIV infection.[29,30] Although this application was never pursued in animal models, the concept formed the basis for imaging cell proliferation in tumors.

In the present study 28 patients with unclear central focal lesions were included, and PET imaging with FLT was performed in all patients. For preoperative staging, all patients additionally underwent FDG-PET. With regard to detection of the primary tumor, FDG-PET showed a sensitivity of 95%, which, despite the small number of patients, agrees with sensitivity values reported in the literature (88%-97%).[6,22-24] FDG-PET also returned false-positive results in 2 of 7 patients with inflammatory lesions. The

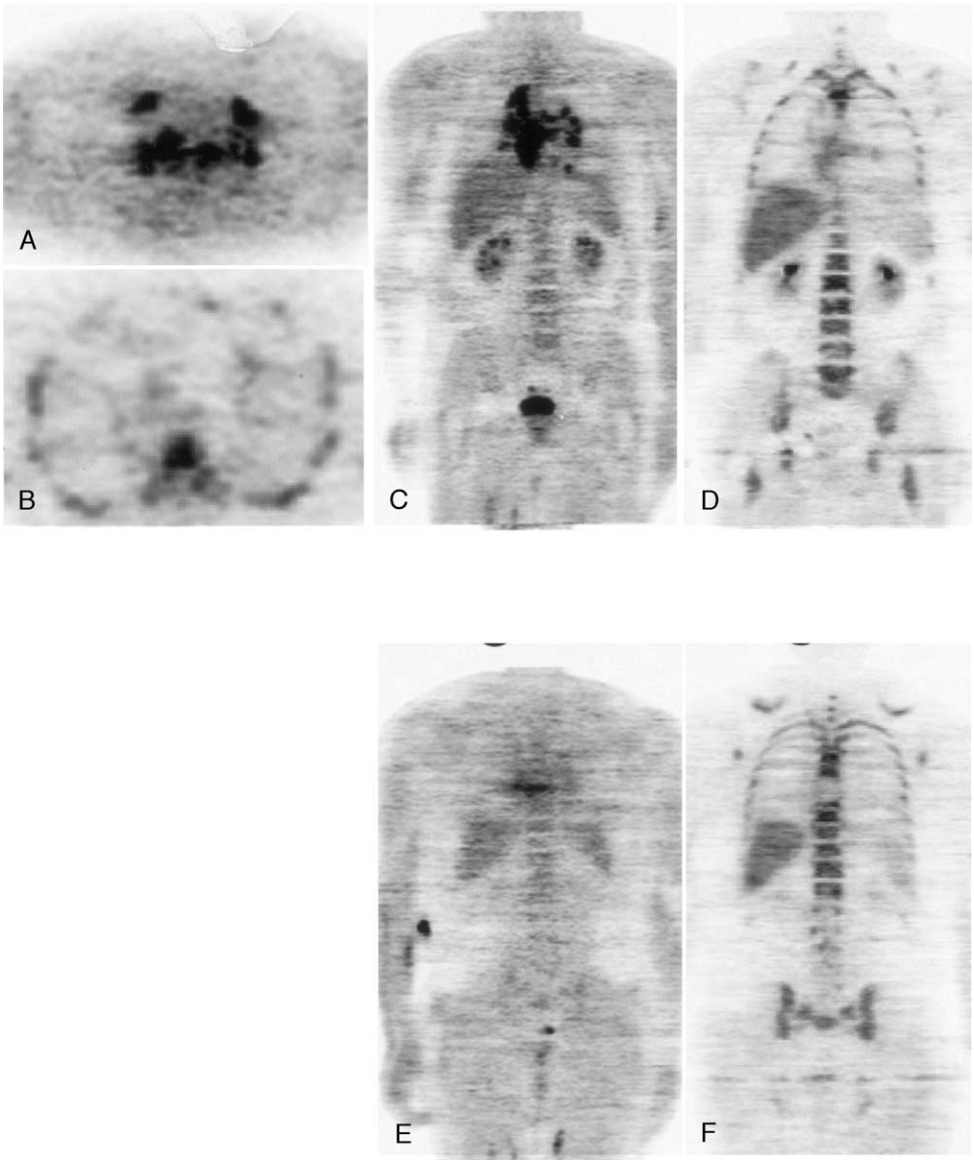

Figure 2. A, FDG-PET of patient 22 with active pulmonary tuberculosis and additional spondylodiscitis. Intense FDG uptake in a central pulmonary lesion on the right side and additional uptake in multiple mediastinal lymph nodes on both sides is shown. B, Corresponding FLT-PET section: no tracer uptake indicates no increased tumoral proliferation. C, Coronal section of FDG-PET demonstrating high tracer uptake in the lesions and physiologic renal excretion of the tracer. D, Corresponding section of FLT-PET demonstrating only physiologic tracer uptake. E, Coronal section of FDG-PET with longitudinal tracer uptake in the thoracic intervertebral disc 5/6 indicating tuberculosis related discitis. F, Corresponding FLT-PET scan shows no tracer uptake in the inflammatory process and in the neighboring vertebrae 5 and 6.

decreased specificity of FDG-PET is also well documented in the literature.[4,6,7] However, there were no false-positive findings reported for FLT-PET, yielding a specificity of 100%. False-negative FLT-PET findings were returned in 3 patients. Therefore FLT-PET was less sensitive when compared with FDG in our series. The histologically confirmed diagnosis in one of these patients was carcinoma in situ, whereas a second patient exhibited a highly differentiated adenocarcinoma, and a third exhibited an atypical carcinoid. These findings correspond to data published by Buck and associates[18] describing less favorable results for FLT-PET in patients with well-differentiated tumors. The carcinoma

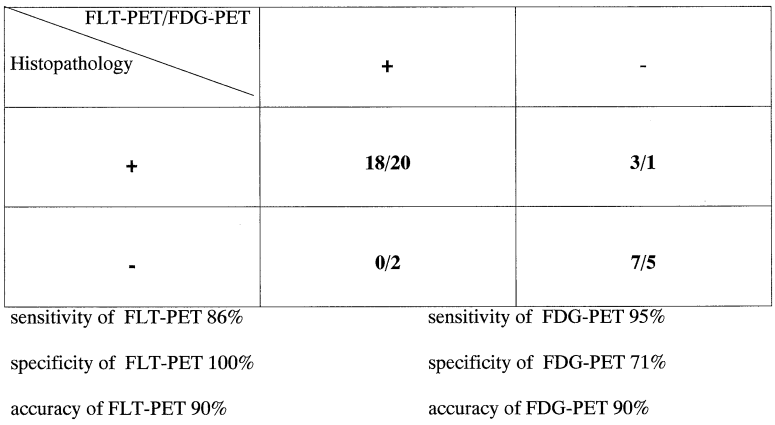

Figure 3. PET findings: malignant and benign primary tumors.

TABLE 1. Characteristics of 28 patients with central focal lesions, comparison of FLT-PET and FDG-PET findings, and corresponding histopathologic diagnosis

Patient no.	Histopathology	TNM	FLT-PT	FLT-N	FDG-PT	FDG-N
1	Adenocarcinoma	T1 N3	TP	FN	TP	TP
2	NSCLC	T2 N0	TP	TN	TP	TN
3	NSCLC	T2 N2	TP	FN	TP	FN
4	NSCLC	T3 N3	TP	TP	TP	TP
5	NSCLC	T2 N3	TP	TP	TP	TP
6	LCC	T2 N0	TP	TN	TP	TN
7	SCC	T4 N1	TP	TP	TP	TP
8	Adenocarcinoma	T2 N1	FN	FN	TP	TP
9	SSC	T3 N0	TP	TN	TP	TN
10	SCC	T4 N2	TP	TP	TP	TP
11	SSC, carcinoma in situ	T1 N0	FN	TN	FN	TN
12	LCC	T2 N2	TP	TP	TP	TP
13	Adenocarcinoma	T4 N1	TP	FN	TP	FN
14	Adenocarcinoma	T1 N2	TP	FN	TP	TP
15	Adenocarcinoma	T2 N0	TP	TN	TP	TN
16	SCC	T3 N1	TP	TP	TP	TP
17	SCC	T2 N1	TP	TP	TP	TP
18	NSCLC	T2 N0	TP	TN	TP	TN
19	SCC	T1 N1	TP	TP	TP	TP
20	SCC	T2 N2	TP	FN	TP	TP
21	TBC	–	TN	TN	FP	TN
22	Nonspecific bronchitis	–	TN	TN	TN	TN
23	Atypical lipoma with inflammatory change	–	TN	TN	TN	TN
24	Nonspecific bronchitis	–	TN	TN	FP	TN
25	Bronchopulmonary chondroma	–	TN	TN	TN	TN
26	Anthrakotic LN	–	TN	TN	TN	TN
27	Cholesterol granuloma	–	TN	TN	TN	TN
28	Atypical carcinoid	–	FN	TN	TP	TN

FLT, [^{18}F] 3-deoxy-3'-fluorothymidine; *PT,* primary tumor; *N,* lymph node status; *FDG,* [^{18}F]-fluoro-2-deoxy-D-glucose; *TP,* true positive; *FN,* false negative; *NSCLC,* non–small cell bronchial carcinoma; *TN,* true negative; *LCC,* large-cell bronchial carcinoma; *SCC,* small-cell bronchial carcinoma; *SSC,* squamous cell carcinoma; *TBC,* tuberculosis; *FP,* false positive; *LN,* lymph node.

in situ was also missed with FDG-PET, which is probably related to partial volume effects.

With regard to the patients' lymph node status, FLT-PET again showed a high specificity of 100% and a decreased sensitivity of 57%. True-positive findings on FLT-PET were returned in only 7 of 12 patients, which, even in this small patient collective, would suggest that FLT-PET is less sensitive for lymph node staging. For N staging, FDG-PET

FLT-PET/FDG-PET / Histopathology	+	-
+	8/12	6/2
-	0/0	14/14

sensitivity of FLT-PET 57%
specificity of FLT-PET 100%
accuracy of FLT-PET 82%

sensitivity of FDG-PET 86%
specificity of FDG-PET 100%
accuracy of FDG-PET 93%.

Figure 4. PET findings: malignant and benign lymph nodes.

exhibited a sensitivity of 86% and a specificity of 100% (Figure 3).

Considering the data as a whole, we see a decreased sensitivity of FLT-PET in terms of detection of well-differentiated tumors. Corresponding findings for primary tumors have also been reported by Buck and associates,[18] who calculated a correlation coefficient of 0.9 for tumoral FLT uptake and the proliferative activity measured by Ki-67 immunohistochemistry. For FDG-PET, Veselle and colleagues[13] and Higashi and coworkers[25] reported a correlation coefficient of 0.7 for tumoral FDG uptake and proliferative activity. This suggests that FDG uptake is not dependent solely on tumor proliferation leading to an increased tumoral tracer uptake.

For lymph node staging, it was found that lymph node metastases of poorly differentiated primary tumors were also frequently missed (false-negative findings in 6 of 13 patients). Because detailed histopathologic examination of lymph nodes has not been performed, precise information about the origin of false-negative findings cannot be given. However, small lesions might be missed with PET because of low tracer uptake, motion artifacts, or partial volume effects. Because the glucose analog FDG additionally accumulates in inflammatory cells rather than tumor cells alone, a higher sensitivity of FDG-PET seems feasible. This issue deserves to be investigated in further studies to determine both the lymph node proliferation rate and the detection rates of FLT-PET.

In conclusion, FLT-PET is potentially a useful adjunct to FDG-PET in assessing the malignancy of central focal lesions. Its strength lies in identifying those instances in which false-positive FDG-PET findings are related to inflammatory processes. Another potential role of the method lies in its use for monitoring therapeutic response. For primary staging, FLT-PET does not appear suitable as a substitute for FDG-PET because of its weakness in detecting well-differentiated tumors and in lymph node staging. Further studies with larger numbers of patients are required to definitively resolve these questions.

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