Occult lung infarction may induce false interpretation of ^{18}F-FDG PET in primary staging of pulmonary malignancies

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Abstract. *Purpose:* The aim of the present report is to describe abnormal ^{18}F-fluorodeoxyglucose (FDG) accumulation patterns in the pleura and lung parenchyma in a group of lung cancer patients in whom lung infarction was present at the time of positron emission tomography (PET).
Methods: Between November 2002 and December 2003, a total of 145 patients (102 males, 43 females; age range 38–85 years) were subjected to whole-body FDG PET for initial staging (n=117) or restaging (n=11) of lung cancer or for evaluation of solitary pulmonary nodules (n=17). Of these patients, 24 displayed abnormal FDG accumulation in the lung parenchyma that was not consistent with the primary lesion under investigation (ipsilateral n=12, contralateral n=9 or bilateral n=3). Without correlative imaging, this additional FDG uptake would have been considered indeterminate in differential diagnosis.
Results: Of the 24 patients who were identified as having such lesions, six harboured secondary tumour nodules diagnosed as metastases, while in three the diagnosis of a synchronous second primary lung tumour was established. Additionally, nine patients were identified as having poststenotic pneumonia and/or atelectasis (n=6) or granulomatous lung disease (n=3). In the remaining six (4% of all patients), a diagnosis of recent pulmonary embolism that topographically matched the additional FDG accumulation (SUV_{max} range 1.4–8.6, mean 3.9) was made. Four of these six patients were known to have pulmonary embolism, and hence false positive interpretation was avoided by correlating the PET findings with those of the pre-existing diagnostic work-up. The remaining two patients were harbouring small occult infarctions that mimicked satellite nodules in the lung periphery. Based on histopathological results, the abnormal FDG accumulation in these two patients was attributed to the inflammatory reaction and tissue repair associated with the pathological cascade of pulmonary embolism.
Conclusion: In patients with pulmonary malignancies, synchronous lung infarction may induce pathological FDG accumulation that can mimic active tumour manifestations. Identifying this potential pitfall may allow avoidance of false positive FDG PET interpretation.

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Introduction

^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) has an established role in the management of pulmonary malignancies [1, 2]. The high sensitivity of FDG PET permits accurate identification of disease extension and hence minimises the need for additional diagnostic procedures [3, 4]. However, a variety of inflammatory and benign disorders have been shown to accumulate remarkable amounts of FDG, misleadingly mimicking locoregional or distant tumour foci [5]. Disproving false positive results may result in considerable morbidity for the patient, especially if tissue sampling is required.

In non-small cell lung cancer (NSCLC), locoregional metastasis within the ipsi- or contralateral lung parenchyma is frequently observed. While isolated tumour nodules within the ipsilateral lobe containing the primary tumour are consistent with stage T4, metastatic deposits in other pulmonary lobes are classified as stage IV, inconsistent with curative surgical resection [6, 7]. Accordingly, additional pathological FDG uptake in the lung parenchyma distinct from the primary tumour localisation must be considered seriously.

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The aim of the present report is to describe abnormal FDG accumulation patterns in the pleura and lung parenchyma in a group of patients who were harbouring synchronous lung infarctions in addition to diagnosed or suspected pulmonary malignancy at the time of their initial staging using PET.

Materials and methods

Patients

From November 2002 to December 2003, a total of 145 patients (102 males, 43 females; age range 38–85 years) were subjected to whole-body FDG PET scan for initial staging (n=117) or restaging (n=11) of lung cancer or for evaluation of a solitary pulmonary nodule (SPN) (Table 1). Unless otherwise requested for a research protocol, interpretation of PET was usually done with full access to clinical data, associated cross-sectional imaging studies and histopathological results, if available. Abnormal FDG accumulation was defined as tracer uptake exceeding that of the normal mediastinal activity. Besides visual analysis, we performed semi-quantitative measurements of the detected lesions by means of the maximal standardised uptake value (SUV_{max}) normalised to body weight. Twenty-four of the studied patients displayed abnormal FDG accumulation patterns in the lung parenchyma that were not consistent with the primary lesion under investigation (ipsilateral n=12, contralateral n=9 or bilateral n=3). Pre-PET diagnostic work-up of these 24 patients included contrast-enhanced CT of the chest and upper abdomen with (n=7) or without (n=16) ventilation and/or perfusion (V/Q) lung scintigraphy. One patient was referred to PET after incidental detection of an SPN on pulmonary CT angiography confirming pulmonary embolism. Since histopathological verification was not always available for these additional FDG PET findings, correlative imaging studies and patient outcome were accepted as two complementary standards of reference.

PET protocol

To increase image quality and to suppress myocardial glucose utilisation, patients were asked to fast for at least 6 h before undergoing the FDG PET examination. Patients received an intravenous injection of 300–400 MBq of FDG and rested for 40–50 min to allow organ uptake. Before PET scanning, patients were encouraged to void to minimise activity in the bladder due to renal excretion of FDG. Then, patients were transferred to the table of the PET scanner. Fifty to sixty minutes after injection of FDG, a static whole-body emission PET scan was initiated covering the patient from the pelvic floor to the head. All images and data acquisition were performed using an Advance NXi PET scanner (GEMS), as previously described [3]. Image datasets were reconstructed iteratively and attenuation correction was performed using the ^{68}Ge rotating sources algorithm.

Results

Among the 24 patients who were identified as having additional foci of FDG accumulation in the lung parenchyma aside from the primary lesions under investigation (Table 1), six were harbouring secondary tumour manifestations consistent with M1 (contralateral, n=5; bilateral, n=1) while three patients with contralateral additional FDG uptake were diagnosed as having a synchronous second primary lung cancer. These findings were verified by histopathological examination (n=4) or correlative CT scanning together with final outcome (n=5). Additionally, nine patients were identified as having post-stenotic pneumonia and/or atelectasis (n=6) or granulomatous lung disease (ipsilateral n=1, contralateral n=1 or bilateral n=1). Although the diagnosis of these abnormalities was basically dependent on CT, pathological examination con-

Table 1. Clinical indications for PET, distribution of the additional foci of FDG uptake (per patient) and final diagnoses or outcome

Indication for FDG PET	FDG PET results		Additional FDG uptake in the lung			Final diagnoses/outcome (n=145)	
		Malignant (n=9)	Inflammatory (n=9)	Lung infarction (n=6)			
Tumour staging (n=117)	Potentially resectable (n=79)	Non-resectable (n=38)	Contralateral (n=7) Bilateral (n=1)	Ipsilateral (n=5)	Ipsilateral (n=3) Bilateral (n=1)	Stage I–IIIa (n=72)[a]	Stage IIIb–IV (n=45)[a]
Tumour restaging (n=11)	Metabolically inactive (n=3)	Metabolically active (n=8)	Contralateral (n=1)	–	–	In remission (n=3)	Residual/ recurrent (n=8)
Evaluation of an SPN (n=17)	Non-FDG avid (n=5)	FDG avid (n=12)	–	Ipsilateral (n=2) Contralateral (n=1) Bilateral (n=1)	Ipsilateral (n=2)[b]	Benign (n=6)	Malignant (n=11)

SPN solitary pulmonary nodule

[a]False up-staging (n=4) was mainly related to reactive contralateral lymph nodes, whereas false down-staging (n=11) was associated with contralateral microscopic nodal disease or cerebral metastases

[b]Based upon cytological examination, one patient was expected to have primary adenocarcinoma. However, wedge resection revealed only a previously suspected "FDG-accumulating" lung infarction

firmed these findings in three patients who underwent thoracotomy.

Of the remaining six patients, four had previously been identified as having thromboembolic lung disease no more than 2 weeks before the PET scan, whereas the other two had no such diagnosis at the time of their initial staging. In the former four patients, who were diagnosed with (*n*=2) or suspected of having (*n*=2) NSCLC, the diagnosis of lung infarction located ipsilaterally (*n*=3) or bilaterally (*n*=1) was established on the basis of the clinical presentation and lung scintigraphy (*n*=3) or pulmonary CT angiography (*n*=1). In these four patients, the topographic distribution of the secondary FDG uptake, in each case at the lung periphery, was in accordance with that of the known pulmonary embolism, and thus suggested accumulation at the site of the embolus. For these lesions, SUV_{max} ranged from 1.4 to 8.6 (mean 3.5). One patient, in whom cytology revealed abnormal cells possibly consistent with adenocarcinoma, underwent a thoracoscopic resection of a peripheral lesion considered as a pulmonary infarct on the basis of V/Q and CT scan (Fig. 1). This diagnosis was histopathologically confirmed; no malignant cells were found.

The other two patients displayed four isolated foci of peripheral FDG accumulation in the lung parenchyma of the right upper lobe. The SUV_{max} of these four lesions ranged from 3.8 to 5 (mean 4.4). At the time of the PET scan, these two patients were harbouring a centrally located primary tumour that extended to the right upper lobe. Since neither the clinical picture nor the contrast-enhanced CT suggested the existence of pulmonary embolism in either patient, our provisional diagnosis was consistent with distally located satellite tumour nodules in the right upper lobe (i.e. stage T4) and/or involvement of the pleura. These two patients were subjected, however, to curative surgical resection since FDG PET identified neither mediastinal lymph node involvement nor distant metastases. Ensuing histopathological examination revealed that these isolated peripheral foci of FDG uptake were consistent with lung infarction; there was accompanying haemorrhagic inflammation of the pleura in one patient (Fig. 2), while the other had isolated lung infarction. In both, inflammatory changes and myofibroblastic proliferation were surrounding these lung infarctions (Fig. 2D). Additionally, proximal thrombotic changes of the pulmonary artery were identified, as well as an angiosarcoma in one patient and squamous cell carcinoma invading the superior branch of the pulmonary artery in the other.

The identification of FDG-avid infarction sequelae in the aforementioned six patients had no impact on management: four patients with ipsilateral (*n*=3) or bilateral (*n*=1) lung infarction (known, *n*=2, or occult within the primary tumour lobe, *n*=2) were subjected to pneumonectomy (*n*=1), lobectomy (*n*=1) or wedge resection (*n*=2). Postoperative histopathological examination confirmed malignant pulmonary tumours in three of them. In the fourth patient with suspected lung infarction and atypical ipsilateral cells at cytology, wedge resection confirmed the diagnosis

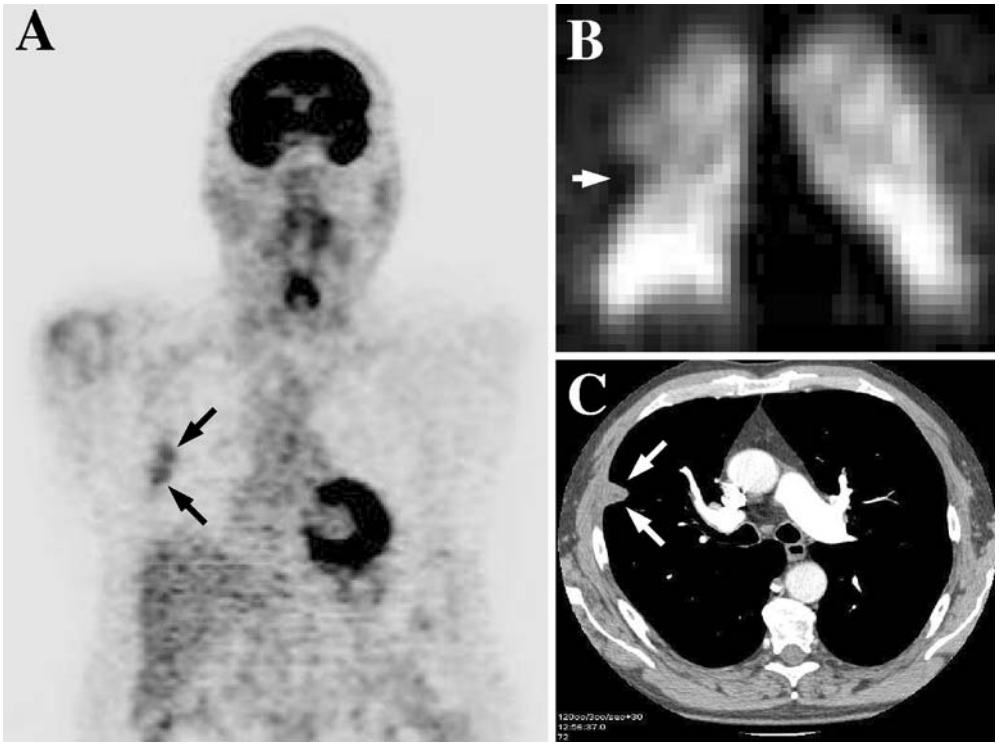

Fig. 1 **A** Coronal FDG PET in a 71-year-old male patient, known to have chronic thromboembolic lung disease, showing peripheral FDG accumulation in the upper lobe of the right lung (*arrows*; SUV_{max} 3.3). **B** Correlative subsegmental perfusion defect (*arrow*) on the coronal ^{99m}Tc-MAA perfusion single-photon emission computed tomography (SPECT) image. **C** Subpleural wedge-shaped opacity (*arrows*) on CT consistent with lung infarction

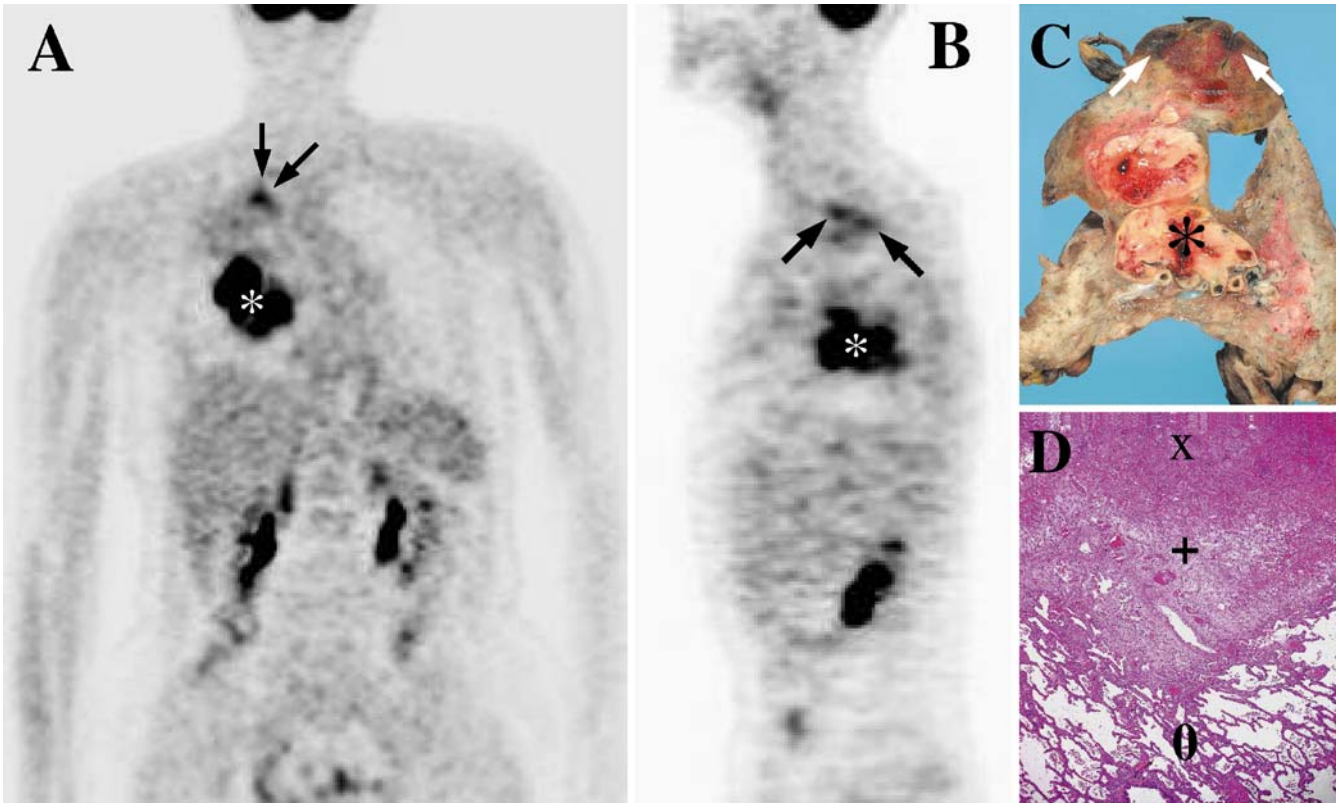

Fig. 2 **A** Coronal and **B** sagittal FDG PET in a 62-year-old female patient showing a right hilar FDG-avid tumour (✻) selectively extending to the upper lobe as well as isolated subpleural FDG accumulations (SUV_{max} 5) in the lung apex (*black arrows*). **C** A sagittally sectioned macroscopic specimen. **D** A corresponding (haematoxylin–eosin stained) histological slice at the level of the isolated apical FDG accumulations, revealing two small lung infarctions (*white arrows*), an area of necrosis (x) surrounded by active inflammatory and myofibroblastic proliferation zones (+), and normal lung tissue (*θ*). Based on these findings, the diagnosis of pulmonary embolism-induced lung infarctions was established

of infarction (Fig. 1); no malignant tissue was found. A non-FDG-avid SPN in another low-risk patient, with ipsilateral lung infarction, remained stable on subsequent CT follow-up. The remaining patient with lung infarction-induced ipsilateral additional uptake was not subjected to curative surgery because of distant metastases.

Discussion

Diagnostic pitfalls inherent in FDG PET represent an obvious limitation of functional imaging. Consequently, direct correlation of PET findings with those obtained from cross-sectional structural modalities such as CT or MRI has been advocated to add a high level of specificity to lesion categorisation [8, 9]. Nonetheless, consideration of the patient's clinical data (if any are available) may allow many erroneous diagnostic pathways to be avoided. Synchronous pulmonary embolism in patients with lung cancer is not uncommon (prevalence of 3% in our study population). Currently, there is no single best test to assure the diagnosis of pulmonary embolism [10, 11]. Furthermore, the significant overlap of symptoms among different thoracic pathologies may be misleading; in other words, cough, dyspnoea, haemoptysis or chest pain in a patient with lung cancer is most often attributed to the existing neoplasia.

Degradation products of cross-linked fibrin (D-dimer) are known to be highly sensitive but poorly specific in detecting pulmonary embolism. In fact, D-dimer can be elevated in up to 86% of patients with NSCLC [12]. A normal plasma value can thus exclude with very high probability the existence of venous thromboembolic disease, especially in patients with lung cancer [12, 13]. However, a D-dimer test is not necessarily performed in the absence of clinical symptoms; consequently, silent pulmonary embolism is invariably liable to be missed.

To the best of our knowledge, this is the first report to characterise pathological FDG accumulation in the sequelae of lung infarction. In this series, six patients diagnosed with or suspected of having pulmonary malignancy displayed additional foci of FDG accumulation in the lung parenchyma that topographically matched proven sites of lung infarctions; all of the additional foci were located at the lung periphery. Four of these patients were known to have pulmonary embolism, and hence erroneous interpretation was avoided after correlating the PET findings with those obtained from the pre-existing diagnostic work-up (Fig. 1). These secondary parenchymal FDG accumulations showed a wide range of SUV_{max} values (1.4–8.6), most probably

reflecting different healing phases after lung infarction; this hypothesis is strengthened by the absence of similar FDG uptake in the lungs of patients with older pulmonary embolism (data not shown).

In a previous report, Hany et al. described the iatrogenic occurrence of an FDG-avid pulmonary microembolism caused by a dislodged blood clot from the injection site in the patient's peripheral vein [14]. This tiny thrombus, which transferred and homed within the distal pulmonary vasculature, gave rise to erroneous interpretation of FDG PET. Furthermore, in a small series of nine patients with septic thrombophlebitis, Miceli et al. observed strong FDG uptake in the involved veins (SUV range, 3.8–21.4) that resolved completely in six of the patients who underwent subsequent PET scanning after appropriate antimicrobial therapy [15]. Contrary to Hany et al.'s observation, our data suggest that FDG uptake is not necessarily linked to the thrombus itself but may also reflect postembolic changes in the infarcted lung parenchyma and can thus indirectly lead to false positive PET interpretation.

Two patients with occult lung infarction displayed isolated peripheral FDG uptake in the upper lobe of the right lung in addition to their ipsilateral primary tumour manifestations (Fig. 2). Since neither the clinical picture nor the CT findings suggested the existence of lung infarction in either patient, these FDG-avid foci were initially interpreted as potential satellite nodules in the affected lung lobe. Given the opinion that some cases of "local T4" disease may benefit from aggressive surgical management [16], both patients were considered operable after both regional lymph node and distant metastases had been excluded.

In the regions where FDG PET falsely indicated additional ipsilateral satellite nodules in the lung parenchyma, histological examination revealed the existence of lung infarction, with or without complicating haemorrhagic inflammation of the pleura (Fig. 2). It is of note that a remarkable myofibroblastic proliferation zone and an overt inflammatory reaction were observed around these infarctions. These findings are in accordance with the known avidity of both acute and chronic inflammatory infiltrates for FDG [17, 18]. Similarly, in an experimental model of lung injury, Chen and co-workers observed that neutrophil activation is the source of increased FDG uptake in acutely injured lungs [19]. This is primarily related to the intrinsic activation of specific glucose transporter molecules within the phagocytes [20].

It is well recognised that tumours that originate from or encroach on a major vascular pedicle may lead to bloodstream slowing and/or stagnation that may result in thrombus formation. In the aforementioned two patients, in addition to an angiosarcoma in one and a squamous cell carcinoma that invaded the superior branch of the pulmonary artery in the other, frank thrombotic changes of the right main pulmonary artery (n=1) or its right upper branch (n=1) were identified at histopathological examination. The arterial involvement had certainly contributed to the pathogenesis of these occult lung infarctions, in conjunction with the known paraneoplastic coagulation abnormalities associated with some pulmonary malignancies [21].

The low number of patients identified with lung infarction showing FDG uptake certainly represents a limitation of the present study. However, since histopathological verification could be obtained in half of the patients (three of six), we believe that our observations are constant and valid.

Conclusion

Recent lung infarction may show remarkable FDG uptake and consequently can induce false interpretation of FDG PET in patients with pulmonary malignancies. This is primarily attributed to the inflammatory consequences of abrupt pulmonary devascularisation. The existence of subpleural foci of FDG uptake either unilaterally or bilaterally in subjects with a history consistent with possible thromboembolic lung disease merits further diagnostic work-up. Ventilation/perfusion SPECT might be the investigation of choice in patients with peripheral lesions rather than CT angiography. Furthermore, in patients with central pulmonary malignancy possibly invading a pulmonary artery, very peripheral FDG accumulation close to or involving the pleura of the same lung may suggest lung infarction that does not preclude curative surgical resection.

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