FDG-PET as a "metabolic biopsy" tool in non-lung lesions with indeterminate biopsy

A.D. Beggs[1], S.F. Hain[1, 2], K.M. Curran[1], M.J. O'Doherty[1]

[1] The Clinical PET Centre, Guy's, Kings and St Thomas' School of Medicine, Guy's and St Thomas' Hospitals, London UK
[2] *Correspondence to:* The Clinical PET Centre, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK,
e-mail: sharon.hain@kcl.ac.uk, Tel.: +44-20-79228106, Fax: +44-20-76200790

Received 25 August and in revised form 21 November 2001 / Published online: 27 February 2002
© Springer-Verlag 2002

Abstract. The differentiation of benign versus malignant disease in a lesion identified on conventional imaging is a commonly encountered problem. Attempted biopsy is often unsuccessful or falsely reassuring and may lead to the patient being sent for more invasive and potentially morbid investigations. Having previously identified the value of fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) in this circumstance in patients with lung lesions, our current aim was to investigate the role of FDG-PET in helping to identify more accurately those patients with malignant lesions outside the lung. FDG-PET scanning was performed in 50 patients; most had undergone unsuccessful biopsy of a lesion outside the lung, while in a smaller number no attempt at biopsy had been made as it had been considered too dangerous. Follow-up was by histology or, if this was unavailable, by clinical progress to death or a minimum of 12 months post scan. Visual and quantitative analysis was performed. On visual analysis, the positive and negative predictive values were 89% and 100%, respectively. On quantitative (SUV>2.5) analysis, positive and negative predictive values were 93% and 86%, respectively. A negative FDG-PET study in these circumstances virtually excludes malignancy and allows the patient to be reassured. A positive scan encourages the clinician to pursue further biopsy to confirm a histological diagnosis. FDG-PET therefore assists in deciding which patients need to undergo further investigation.

Keywords: FDG-PET – Biopsy – Cancer

Eur J Nucl Med (2002) 29:542–546
DOI 10.1007/s00259-001-0736-7

S.F. Hain (✉)
The Clinical PET Centre, Guy's,
Kings and St Thomas' School of Medicine,
Guy's and St Thomas' Hospitals, London UK

Introduction

Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) scanning has an established place in the differentiation of benign from malignant disease [1], although there is still overlap between benign inflammatory conditions and malignant disease [2]. In the diagnosis and staging of patients with or suspected of having malignancy, it is standard practice to perform imaging, in particular a range of radiology procedures including planar X-ray, computed tomography (CT) and/or magnetic resonance imaging. If these diagnostic tests suggest the presence of an abnormality then CT-guided or other biopsy methods are normally performed to confirm the nature of the abnormality. These procedures are not without risk, and most have a complication rate. A significant group of lesions also return non-diagnostic material from these biopsies, resulting in the need for more invasive and potentially morbid diagnostic procedures. Furthermore, there are a smaller number of lesions that are difficult or too dangerous to biopsy, where a further imaging test may have a role in determining whether treatment may be given without a definitive biopsy. In these circumstances FDG-PET, with its unique ability to differentiate benign from malignant disease, may provide a "metabolic biopsy" as an alternative to tissue biopsy and separate those requiring further investigation from those who do not.

We have previously reported on the use of FDG-PET as a metabolic biopsy in lung lesions, our findings showing that in this circumstance the use of FDG-PET is non-invasive and highly sensitive in diagnosing malignancy [3]. No study, however, has yet answered the question of whether FDG-PET can be used as a metabolic biopsy tool in imaging lesions outside the lung.

This study investigated the clinical problem in which a biopsy of a lesion outside the lung had been attempted but failed or was impossible. The FDG-PET scan was performed in these difficult cases to assess whether further potentially more invasive and morbid procedures should be performed.

Materials and methods

Patients. Fifty patients, 31 male and 19 female, with a mean age of 52.2 years (range 19–88 years) who presented for FDG-PET were studied. The patients had either single (*n*=27) or multiple (including a suspected primary site) (*n*=23) abnormalities that were suspected to be malignant, and either had undergone biopsy with indeterminate findings, i.e. inability to determine whether the lesion was benign or malignant owing to insufficient sample or indeterminate analysis, or had a lesion that was not amenable to biopsy. The biopsy attempts were as follows:

- Fine-needle aspirations: *n*=13
- True cut/punch/excision: *n*=11
- Stereotactic brain biopsy: *n*=3
- Lumbar puncture: *n*=1
- Laparoscopy of abdominal/pelvic lesions: *n*=9
- Bone marrow aspirate and trephine: *n*=5
- Lesions too dangerous or difficult to perform a biopsy upon: *n*=8

Figure 1 shows the sites of the original biopsies.

The final diagnosis was confirmed by histology (*n*=45) or by clinical follow-up (*n*=5). In the latter group (range 6–18 months), absence of malignancy was assumed if there was no clinical deterioration and the lesions remained stable or showed resolution on subsequent imaging review (minimum follow-up: 1 year). Malignancy was assumed if the treating physician felt that malignancy was present without further investigation and the patient underwent treatment and either showed response to treatment on conventional imaging or died from the disease. All patients followed up for less than 12 months died within this period.

PET scanning. After a 6-h fast, patients were injected with 350 MBq of ^{18}F-FDG, and after a 60-min uptake period, standard half-body studies were obtained on an ECAT 951/31R system (Siemens/CTI, Knoxville,Tenn.). Emission data were collected at 5 min/bed position with no attenuation correction. Localised emission views (20 min per bed position) were obtained if this was determined to be necessary by the supervising nuclear medicine physician, and a transmission scan was performed using a germanium-68 source for attenuation correction with a spatial resolution of 13 mm. Images were reconstructed and displayed as coronal, transaxial and sagittal sections. All scans were reported independently by two nuclear medicine physicians and a consensus report issued. Areas of non-physiological increased tracer uptake were reported.

Standard uptake values (SUVs; degree of tracer uptake relative to body norm) of the main lesion for quantitative analysis were calculated using the attenuation-corrected local image, where available (in 42 patients). One observer positioned a 4.5-mm region of interest over the maximum pixel in the lesion and the average of two perpendicular diameters of the lesion was noted. The SUV was calculated by the formula: tissue concentration of FDG measured by PET divided by the injected dose divided by body weight. No corrections were performed for glucose or partial volume. A separate analysis of the SUV data was performed. Lesions with an SUV greater than 2.5 were considered malignant [4].

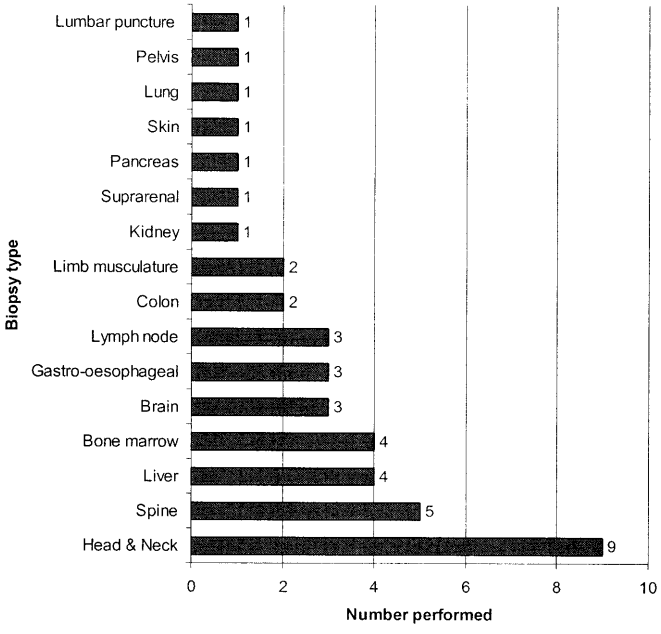

Fig. 1. The body areas in which the biopsy attempts were performed

Results

Of the 50 patients studied, 23 had a malignant process.

On qualitative analysis, it was found that 23/50 (46%) of the scans were true positive (Table 1, Fig. 2). False positive results were obtained in 3 of the 50 patients (6%). One false positive was due to reactive lymphadenopathy, one to an organising haematoma and one to a peri-pancreatic mass of unknown origin that resolved after a 2-week steroid course (Fig. 3). True negative results were obtained in 24 of the 50 patients (48%) (Fig. 4). There were no false negatives.

On quantitative analysis (with an SUV >2.5 considered indicative of malignancy), 13/42 (31%) cases were true positive (Table 1), 1/42 (2%) was false positive, 24/42 (57%) were true negative and 4/42 (10%) were false negative. The false positive was the patient with a

Table 1. Tumour types in patients with true positive PET scans on qualitative analysis and the corresponding SUV values

Tumour type	No. of patients	SUV range
Adenocarcinoma	7	2.9–14.3
Lymphoma	6	2.0–18.7
Squamous cell carcinoma	3	9.0
Other (liposarcoma, lymphoproliferative space-occupying tumour, malignant neurofibromata)	3	2.9–6.0
Neuroectodermal/neuroendocrine	2	–
Ependyoma	1	2.0
Astrocytoma	1	–

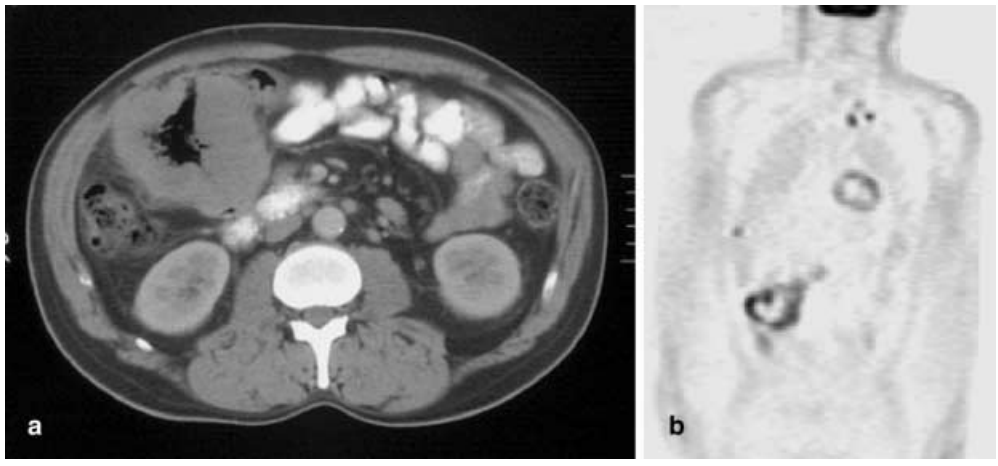

Fig. 2. a CT scan of the abdomen showing a massive colonic lesion. Biopsy was non-diagnostic. **b** Coronal whole-body PET scan of the same patient showing FDG uptake in the right hemicolon and metastases in the left lung and liver. On surgical resection the mass proved to be malignant

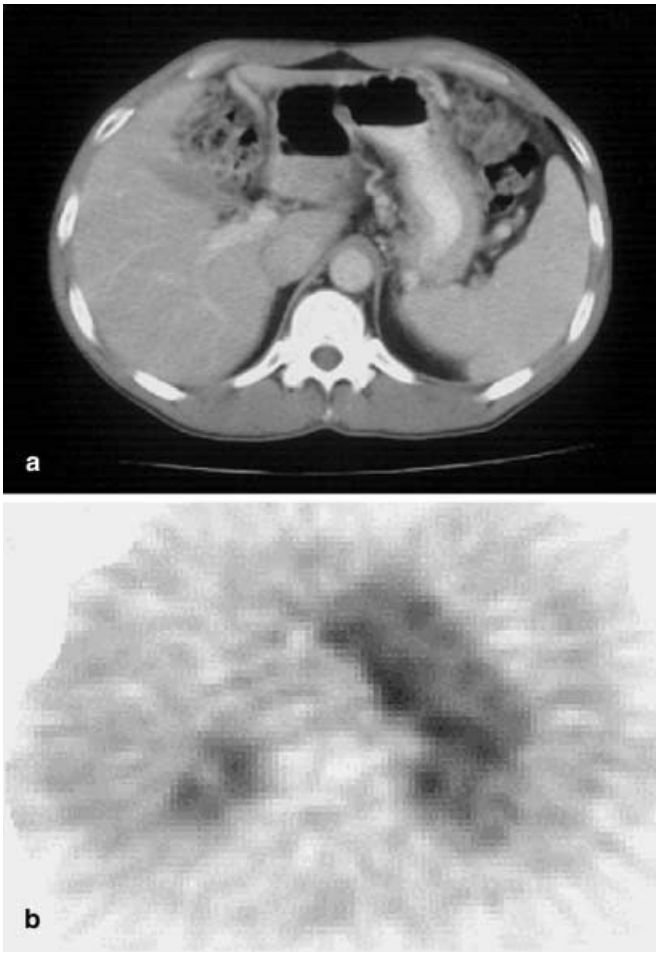

Fig. 3. a CT scan showing suspicious peri-pancreatic mass with non-diagnostic biopsy. **b** Transaxial local attenuation-corrected PET scan of the same patient, showing intense uptake in the region of the pancreas. The mass disappeared after a 2-week course of steroids

Table 2. The sensitivity, specificity and positive and negative predictive values determined for PET for qualitative and SUV evaluations

Statistics	Qualitative evaluation	SUV evaluation
Sensitivity	100%	77%
Specificity	89%	96%
Positive predictive value	89%	93%
Negative predictive value	100%	86%
Accuracy	94%	88%

peri-pancreatic mass, who was also false positive on visual analysis. Of the four cases with scans that were false negative, two were non-Hodgkin's lymphoma, one was an enteropancreatic neuroendocrine tumour and one was a cord ependymoma. They had SUV values of 2.0, 1.0, 1.3 and 2.0, respectively.

The sensitivity, specificity, and positive and negative predictive values determined for PET for qualitative and SUV evaluations are shown in Table 2.

Discussion

Histological proof of anatomical abnormalities seen on imaging is normally a prerequisite for optimum management. However, there are many circumstances in which this is not always achievable, and often it is difficult for the clinician to decide how hard to pursue a histological diagnosis. Many biopsy procedures have specific dangers, such as potential seeding of malignancy along a track [5] and intraperitoneal haemorrhage [6], and there is a high failure rate of biopsy attempts in specific areas [7]. In the brain, deep lesions are difficult to biopsy, and even with stereotactic biopsy there is a small but definable failure rate of 3.6% and a complication rate of 1.6% [8]. Similar problems have been found within the thorax, and FDG-PET appears to be helpful in this setting [3].

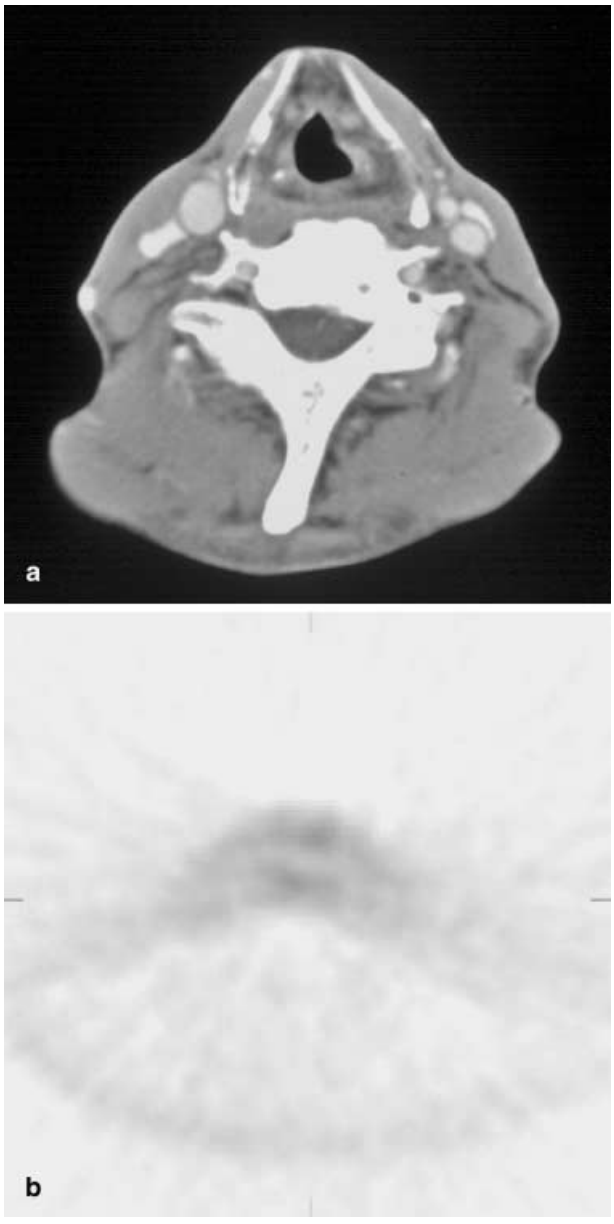

Fig. 4. a CT scan of the vocal cords showing swelling in the left vocal cord. Biopsy was non-diagnostic. **b** Transaxial local attenuation-corrected PET scan of the same patient showing physiological distribution of tracer only

The current study specifically looked at the situation where, prior to referral for PET scanning, patients with a lesion suspected to be malignant on the basis of conventional imaging either had undergone a biopsy that proved indeterminate or, less commonly, had been unable to undergo biopsy for a variety of patient- or lesion-related reasons. It was postulated that, as had been found in this circumstance in the lung [3], FDG-PET could be used as a "metabolic biopsy", given its ability to identify increased metabolism in a lesion.

Despite the variety of histopathological processes and the diverse body areas, this study demonstrates that PET shows a high sensitivity, accuracy and negative predictive value on visual analysis. In particular, the high negative predictive value means that truly benign lesions had no uptake of FDG and that such patients do not need to undergo further investigation. The high positive predictive value also means that all patients with a positive scan must undergo further evaluation as they are highly likely to have a malignancy.

The small number of false positives on visual analysis were caused by inflammatory masses, and it is well known that inflammatory processes will be PET positive [2]. Some caution needs to be exercised in patients with a high chance of inflammation, particularly in regions with high rates of granulomatous disease.

When SUV score analysis was used, more malignant lesions were classified as benign. All of these, however, were appropriately classified on visual analysis and were tumours with known low-grade uptake (low-grade lymphoma, ependymoma, neuroendocrine tumours) [9, 10, 11]. This is not surprising since an arbitrary cut-off of 2.5 was used, as has been found applicable in lung cancer [4]. Different tumour types are known to have a variety of uptakes depending on the grade of malignancy and possibly the timing of the scan. Patients are currently scanned at 60 min post injection of FDG and SUV is measured at 90 min. In a study of patients with soft tissue masses it was found that in benign lesions, FDG uptake reached a peak within 1 h and then rapidly decreased, whereas in high-grade sarcomas a plateau of FDG uptake was not seen until 4–6 h post injection [12]. This indicates that for soft tissue sarcoma a later scanning time provides better differentiation between benign and malignant lesions. Similarly, lesion detectability was found to be enhanced in cases of breast cancer when images were obtained at 3 h post injection, rather than earlier [13]. Further study of the time to peak FDG uptake should be carried out in a wide variety of tumours and might lead to even better differentiation between benign and malignant disease. Recently scanning times of 2 h for half-body FDG scans have been proposed to demonstrate metastases [14].

We have previously shown that the metabolic biopsy is useful in the interpretation of lung lesions [3]. The current results suggest that metabolic biopsy also has widespread application throughout the rest of the body. In this circumstance it may be even more valuable, as biopsy of other body cavities can have a more significant morbidity and mortality.

Conclusion

In patients in whom it is not possible to obtain a tissue diagnosis, a metabolic biopsy using FDG-PET is highly sensitive for the diagnosis of malignancy. Although a small number of false positives do occur, a lesion with FDG uptake is highly likely to be malignant and will

need further investigation. A negative study, on the other hand, virtually excludes malignancy. In the present study, 24/50 patients could accordingly be reassured that there was no evidence of malignancy. In such cases, further biopsy procedures can be avoided.

References

1. Weber WA, Avril N, Schwaiger M. Relevance of positron emission tomography in oncology. *Strahlenther Onkol* 1999; 175:356–357.
2. Bakheet SM, Saleem M, Powe J, et al. F-18 fluorodeoxyglucose chest uptake in lung inflammation and infection. *Clin Nucl Med* 2000; 25:273–278.
3. Hain SF, Curran KA, Beggs AD, et al FDG-PET as a "metabolic biopsy" tool in thoracic lesions with indeterminate biopsy. *Eur J Nucl Med* 2001; 28:1336–1340.
4. Patz EJ, Lowe VJ, Hoffman JM, et al. Focal pulmonary abnormalities: evaluation with F-18 fluorodeoxyglucose PET scanning. *Radiology* 1993; 188:487–490.
5. Sawabata N, Ohta M, Maeda H. Fine-needle aspiration cytologic technique for lung cancer has a high potential of malignant cell spread through the tract. *Chest* 2000; 118:936–939.
6. Riemann B, Menzel J, Schiemann U, Domschke W, Konturek JW. Ultrasound-guided biopsies of abdominal organs with an automatic biopsy system. A retrospective analysis of the quality of biopsies and of hemorrhagic complications. *Scand J Gastroenterol* 2000; 35:102–107.
7. Yasuda K, Uno M, Tanaka K, Nakajima M. EUS-guided fine aspiration biopsy (FNA) – indications and hazards. *Endoscopy* 1998; 30 (Suppl 1):A163–A165.
8. Yu X, Liu Z, Tian Z, et al. CT-guided stereotactic biopsy of deep brain lesions: report of 310 cases. *Chin Med J* 1998; 111:361–363.
9. Carr R, Barrington SF, Madan B, et al. Detection of lymphoma in bone marrow by whole-body positron emission tomography. *Blood* 1998; 91:3340–3346.
10. Wilmshurst JM, Barrington SF, Pritchard D, et al. Positron emission tomography in imaging spinal cord tumors. *J Child Neurol* 2000; 7:465–472.
11. Adams S, Baum R, Rink T, et al. Limited value of fluorine-18 fluorodeoxyglucose positron emission tomography for the imaging of neuroendocrine tumours. *Eur J Nucl Med* 1998; 25:79–83.
12. Lodge MA, Lucas JD, Marsden PK, et al. A PET study of ^{18}FDG uptake in soft tissue masses. *Eur J Nucl Med* 1999; 26:22–30.
13. Boerner AR, Weckesser M, Herzog H, et al. Optimal scan time for fluorine-18 fluorodeoxyglucose positron emission tomography in breast cancer. *Eur J Nucl Med* 1999; 26:226–230.
14. Kubota K, Itoh M, Ozaki K, et al. Advantage of delayed whole-body FDG-PET imaging for tumour detection. *Eur J Nucl Med* 2001; 28:696–703.