F-18 Fluorodeoxyglucose Gamma Camera Positron Emission Tomography identifies those patients with non-small cell lung cancer who are suitable for surgery?

Hanney MB[1], Van Beek EJR[1*], Lorenz E[1], Matthews S[1], Peck R[1], Vaughan R[2], Mitchell S[1], Tindale WB[1]

[1] Departments of Medical Imaging & Medical Physics, Sheffield Teaching Hospitals NHS Foundation Trust, Glossop Road, Sheffield, S10 2JF

[2] Cardiothoracic Services, Sheffield Teaching Hospitals NHS Foundation Trust, Glossop Road, Sheffield, S10 2JF, UK.

* Current Address: Department of Radiology, Carver College of Medicine, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242-1077, USA.

Funded by Yorkshire Cancer Research

Abstract

This study assessed the accuracy of positron emission tomography using a modified gamma camera (GC-PET) versus that of CT for staging mediastinal involvement in non-small cell lung cancer. The potential impact of GC-PET imaging on patient management was also estimated. 98 patients underwent CT imaging as part of routine management followed by GC-PET imaging as part of the study. GC-PET images were reported without knowledge of CT findings. For each patient, nodal resectability status derived from GC-PET and that from CT were compared with the histological stage established by mediastinoscopy or surgery. Potential impact on management was assessed by comparing actual management with that which would have resulted had the guidelines of the National Institute for Health and Clinical Excellence (NICE) for the use of dedicated PET been applied to GC-PET results. GC-PET differentiated resectable from unresectable lymph node involvement with an accuracy of 90%. Sensitivity and specificity were 79% and 93% respectively (ppv 73%, npv 95%). CT differentiated resectable from unresectable lymph node involvement with an accuracy of 72%, and a sensitivity and specificity of 64% and 74% respectively (ppv 39%, npv 89%). Management based on GC-PET results and NICE recommendations would have avoided 14 unnecessary mediastinoscopies and prevented three or possibly four abandoned resections. Two additional unnecessary mediastinoscopies would have resulted. This study suggests that GC-PET is more accurate than CT for nodal staging in NSCLC, and likely to impact favourably on management where dedicated PET is unavailable.

Key Words: GC-PET, Lung Cancer, Staging.

World J Nucl Med 2007;6:63-66

Correspondence:
Michael Hanney
Medical Imaging & Medical Physics
Ist Floor, Royal Hallamshire Hopital
Glossop Road
Sheffield S10 2JF, UK
Email: Michael.Hanney@sth.nhs.uk

Introduction

The accurate identification of those patients who may benefit from surgical resection remains a significant challenge in the treatment of non-small cell lung cancer (NSCLC). Curative surgery attempted in cases of advanced disease is unlikely to be successful and may be detrimental to the patient's quality of life, whilst failure to identify and treat early stage disease may mean that the opportunity of a cure is lost. Appropriate management decisions are therefore dependent on reliable preoperative staging.

Computed Tomography (CT) was traditionally the staging technique of choice, but inaccuracy due to its sole reliance on morphological changes has been a limiting factor. Critically, the assessment of mediastinal lymph node involvement based on the size of nodes on CT imaging is associated with significant false positive and false negative rates. Enlarged nodes (with a short-axis diameter exceeding 10mm) are identified as malignant, with normal sized nodes classed as benign. In fact, it has been reported that in this patient group 37% of nodes between 20mm and 40mm are benign whilst 13% of sub-10mm nodes contain metastatic disease (1). The sensitivity and specificity of CT for staging mediastinal involvement are 61% and 79% respectively (2).

Positron Emission Tomography (PET) is an imaging technique that exploits the altered physiology of cancer cells and has been shown to offer improved accuracy for

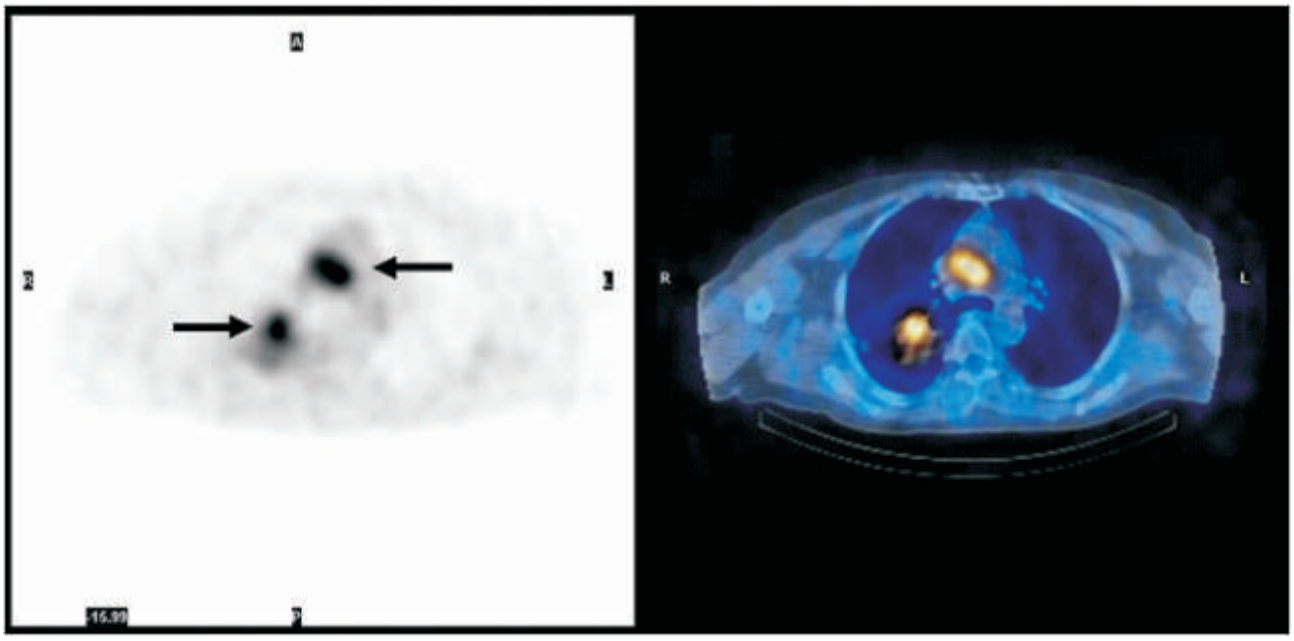

Figure 1. GC-PET / CT images. Left, a trans-axial slice showing abnormally raised FDG uptake in a primary lung tumour and mediastinal lymph nodes (arrowed). Right, GC-PET images of the same patient co-registered with low-resolution CT for anatomical localisation.

staging mediastinal involvement (2,3). The basis of almost all clinical PET investigations is tomographic imaging of the distribution of a radioactive glucose analogue, F-18 Fluorodeoxyglucose (FDG). After intravenous injection, the increased glycolytic rate of tumour cells results in the preferential uptake of FDG in malignant tissues. By differentiating malignant from benign on the basis of physiology rather than anatomy, PET imaging is more able to identify disease in normal sized nodes and less likely than CT to yield false-positive results in the presence of benign enlarged nodes.

Whilst the availability of PET imaging in the UK is set to increase, current access is limited, and a possible interim solution is the use of dual-headed gamma cameras adapted to perform PET imaging (GC-PET). GC-PET employs the same principle as dedicated PET systems, although the geometry of the imaging system results in reduced sensitivity for the detection of radiation and consequently reduced image quality relative to that of dedicated PET (4,5). While the imaging characteristics of GC-PET are known to be inferior to those of dedicated scanners, the clinical significance of the reduction in imaging quality remains unclear.

The objective of this study was to evaluate the accuracy of GC-PET imaging in the preoperative staging of mediastinal lymph node involvement in patients with known or suspected NSCLC. The accuracy with which GC-PET was able to differentiate between resectable and non-resectable nodal disease was compared with that of CT imaging in the same patient group. Importantly, the study also allowed the potential impact of GC-PET on patient management to be estimated.

Materials and methods

The GC-PET system used in this study (Millennium Hawkeye, GE Medical Systems, Chalfont St Giles, United Kingdom) is equipped with an integrated low-dose CT system for attenuation correction and anatomical localisation.

Ninety eight patients (60 male, 38 female) with an average age of 65 years (ranging from 36 to 79 years) underwent GC-PET imaging as part of the study. Ethics Committee approval was obtained prior to commencement and all patients gave informed consent. All patients had known or suspected NSCLC and were considered candidates for curative surgery based on routine clinical assessment, including contrast-enhanced CT of chest and upper abdomen. For the purpose of the study, CT scans were re-reported and given a radiological TNM stage by two experienced thoracic radiologists (SM and RP) blinded to GC-PET findings.

Patients fasted for 6 hours prior to GC-PET imaging. Plasma glucose levels were measured in all cases and confirmed below 10mmol/l. After intravenous injection of 300MBq of F-18 FDG, patients remained in a dedicated waiting room and were asked to keep still and quiet in order to minimise background tracer uptake. Imaging commenced one hour post injection. Low-dose, low-resolution CT images were acquired sequentially with GC-PET images using the integrated CT system, and used for attenuation correction and anatomical localisation (Figure 1). Patients were imaged over the thorax and abdomen with a total acquisition time of 90 minutes. Images were reconstructed using an Ordered Subset Expectation Maximisation iterative algorithm (10 subsets, 2 iterations)

and a Hanning post filter with a critical frequency of 0.85.
Attenuation correction maps derived from the co-registered CT images were incorporated into the reconstruction algorithm in order to correct for the effects of scatter and absorption of radiation within the patient. Both attenuation corrected and non-attenuation corrected images were reviewed by radiologists experienced in PET-CT (EvB, EL), without knowledge of diagnostic CT results or clinical information. Areas of suspicious FDG uptake were classified according to the degree of tracer uptake and the likelihood of the uptake representing malignancy.
Quantification of FDG uptake using standardised uptake values is not generally performed using GC-PET systems due to count rate-dependent variations in the sensitivity of the detector system. The degree of uptake was therefore assessed visually and scored from 1 to 3 where:

1 = faintly raised tracer uptake relative to surrounding tissue
2 = definitely raised relative to surrounding tissue, but not high tracer uptake
3 = high tracer uptake relative to surrounding tissue

The likelihood of uptake representing malignancy was scored from -5 (definitely benign) to +5 (definitely malignant). Lesions with an uptake score of 2 or 3 and a malignant / benign score of +3 or greater were considered positive for malignancy. The location of positive lesions was established from the co-registered low resolution CT.
On the basis of GC-PET images, patients were assigned an 'N' stage describing the involvement of mediastinal lymph nodes. Patients with no involved nodes (N0 disease) or with nodal involvement limited to ipsilateral peribronchial and/or hilar nodes (N1 disease) were grouped as resectable. Patients with involved mediastinal or subcarinal nodes or any contralateral nodal involvement (N2 and N3 disease) were grouped as unresectable. A second resectability status was derived from the patient's diagnostic CT scan.
For each patient, the resectability status derived from GC-PET imaging and that derived from diagnostic CT were compared with the histological N stage established at mediastinoscopy or surgery.

Results

Staging

Of the 98 patients scanned as part of the trial, 8 did not go on to have surgery or mediastinoscopy and were excluded from this analysis. One patient did not undergo surgery until three months after GC-PET imaging and was also excluded. In 9 cases, patients underwent surgery but no lymph nodes were sampled. Follow-up could not be obtained for a further 7 patients. Adequate nodal histology, obtained from mediastinoscopy or surgery, was available for 73 patients.
A comparison between GC-PET nodal staging and the histologically confirmed N stage is given in table 1. The accuracy with which GC-PET was able to differentiate between resectable and non-resectable lymph node involvement was 90%, with a sensitivity and specificity of 79% and 93% respectively (ppv 73%, npv 95%).

		Histological N Stage		
		N0/N1	N2/N3	Total
GC-PET N Stage	N0/N1	55	3	58
	N2/N3	4	11	15
	Total	59	14	73

Table 1. Comparison of GC-PET 'N' stage with histological findings

		Histological N Stage		
		N0/N1	N2/N3	Total
CT N Stage	N0/N1	40	5	45
	N2/N3	14	9	23
	Total	54	14	68

Table 2. Comparison of CT 'N' stage with histological findings

CT scans could not be obtained for study reading for 5 of the patients with a histologically confirmed N stage. Results for the remaining 68 patients are shown in table 2. The accuracy with which CT was able to differentiate between resectable and non-resectable lymph node involvement was 72%, with a sensitivity and specificity of 64% and 74% respectively (ppv 39%, npv 89%).

Effect on Management

•The potential impact on patient management of GC-PET imaging was assessed by comparing the actual management of patients with the management that would have resulted had the guidelines of the National Institute for Health and Clinical Excellence (NICE) for the use of dedicated PET (6) been applied to the GC-PET results. NICE recommendations may be summarised as:

- Where PET is negative for N2 /N3 disease, histological confirmation is not required prior to resection.
- Disease stage should be confirmed histologically prior to resection where PET is positive for N2/N3 disease, except where PET shows a high probability of metastatic nodal disease.

For the purposes of this analysis, scans reported as showing N2 or N3 disease with a minimum of three PET-positive nodes, each with an uptake score of 3 and a benign/malignant score of +4 or +5, were considered to demonstrate a high probability of metastatic nodal involvement. Scans showing abnormal but lower grade uptake, or intense uptake in fewer than three nodes were classified as suspicious for nodal involvement. Scans were classed as negative where there was an absence of abnormal nodal uptake or where raised uptake was limited to N1 nodes.
Eighty six patients recruited onto the study underwent a total of 97 surgical procedures [mediastinoscopy (n=22), mediastinotomy (n=4), and surgery with curative intent (n=71)]. Six of these 86 patients had a high probability of N2/N3 disease on GC-PET, of whom three were found to

have unresectable nodal disease at subsequent mediastinoscopy. One patient was negative for nodal involvement at mediastinoscopy but was found to have N2 disease at surgery. The two remaining patients proceeded directly to surgery where one was found to have N2 involvement and the second had resection abandoned due to an unresectable primary. This group of patients would have been staged as unresectable from GC-PET had NICE guidelines been applied, with the consequent avoidance of four mediastinoscopies and three abandoned or unsuccessful resections.

GC-PET was suspicious for N2/N3 disease in 12 of 86 patients. Under NICE guidance, this group require histological investigation to confirm disease stage prior to resection. Three of these 12 proceeded directly to surgery with curative intent; in two cases resection was successful, in the third case the procedure failed, with N2 nodal involvement found. Application of NICE guidance in this group would have therefore resulted in two additional unnecessary mediastinoscopies being carried out, but may have lead to the identification of unresectable disease prior to failed surgery in one case.

Sixty eight of 86 patients were negative for N2 disease on GC-PET and would have proceeded directly to surgery under NICE guidelines. In fact, ten of these patients underwent mediastinoscopy for staging prior to surgery. Nine were negative for N2 disease at mediastinoscopy and subsequent surgery. Mediastinoscopy was also negative in the tenth case, although the suspicious lung lesion subsequently resolved and surgery was considered unnecessary.

Management based on GC-PET results and NICE recommendations in this patient group would therefore have resulted in the avoidance of 14 unnecessary mediastinoscopies and prevented three or possibly four abandoned resections. Two additional unnecessary mediastinoscopies would have been performed.

Discussion

It is recognised that the imaging characteristics of dedicated PET systems are superior to those of GC-PET and that dedicated PET is therefore the modality of choice, however, this study was designed to assess the value of GC-PET where staging would otherwise be based on CT alone.

The evaluation of mediastinal nodes on CT is, in broad terms, based on size, with nodes having a short axis diameter greater than 10mm regarded as likely to be malignant. In this context, it might be expected that the reduced sensitivity of GC-PET for the detection of small volume disease (5) would limit its value; nevertheless, this study demonstrates clear improvements in sensitivity relative to CT, as well as specificity and overall accuracy.

Comparison of patient pathways in the absence of PET with those recommended by NICE where PET is available implies that the increased accuracy provided by GC-PET is likely to translate into improved management, with 18 unnecessary or futile procedures potentially avoided and only 2 additional mediastinoscopies performed unnecessarily

Conclusion

Whilst acknowledging the limitations of GC-PET, this study suggests that it is more accurate than CT alone for staging mediastinal involvement, and therefore likely to impact favourably on patient management where dedicated PET is unavailable.

References

1. McLoud TC, Bourgouin PM, Greenberg RW, et al. Bronchogenic carcinoma: analysis of staging in the mediastinum with CT by correlative lymph node mapping and sampling. Radiology 1992;182: 307-9.
2. Gould MK, Kuschner WG, Rydzak CE, et al. Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis. Ann Intern Med 2003;139:879-892.
3. Pieterman RM, van Putten JW, Meuzelaar JJ, et al. Preoperative staging of non-small-cell lung cancer with positron-emission tomography. N Engl J Med 343; 254-61: 2000.
4. Bird NJ, Old SE, Barber RW. Gamma camera positron emission tomography. Br J Radiol 2001; 74*:* 303-306.
5. Koga H, Sasaki M, Kuwabara Y, et al. Lesion detectability of a gamma camera based coincidence system with FDG in patients with malignant tumours: A comparison with dedicated positron emission tomography. Ann Nucl Med 2004; 18: 131–136.
6. National Institute for Health and Clinical Excellence. The Diagnosis and Treatment of Lung Cancer. February 2005