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Lymph node staging in non-small cell lung cancer: evaluation by [^{18}F]FDG positron emission tomography (PET)

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Abstract

***Background* – A study was undertaken to investigate the accuracy of positron emission tomography (PET) with 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) in the thoracic lymph node staging of non-small cell lung cancer (NSCLC).**

***Methods* – Forty six patients with focal pulmonary tumours who underwent preoperative computed tomographic (CT) and FDG-PET scanning were evaluated retrospectively. Thirty two patients had NSCLC and 14 patients had a benign process. The final diagnosis was established by means of histopathological examination at thoracotomy, and the nodal classification in patients with lung cancer was performed by thorough dissection of the mediastinal nodes at surgery.**

***Results* – FDG-PET was 80% sensitive, 100% specific, and 87.5% accurate in staging thoracic lymph nodes in patients with NSCLC, whereas CT scanning was 50% sensitive, 75% specific, and 59.4% accurate. The absence of lymph node tumour involvement was identified by FDG-PET in all 12 patients with N0 disease compared with nine by CT scanning. Lymph node metastases were correctly detected by FDG-PET in three of five patients with N1 disease compared with two by CT scanning, in nine of 11 with N2 disease compared with six by CT scanning, and in all four with N3 nodes compared with two by CT scanning.**

***Conclusions* – FDG-PET provides a new and effective method for staging thoracic lymph nodes in patients with lung cancer and is superior to CT scanning in the assessment of hilar and mediastinal nodal metastases. With regard to resectability, FDG-PET could differentiate reliably between patients with N1/N2 disease and those with unresectable N3 disease.**

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Keywords: lung cancer, FDG-PET, lymph node staging.

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Treatment of bronchogenic carcinoma varies with a number of factors including cell type and stage at initial diagnosis.[1] Cure of non-small cell lung cancer (NSCLC) is possible if the disease is diagnosed early in its course before mediastinal lymph node or systemic metastases occur. The presence and site of nodal metastatic disease has a significant effect on prognosis and management.[1 2] Metastases to contralateral mediastinal lymph nodes (N3 disease) indicates unresectable disease.[3]

Current non-invasive methods for evaluating the mediastinum include computed tomographic (CT) scanning and magnetic resonance imaging (MRI)[3] which depend primarily on anatomical imaging features and are of limited sensitivity and specificity in staging mediastinal nodal metastases.[4–7] By contrast, positron emission tomography (PET) depends primarily on the metabolic characteristics of a tissue for the diagnosis of disease.

PET using the glucose analogue 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) takes advantage of the enhanced glucose uptake observed in neoplastic cells.[8] It has been successfully used to detect primary and recurrent lung cancer[9–21] and to differentiate, with a high degree of accuracy, malignant from benign solitary pulmonary nodules less than 4 cm in diameter.[10 11 13 15 20 21] In addition, FDG-PET was suggested as a most promising non-invasive technique in detecting regional lymph node metastases of NSCLC[16 22–24] and defining the systemic extent of lung cancer by whole body imaging.[12 14 16] The aim of this study was to assess the accuracy of FDG-PET for preoperative staging of thoracic lymph nodes in patients with NSCLC and to determine its ability to differentiate between conventionally resectable lung cancer and unresectable N3 disease.

Methods

PATIENT SELECTION

The case histories of 46 consecutive patients (41 men) of mean age 56.7 years (range 24–78) who underwent thoracotomy for lung tumours from 1994 to August 1995 were analysed. All patients underwent contrast enhanced CT scanning of the chest and mediastinum as well as FDG-PET imaging during the three weeks before surgery.

Of the 46 tumours, 32 were NSCLC (19 squamous cell carcinoma, seven adenocarcinoma, six large cell carcinoma). There were 14 benign diseases (four pneumonia, three tuberculosis, and one each of florid abscess, sarcoidosis, aspergilloma, hamartoma, aneurysm of the subclavian artery, lung fibrosis, and inflammatory pseudotumour). The final diagnosis and the TN classification in patients with lung cancer were established by histo-

Table 1 Accuracy of FDG-PET imaging versus CT scanning in lymph node staging of non-small cell lung cancer

Modality	*N0*	*N1*	*N2*	*N3*	*Overall accuracy*	*Sensitivity*	*Specificity*
PET	100% (73 to 100) (12/12)	60% (15 to 95) (3/5)	82% (48 to 98) (9/11)	100% (40 to 100) (4/4)	87.5% (71 to 96) (28/32)†	80% (56 to 94) (16/20)	100% (73 to 100) (12/12)
CT	75% (43 to 95) (9/12)	40% (5 to 85) (2/5)	54% (23 to 83) (6/11)	50% (7 to 93) (2/4)	59.4% (41 to 76) (19/32)	50% (27 to 73) (10/20)	75% (43 to 95) (9/12)

Values are percentages with 95% confidence intervals. Numbers in parentheses are numbers of patients.
† $p<0.02$ compared with CT scanning (McNemar test).

pathological examination. Tumour cell type and stage of disease were classified according to internationally adopted criteria.[25 26] Surgical treatment (lobectomy or pneumonectomy) was performed for curative reasons in those with UICC stages I–IIIa disease or for various palliative reasons (bronchial bleeding, destroyed lung, etc) in those with UICC stage IIIb disease. In any case, thorough dissection of mediastinal nodes at surgery as a prerequisite for accurate lymph node staging was a consistent part of all resection strategies. Mediastinal lymph node staging was performed according to the mapping system devised by Naruke *et al*.[27] Three patients were staged T1, 12 T2, 10 T3, and seven T4. There were 12 patients with N0 disease, five with N1, 11 with N2, and four with N3 disease. The presence of a benign finding was proved intraoperatively by histopathological examination of the completely resected lesion at thoracotomy.

THORACIC COMPUTED TOMOGRAPHIC SCANNING

During the two weeks before FDG-PET imaging contrast-enhanced chest CT scanning was performed with a Pace-scanner (GE Medical Systems, Milwaukee, Wisconsin, USA) from the supraclavicular region to the adrenal glands as described previously.[28] Each CT scan was evaluated by two experienced radiologists blinded to the clinical and PET findings. Mediastinal lymph nodes were considered diseased if they exceeded 10 mm in the short axis diameter.

POSITRON EMISSION TOMOGRAPHY

PET was performed with a Siemens-CTI-ECAT 931 Scanner (Knoxville, Tennessee, USA) using attenuation correction and iterative image reconstruction as described previously.[29] Static emission scans from the supraclavicular region to the adrenal glands were obtained 50 minutes after administration of ^{18}F-FDG at a mean dose of 250 MBq (range 175–350 MBq). Qualitative evaluation of PET scans was performed blinded and independently by two board-certified nuclear medicine physicians experienced in PET imaging.

Table 2 Relationship between the nodal short axis diameter and FDG-PET findings in patients with non-small cell lung cancer

Nodal short axis diameter (mm)	*N0*		*N1*		*N2*		*N3*	
	PET+	*PET−*	*PET+*	*PET−*	*PET+*	*PET−*	*PET+*	*PET−*
<5	—	5	—	1	—	—	1	—
5–10	—	4	1	1	5*	—	1	—
11–15	—	1	2	—	4	—	—	—
16–20	—	2	—	—	1	—	2	—
21–25	—	—	—	—	1	—	—	—

Values are numbers of patients.
* Two patients with N2a nodes were classified as N1 with PET; one patient with N2 disease was classified as N1 with CT.

ANALYSIS OF DATA

The results of chest CT and FDG-PET scans were compared with the histological findings in the resected lymph nodes to determine their diagnostic specificity (TN/(TN+FP)), sensitivity (TP/(TP+FN)), and accuracy ((TP+TN)/(TP+TN+FP+FN)) in the N staging of NSCLC (TN=true negative, TP=true positive, FP=false positive, FN=false negative). Proportions were furnished with their 95% confidence interval. The relative accuracy of PET imaging compared with CT scanning was compared by the McNemar test.

Results

The results of histological analysis of thoracic lymph nodes were available from all of the 32 patients with NSCLC (table 1). FDG-PET was 87.5% accurate for the diagnosis of the presence or absence and involved station of thoracic nodal disease whereas CT scanning was 59.4% accurate ($p<0.02$). Two patients with N1 disease were classified as N0 and two with N2a disease were classified as N1 by PET imaging. Three patients with NSCLC had enlarged lymph nodes on the CT scan, suggesting N2 disease, which were negative at PET imaging (table 2). All nodes were histologically negative for tumour involvement but had characteristic signs of non-specific inflammation. Four patients with N2 disease had increased FDG uptake in normal sized nodes at CT scanning; all had tumour involvement at pathological examination. With regard to definitive surgical treatment, FDG-PET could reliably identify patients with unresectable N3 disease while CT scanning failed in two out of four.

In two patients with benign lung processes (aspergilloma, tuberculosis) there were positive ipsilateral hilar lymph nodes at FDG-PET imaging which were enlarged on the CT scan and had histopathologically characteristic signs of non-specific inflammation. In another three patients with benign lung lesions (sarcoidosis, inflammatory pseudotumour, pneumonia) enlarged ipsilateral hilar lymph nodes on the CT scan showed no increased uptake of FDG.

In detecting malignancy of the primary lesion, FDG-PET had a sensitivity, specificity, and accuracy of 93.8%, 85.7%, and 91.3%, respectively. The false negative findings were a 1 cm intrapulmonary metastasis of an adenocarcinoma showing no increased FDG uptake

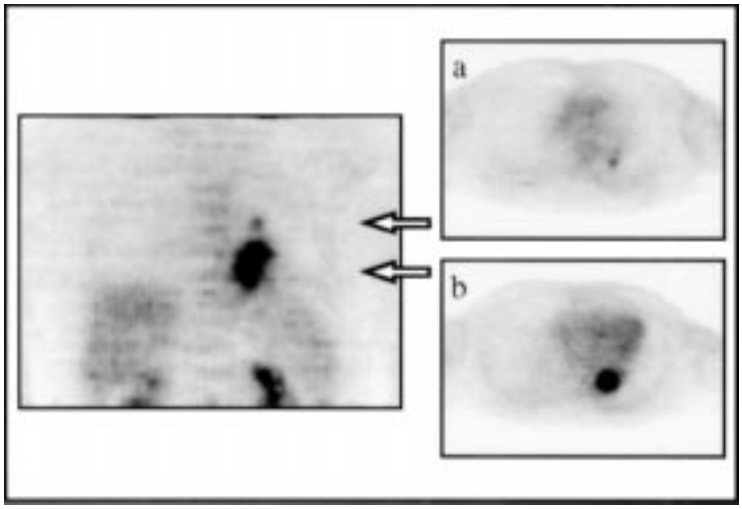

Figure 1 Coronal (left) and corresponding transaxial (right) FDG-PET scans of a patient with squamous cell carcinoma (pT3 pN1) of the left lower lobe. An ipsilateral peribronchial lymph node metastasis (a) as well as the primary tumour (b) are clearly visualised by focal FDG uptake.

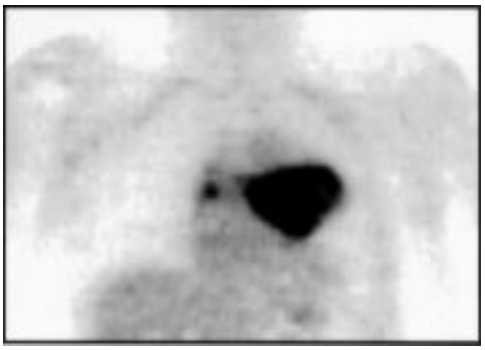

Figure 2 Coronal FDG-PET image of a patient with squamous cell carcinoma stage IIIb. The primary tumour, as well as the pathologically proved contralateral mediastinal lymph node metastasis, shows intense uptake of FDG corresponding to N3 disease.

and a bronchioloalveolar carcinoma which was considered benign due to less intense, diffuse, and heterogeneous FDG uptake. The false positive lesions were an aspergilloma with active inflammation and a florid abscess.

Representative PET images are shown in figs 1 and 2. Figure 1 shows intense FDG uptake in the primary tumour. Additionally, an ipsilateral peribronchial lymph node metastasis is clearly visualised. The corresponding CT scan showed no enlarged lymph nodes. In fig 2 a normal sized lymph node seen contralateral to the primary lung tumour on the CT scan shows increased FDG uptake indicating N3 disease which was confirmed pathologically.

Discussion

Accurate staging of locoregional lymph nodes in patients with known or suspected NSCLC is necessary, not only to determine the presence of N3 disease and unresectability, but also to assist in the selection of those patients with N2 disease who may be candidates for adjuvant or neoadjuvant treatment protocols.[30] CT scanning is currently the most accepted non-invasive method for evaluating regional lymph nodes in patients with NSCLC.[3 4] Regional lymph nodes are considered abnormal by CT scanning if they are more than 1 cm in short axis diameter.[6 7] However, enlarged lymph nodes may be merely hyperplastic and normal sized ones may contain tumour. According to recent studies, malignant mediastinal lymph nodes are not larger than benign nodes and small mediastinal lymph nodes are not infrequently malignant.[31 32] Consequently, the sensitivity and specificity of CT scanning for detecting metastases to mediastinal lymph nodes from NSCLC is as low as 52% and 69%, respectively.[5]

Unlike CT scanning and MRI which provide anatomical information and may be valuable for the preoperative assessment of mediastinal or chest wall invasion of lung cancer,[3 4] FDG-PET imaging provides information on increased tumour metabolism.[8 33 34] The ability of FDG-PET to detect microscopic amounts of metabolically highly active tumour in otherwise clinically normal lymph nodes[24] may partly explain why FDG-PET imaging is more accurate than CT scanning for staging regional lymph nodes in patients with NSCLC. Equally interesting was the observation that, in three histologically confirmed cases, enlarged N2 nodes seen on the CT scan showed no FDG uptake and were not involved with tumour (table 2). Thus, FDG-PET imaging correctly predicted the absence of tumour involvement, while CT scanning falsely suggested the presence of tumour. Our initial data suggest that FDG-PET may supplant invasive diagnostic procedures such as mediastinoscopy in these patients.

Wahl *et al*[22] reported that FDG-PET alone was 82% sensitive and 81% specific for detecting hilar and mediastinal lymph node metastases in patients with NSCLC while CT scanning alone was 65% sensitive and 44% specific. Additionally, in two recently published studies FDG-PET imaging has been shown to be superior to CT scanning in the detection of thoracic lymph node metastases of NSCLC with accuracies of 100%[35] and 82%[36] compared with 69% for CT scanning; however, they failed to differentiate various nodal stations[35] and N2/N3 disease.[36] These studies are therefore of limited clinical value for distinguishing between patients who are potentially suitable for surgical resection and those with unresectable N3 disease. The most important finding of our study was that FDG-PET could differentiate reliably between patients with N1/N2 disease and those with unresectable N3 disease. Thoracotomy for curative resection would have been avoided in two of our patients with N3 disease and normal sized contralateral lymph nodes on the CT scan. In a recent report, using decision tree analysis, the cost effectiveness of FDG-PET in the staging of NSCLC has been shown.[37]

Two false negative findings in N1 disease do not devalue FDG-PET imaging since the specific level of N1 nodes does not influence surgical treatment and does not appear to have any prognostic implications.[1] Furthermore, a more reliable although clinically less significant

differentiation between tumour involvement in peribronchial hilar nodes (N1 disease) and mediastinal nodes adjacent to the bronchus (N2a disease) may be possible by combining anatomical information from the CT scan with metabolic information from the PET image.[22] Our findings concerning the high accuracy of FDG-PET imaging in differentiating malignant from benign lung tumours are in line with the results of others who have reported sensitivities for detecting malignancy in the range of 83–100%, specificities of 78–100%, and accuracies of 86–100%.[10 11 13 15 20 21 38] Inaccuracies may arise with FDG-PET imaging of lung tumours whenever small tumours with low proliferative activity are imaged or active inflammation is present.[23] Since inflammatory cells such as activated macrophages also avidly take up FDG,[39] false positive findings have been reported in active lung diseases such as granulomas and abscesses.[10 13 15 23]

In conclusion, FDG-PET imaging as a complementary adjunct to CT scanning should lead to more accurate non-invasive lymph node staging of lung cancer, resulting in improved treatment planning and prognostic information while decreasing the need for invasive diagnostic procedures such as mediastinoscopy.

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