Whole-body ¹⁸FDG positron emission tomography in the staging of non-small cell lung cancer

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ABSTRACT: Despite advances in morphological imaging, some patients with lung cancer are found to have nonresectable disease at surgery or die of recurrence within yr of surgery.

We performed a prospective study in 109 patients to compare the accuracy of whole-body positron emission tomography (PET) using fluorine-18 deoxyglucose (¹⁸FDG) and conventional imaging (CI) methods for the staging of non-small cell lung cancer (NSCLC). When CI or PET study suggested metastatic disease, confirmation was obtained by biopsy or follow-up information.

As compared to CI, ¹⁸FDG-PET correctly changed the N stage in 22 patients (33%) and the M stage in 15 patients (14%). For the detection of distant metastases, PET study showed five false-positive sites and no false-negative cases. Currently, the accuracy of PET in the detection of M stage is 96%.

Our study shows that visual interpretation of whole-body fluorine-18 deoxyglucose-positron emission tomography images can improve the diagnostic accuracy in the staging of non-small cell lung cancer. Further experience is needed to establish if metabolic imaging would be a cost-effective tool in the future management of lung cancer.
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Preoperative tumour staging in patients with non-small cell lung cancer (NSCLC) is important to identify those patients with localized disease who are likely to benefit from surgical resection. The intrathoracic and extrathoracic staging of NSCLC is a multidisciplinary process using morphological imaging, bronchoscopy and biopsy.

Despite this initial evaluation, some patients are found to have unresectable tumour during surgery or die of recurrent disease within 1 yr of the surgery that was intended to cure it [1, 2]. Indeed the current noninvasive methods have significant limitations for evaluating the mediastinum and potential extrathoracic metastases [3–6]. For example, about 60% of adrenal masses are of nonmetastatic origin and the false-positive rate in the case of bone scans can be up to 40% [7–9]. For these reasons, there is a need for the development of new imaging technologies.

Compared to the tissues from which they originate, malignant tumours have a markedly accelerated metabolism, especially glycolysis, deoxyribonucleic acid (DNA) synthesis, and protein synthesis. This increase in metabolic activity may be assessed by positron emission tomography (PET). For practical reasons, fluorine-18 deoxyglucose (¹⁸FDG) has found widespread use in PET and is the standard radiopharmaceutical for metabolic studies. Its use for *in vivo* cancer imaging results

from the observation of enhanced glycolysis in tumour cells. This phenomenon has been linked to both an increase in the amount of glucose membrane transporters and to an increase in the activity of the principal enzymes controlling the glycolytic pathways [10, 11]. In preliminary studies, we have already reported the value of ¹⁸FDG-PET for the evaluation of solitary pulmonary nodules and staging in NSCLC [12–14].

The current prospective study was designed to assess the clinical impact of whole-body ¹⁸FDG-PET, when evaluation is based on qualitative criteria, in the noninvasive staging of NSCLC.

Patients and methods

Between September 1994 and October 1996, whole-body ¹⁸FDG-PET and conventional imaging methods were performed to determine tumour spreading in 141 consecutive patients with newly diagnosed NSCLC. The diagnosis of NSCLC was obtained by sputum cytology, needle biopsy of a lung nodule or hilar mass, or by flexible bronchoscopy. Conventional imaging (CI) methods included chest and abdominal computed tomographic (CT) scanning and bone scintigraphy. If a lesion was suspected by bone scintigraphy, confirmation was obtained by bone radiography.

Twenty one patients with poor physiological status (inadequate cardiopulmonary function or aged patients contra-indicating an invasive exploration) were excluded from analysis. Eleven patients initially included in the study were later excluded because of inappropriate follow-up (inadequate compliance or no definitive diagnosis). Finally, 109 patients were enrolled in the study. In all cases, CI was performed in a traditional manner before the PET study. CT scanning were performed using a PQ2000 instrument (fourth generation; Picker, Cleveland, Ohio, USA). In the case of the CT scanning of the thorax, spiral volume was obtained from the lung apices to the posterior costophrenic angles with a slice thickness of 10 mm and a reconstruction increment of 8 mm. In some cases, a spiral acquisition of 5 mm thick slice and a reconstruction increment of 3 mm were obtained in the region of hili. A bolus of 120 mL iodinated contrast material (Optiray 300; Codali SA, Laboratoire Guerbert, Aulnay Sous Bois, France) was administered in all cases. To classify mediastinal lymph nodes, the short axis on the transaxial views was measured; if it exceeded 10 mm the node was considered diseased [8]. PET was performed using a Penn PET 240H scanner (UGM, Philadelphia, USA) 60–90 min post ^{18}FDG injection. About 200–300 MBq ^{18}FDG was injected by way of an antecubital vein in patients in a fasting state. The effective field of view is 512 mm in the X and Y directions and 128 mm in the Z direction. Images are reconstructed as 32 transverse planes composed of 4 mm isotropic voxels to form a 128×128 matrix. The whole-body mode acquires multiple overlapping steps at 64 mm intervals. This acquisition sequence corrects for the uneven interplane sensitivity inherent to three dimensional data acquisition schemes. Images were reconstructed using a Hanning filter. Between eight and 12 steps, extending from the neck to the pelvis, were acquired for each patient, with a total scanning time of 50–70 min (4–7 min·step^{-1}). PET data were analysed by visual interpretation of coronal, sagittal and transverse slices alone and in the cross-referenced situation. When CI or PET study suggested mediastinal or extrathoracic metastatic disease, confirmation was obtained by biopsy or radiological follow-up.

Nuclear medicine imaging (PET bone scintigraphy) and CT imaging were read independently by two nuclear medicine physicians and by two radiologists respectively, who had knowledge of the histological diagnosis of the primary tumour. When the two reviewers did not agree, they reviewed the images together to reach a consensus. In the case of PET images, nuclear physicians evaluated the presence or the absence of ^{18}FDG uptake in the intra- or extrathoracic areas. When ^{18}FDG uptake increase was observed, two levels were identified in comparison with normal activity: moderate (more or less twice the activity in a controlateral or reference region) or intense (markedly higher than the reference activity). These two levels of activity were considered positive for metastasis.

Comparison of the results

PET and CI were interpreted separately and the results were then compared to each other and in pertinent cases, with the histological proof (biopsy, media-stinoscopy, thoracotomy). The surgical specimen was obtained within 21 days of the first of the two examinations (CI, PET) in all patients. Mediastinoscopy (n=15) was performed in the majority of patients without extrathoracic metastases when "N2" or "N3" stage was suspected by CT or PET study. At thoracotomy (n=61), all accessible nodes were sampled and examined on frozen section. Only nodes that underwent biopsy or resection were considered for analysis. Distant metastases (n=59) were proven (biopsy or follow-up) in 39 patients. Biopsy (n=21) of suspected distant metastases was carried out whenever possible. For the other suspected metastases (n=38), imaging abnormalities were considered as positive for metastasis because clinical and radiological follow-up were strongly suggestive: symptomatic patient (bone pain, weight loss, anorexia, *etc.*) subsequent imaging progression; and abnormal biochemistry. In the absence of demonstrated metastasis, patients were evaluated regularly by imaging; absence of clinical disease 6 months after a negative imaging was accepted as evidence against metastasis.

Statistical analysis

Sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively) and accuracy of PET imaging were calculated by the classical method for the assessment of mediastinal involvement and distant metastases. For the evaluation of mediastinal involvement, results of surgery were classified as absence (N0) or presence (N1, N2, N3) of node involvement. For each parameter, the 95% confidence interval (95% CI) is given [15]. For the evaluation of distant metastases, results of biopsy and follow-up have been separated into two categories: absence (M0) or presence (M1) of one or more metastatic sites per patient.

Results

Clinical data

One hundred and nine patients (77 males and 32 females) with a mean age of 64 yrs (range 44–83 yrs) were studied. Fifty patients had squamous cell carcinoma, 46 had adenocarcinoma, eight had adenosquamous cell carcinoma and five had undifferentiated large cell carcinoma. The final staging of the disease was: stage I in 32 patients, stage II in eight patients, stage IIIA in 22 patients, stage IIIB in eight patients and stage IV in 39 patients. The mediastinum was evaluated surgically (mediastinoscopy alone n=5; mediastinoscopy and thoracotomy n=10; thoracotomy n=51) in 66 patients. Lymph nodes were involved in 34 of the 66 cases: N0: 32 cases; N1: 20 cases; N2: 10 cases; and N3: four cases. In four patients, the primary tumour invaded mediastinal structures and was classified as a T4 tumour. These four patients, who had no distant metastases, did not undergo surgical verification of mediastinal disease.

Imaging findings

Primary tumour. On the basis of a visual interpretation of PET imaging, all primary tumours showed an increase

in focal [18]FDG uptake which was intense in 101 cases and moderate in eight cases. The histopathological type of the tumour did not influence the intensity of [18]FDG uptake.

Lymph nodes involvement. Only 66 patients underwent an invasive exploration of the mediastinum and were included in statistical analysis. Results of preoperative staging by CT and PET were in agreement in 37 cases: this evaluation was correct in 34 cases (N0: 20 cases; N1: seven cases; N2: five cases; N3: two cases), over-estimated by the two techniques in two cases and under-staged in one case. Results of preoperative radiological (CT *versus* PET) staging disagreed in 29 of 66 cases. Among these 29 cases, PET correctly changed the N stage, as determined by CT, in 22 patients: it decreased the stage in 14 patients and increased it in eight patients. In the other seven conflicting cases, CT correctly changed the N stage as proposed by PET (table 1).

In mediastinal staging, PET-[18]FDG had a sensitivity of 89% (95% CI: 72–96%) and a specificity of 87% (95% CI: 71–97%). The correspondent PPV and NPV were 89% (95% CI: 72–96%) and 87% (95% CI: 71–96%), respectively. Therefore, the accuracy of [18]FDG-PET images for the detection of involved mediastinal lymph nodes was 88%. By comparison, the sensitivity of CT was 79%, the PPV was 75%, the specificity was 71% and the NPV was 76%. Therefore, the accuracy of CT in this analysis was 75%.

Distant metastases. In thirty nine patients, the presence of distant metastases (n=59) was confirmed by biopsy or follow-up information. They were located in nonregional lymph nodes (n=6), lung (n=10), bone (n=13), liver (n=18), adrenal gland (n=10), pleura (n=1) and soft tissue (n=1). All these metastases were detected within the PET axial field of view and showed [18]FDG uptake, which was intense in 51 cases and moderate in eight cases. In seven of these eight cases, the size of the metastasis was less than 2 cm. There were no false-negative distant PET findings. By contrast, 19 metastatic sites were not correctly identified by CI during the first examination: three lung lesions, three hepatic lesions, four ad-

renal lesions, one pleural lesion, five lymph nodes, two bone lesions and one soft tissue lesion.

As shown in table 2, there were five false-positive sites by PET imaging (in four patients) and 14 sites by CI (in eight patients). Concerning PET studies, two patients with moderate [18]FDG uptake in axillary lymph nodes presented nonspecific inflammation at biopsy. The third patient who already suffered from an osseous involvement, presented two false-positive PET abnormalities (one in the controlateral lung probably due to a pneumonia sequelae and one in the thyroid gland due to a benign multinodular goitre). The fourth patient showed a PET abnormality in the liver, but morphological imaging (CT and magnetic resonance imaging) was negative; a retrospective analysis of PET images showed that [18]FDG fixation was, in fact, localized in the area of the hepatic-splenic angle of the colon: repeat CT exploration 3 and 6 months later showed no hepatic involvement.

In the present series, adrenal gland metastasis was suspected either by CT or by PET in 15 patients. In 10 cases, metastasis was confirmed by biopsy (n=7) or follow-up information (n=3). All these adrenal metastases

Table 2. – Comparison of conventional imaging (CI) and positron emission tomography (PET) in the evaluation of distant metastases in 39 patients and 59 sites.

	CI			PET			Metastatic sites*
	FN	TP	FP	FN	TP	FP	n
Liver	3	15	3	0	18	1	18
Bone	2	11	4	0	13	0	13
Adrenal gland	4	6	5	0	10	0	10
Lung	3	7	2	0	10	1	10
Lymph node	5	1	0	0	6	2	6
Pleura	1	0	0	0	1	0	1
Soft tissue	1	0	0	0	1	0	1
Thyroid gland	0	0	0	0	0	1	0

FN: false-negative site; TP: true-positive site; FP: false-positive site. *: confirmation by biopsy or follow-up. Statistical analysis was carried out in accordance with the number of patients correctly classified (i.e. M0 or M1) by the imaging technique.

Table 1. – Comparative performance of computed tomography (CT) and positron emission tomography (PET) in mediastinal staging in conflicting cases (29/66 patients)

Cases n	CT scan	[18]FDG-PET	Histology
Correct changes by PET study			
3	N3	N0	N0
5	N1	N0	N0
4	N2	N1	N1
1	N3	N1	N1
1	N3	N2	N2
4	N0	N1	N1
2	N0	N2	N2
1	N1	N3	N3
1	N2	N3	N3
Correct changes by CT study			
3	N0	N1	N0
2	N1	N0	N1
1	N2	N1	N2
1	N2	N0	N2

[18]FDG: fluorine-18 deoxyglucose.

Table 3. – Correct changes in M stage by positron emission tomography (PET) study

	Patient No.	
Increase in stage	1	Lung lesion
	2	Lung and soft tissue lesions
	3	Lung and two hepatic lesions
	4	Bone lesion
	5	Hepatic lesion
	6	Adrenal lesion
	7	Adrenal lesion
Decrease in stage	8	Adrenal lesion
	9	Adrenal lesion
	10	Adrenal and lung lesions
	11	Hepatic lesion
	12	Adrenal lesion
	13	Hepatic lesion
	14	Adrenal lesion
	15	Hepatic and bone lesions

Increase in stage: absence of metastasis (M0) by conventional imaging (CI) corrected to presence of metastasis (M1) by positron emission tomography (PET); Decrease in stage: M1 corrected to M0 by PET.

showed an increase in ^{18}FDG uptake which was easily identifiable despite the lack of conventional anatomical landmarks. There was no false-positive ^{18}FDG uptake in adrenal glands. In our series, PET correctly changed the M stage, as determined by CI, in 15 patients (14%): it increased the stage in seven patients and decreased it in eight patients (table 3). The sensitivity of ^{18}FDG-PET images for the detection of distant metastasis was 100% (95% CI: 91–100%) with specificity of 94% (95% CI: 86–98%) and accuracy of 96% (95% CI: 90–98%) (table 4). The correspondent PPV and NPV were 90% (95% CI: 78–97%) and 100% (95% CI: 95–100%), respectively. Figure 1 shows whole-body PET images from a 58 yr old woman with adenocarcinoma stage IV and discordance between CT and PET findings on the M stage.

Changes in therapeutic strategy. Not all changes in N or M staging by PET imaging are associated with a change in the therapeutic management of the patient. In this series of patients, PET imaging has modified the therapeutic strategy in 27 patients. Indeed, 10 patients were able to undergo curative surgery. In eight patients, the absence of confirmation of regional or distant meta-

stases by PET modified the treatment by allowing us to adopt a more curative approach (radiotherapy plus chemotherapy). On the other hand, detection by PET of metastases located in contralateral mediastinal lymph nodes or in an extrathoracic site led us to alter our therapeutic approach (to chemotherapy or radiotherapy alone) in nine patients.

Discussion

^{18}FDG-PET is a noninvasive technique that appears to be very efficient for the diagnosis and staging of various types of cancer. The results of our study suggest that whole-body ^{18}FDG-PET with qualitative evaluation is applicable to the staging of lung cancer. In our study, it appears more accurate than conventional imaging in the study of the mediastinum and of distant metastases. ^{18}FDG-PET imaging correctly modified the stage (N and/or M) of the disease in 34% of patients (37 out of 109 patients) thus modifying the therapeutic strategy in more than 20% of patients. In particular, 10 patients were able to undergo surgery with curative intent. In the other patients, PET modified the therapeutic strategy by allowing us to adopt either a more curative approach or a more palliative approach than initially planned. Recent studies have shown that mediastinal ^{18}FDG uptake correlates well with the extent of mediastinal involvement in NSCLC [13, 16–21]. In particular, STEINERT *et al.* [21] showed that ^{18}FDG-PET is superior to CT for nodal staging of NSCLC and help in surgical planning by enabling correct differentiation of N0 or N1 disease from N2 or N3 disease. However, they noted that emission and transmission-corrected PET scans were needed for the exact localization of lymph node metastases according to the American Thoracic Society mapping system. Using uncorrected PET scans, the results of the

Table 4. – Accuracy of imaging studies in the determination of 'M' stage in 109 patients with non-small cell lung carcinomas (NSCLC)

	CI	^{18}FDG-PET
	n	n
True-positive	32	39
True-negative	62	66
False-positive	8	4
False-negative	7	0

CI: conventional imaging; ^{18}FDG-PET: fluorine-18 deoxyglucose-positron emission tomography.
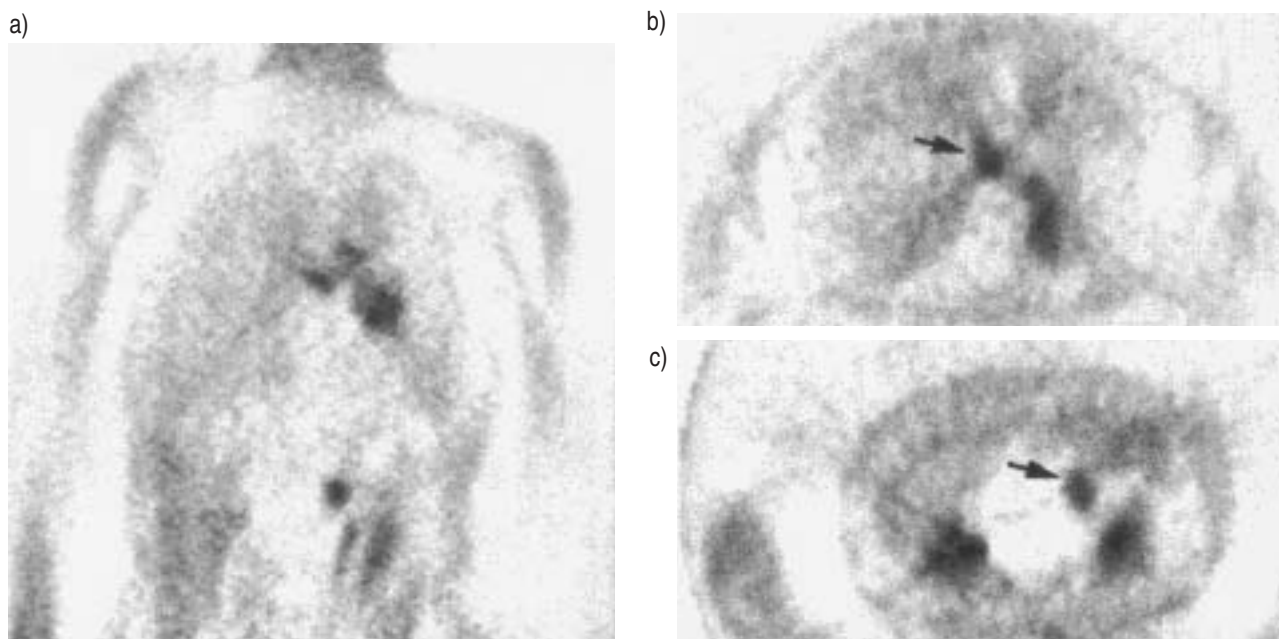
a)

b)

c)

Fig. 1. – Whole-body positron emission tomography (PET) of a 58 yr old woman with adenocarcinoma stage IV. a) Coronal image showing the fluorine-18 deoxyglucose (^{18}FDG) uptake in the primary tumour (left lower lobe), in regional lymph nodes and in a distant site. b) Transverse image in mediastinum showing a N3 disease (arrow). c) Transverse image showing a moderate FDG uptake in the area of the left adrenal gland (arrow). Note the tracer accumulation in the urinary tracts.

present study confirm the value of imaging with PET for diagnosis of mediastinal metastasis. With a visual analysis of PET images, PET correctly changed the N stage, as determined by CT, in 33% of the present patients.

Another objective of the present study was to judge the accuracy of PET scan in the evaluation of M stage. The qualitative evaluation of PET images shows a higher accuracy than CI in the detection of distant metastases. At present, the accuracy of PET in detecting distant metastases is 96%. In our group of patients, PET imaging correctly changed the M stage, as determined by CI, in 14% of patients. This study demonstrates that PET is particularly useful in the evaluation of an adrenal mass. In this situation, ^{18}FDG-PET can permit more precise assessment of an adrenal mass than morphological imaging. This may be helpful to physicians to decide about the necessity of histological exploration.

There were no false-negative distant (M stage) PET findings but five false-positive sites in our study. With more experience, two cases with moderate ^{18}FDG uptake in axillary lymph nodes would now be avoidable because they were situated at the same side as the FDG injection in an antecubital vein, and probably related to extravasation. In the three other false-positive cases proposed by PET, an invasive confirmatory procedure was not performed, but 6 months later the three patients had no clinical evidence of tumour. On the basis of these preliminary data, whole-body PET seems more specific than bone scan in identifying sites of skeletal metastases but a prospective comparative study needs to be carried out; precise localization of individual PET findings was however sometimes difficult because of the lack of anatomical markers. Moreover, the combination of anatomic (CI) and metabolic (PET) imaging data (image fusion) could increase the accuracy and acceptance of this method, facilitating the correct identification of the area of interest by a nonexpert. Our report is in concordance with two earlier studies which suggested that whole-body ^{18}FDG-PET imaging was more precise than CI in the staging of NSCLC [18, 22]. In a retrospective study, LEWIS et al. [22] in 1994 reported that PET scan identified unsuspected malignant lesions in 10 patients (29%) and could improve preoperative assessment of lung cancer patients. VALK et al. [18] concluded that detection of unsuspected metastatic disease by PET could reduce the number of thoracotomies performed for nonresectable disease in the management of NSCLC [18]. In their study, PET showed previously unsuspected distant metastasis in 11 patients (11%), with no false-positive results. Since approximately 33% of patients undergoing surgical resection thought to be curative will survive 5 yrs, it is important to spare patients who have distant metastasis at the time of initial diagnosis unnecessary surgery [23].

The presence of brain metastasis has not been routinely assessed in our study because it requires a dedicated brain acquisition and prolongs the procedure by 20–30 min [24]. New developments allowing considerable reduction of the transmission and emission scanning times have just been installed in our scanner and therefore, were not used in this study. Transmission scanning is now performed after the emission data collection using a single-photon emitter as transmission source (^{137}Cs). This tracer has higher energy photons (660 versus 511 keV) and can be separated from the emission data by spectrometry. Use of a source with greater activity (10 versus 0.5 mCi) will: 1) increase detection efficiency, as the nearby detectors are protected by shielding and, as true coincidence imaging is not performed, reduce scanning time by a factor of 10 (typically from 12 min·step^{-1} per step to 1–2 min·step^{-1}) and 2); allow routine whole-body transmission correction. Also, the use of an iterative reconstruction algorithm (ordered subsets expectation maximization (OSEM)) rather than filtered backprojection, allows the improvement of data quality while reducing scanning time. Reconstruction time is 20 s·slice^{-1} but will decrease to 5 s·slice^{-1} with the current state of the art processor (Ultra Sparc, SUN, California, USA). Also these progresses will make the routine use of quantification (using the standardized uptake value (SUV)) feasible in our institution.

Availability of ^{18}FDG-PET has, up to now, been limited for several reasons. Firstly, whole-body scanners have only lately been made available. Secondly, the availability of ^{18}FDG has been mainly restricted to cyclotron research centres. These have not distributed ^{18}FDG because of the lack of time and the many regulatory and administrative difficulties. Finally, researchers in these cyclotron research centres have, in general, given priority to the pursuit of basic physiopathological research (mainly of the brain and heart) rather than devoting "precious" camera time to clinical indications. This situation is rapidly changing given the spectacular results of ^{18}FDG-PET in clinical oncology, the development of low cost dedicated PET scanners, and the development of coincidence detection with standard dual head gamma cameras. Due to these developments, commercial distribution of ^{18}FDG by radiopharmaceutical companies is becoming a reality (in the USA, Germany and the Netherlands, soon to be followed by Belgium and other countries) and satellite PET imaging centres will develop rapidly. In a recent paper, GAMBHIR et al. [25] have demonstrated, through rigorous decision-tree analysis, the cost-effectiveness of using a PET-based strategy in the management of NSCLC. Their study showed that a CT and PET strategy was more economical and had a marginal increase in patient life expectancy as compared to a conventional strategy (CT alone) of staging patients.

Ideally, in the present study, histological confirmation of the scan abnormalities should have been available. However, we have not had the opportunity to obtain histological confirmation of all distant metastases because of practical considerations. We recognize the nonspecific nature of a positive scan and the need to identify the cause of the abnormality in many patients. When a biopsy was not possible, distant imaging abnormalities were validated on the basis of disease progression (symptomatic patients and imaging progression) or absence of progression. In some cases, the suspicion of a bone metastasis has been validated by the clinical presentation (bone pain) and by bone radiography which is not a sensitive method of detecting bone destruction but has the advantage that the appearances can be quite specific [26].

In conclusion, on the basis of our study, visual interpretation of whole-body fluorine-18 deoxyglucose-positron

emission tomography images may have a clinical significance in the staging of non-small cell lung cancer. Indeed, positron emission tomography imaging is more accurate than conventional imaging in detecting metastatic disease in mediastinal lymph nodes and in identifying the sites of distant metastases. More detailed experience however is needed to establish the reproducibility of our results and to judge if qualitative fluorine-18 deoxyglucose-positron emission tomography imaging would be a cost-effective tool in the future management of lung cancer.

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