



Original Article

Use of Positron Emission Tomography in Assessing Hidden Extrathoracic Metastasis in Non Small Cell Lung Cancer

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ABSTRACT

Introduction: Positron emission tomography combined with computed axial tomography (PET/CT) is used for staging non small cell lung cancer (NSCLC). This study aims to describe PET/CT findings of unsuspected extrathoracic metastasis when used in mediastinal evaluation of patients with apparently resectable NSCLC.

Patients and method: Prospective and concurrent study including all NSCLC patients between June 2004 and November 2006 who underwent PET/CT after considering them as candidates for surgery, with resectable disease after bronchoscopy, thorax and abdominal CT, brain CT and bone gammagraphy evaluation, if metastasis at these locations were suspected. Metastasis were confirmed histopathologically or assumed when they had a compatible evolution.

Results: A total of 91 patients with NSCLC underwent PET/CT. In 24 of them (26%) at least one suspicious extrathoracic uptake was seen. In 7 patients (7.7%) those uptakes were NSCLC extrathoracic metastasis hidden from conventional staging. In 3 of these cases (13.1%) extrathoracic uptakes corresponded to metachronous tumours or pre-malignant conditions. Benign lesions were found in 12 patients (13.1%), and in 2 cases (2.2%) the uptake origins were undetermined.

Conclusions: PET/CT is a complementary diagnosis method for assessing hidden metastases which could modify the therapeutical approach in patients otherwise suitable for surgery.

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Utilidad de la tomografía por emisión de positrones en la detección de metástasis ocultas extratorácicas en el carcinoma broncogénico no células pequeñas

RESUMEN

Palabras clave:

Carcinoma broncogénico
Tomografía de emisión de positrones
Estadificación clínica
Metástasis ocultas

Introducción: La tomografía de emisión de positrones asociada a la tomografía axial computerizada (PET/TC) se utiliza en la estadificación del carcinoma broncogénico no microcítico (CBNM). El objetivo de este trabajo es describir la utilidad de la PET/TC en la estadificación clínica del CBNM para la detección de metástasis extratorácicas insospechadas en una población operable con un tumor aparentemente resecable antes de la evaluación ganglionar mediastínica pretoracotomía.

Pacientes y método: Estudio prospectivo y concurrente de todos los casos de CBNM recogidos entre junio 2004 y noviembre 2006, a los que se realizó una PET/TC tras considerar al paciente operable y al tumor resecable tras realizar broncoscopia, TC toracoabdominal, y TC cerebral o gammagrafía ósea si hubiesen datos clínicos sugerentes de metástasis a esos niveles. La metástasis fueron confirmadas por evidencia citohistológica o por la evolución.

Resultados: Se realizó una PET/TC a 91 pacientes con CBNM. En 24 pacientes (26%) se objetivó la existencia de, al menos, una captación extratorácica. En 7 pacientes (7,7%) la captación correspondió a una metástasis extratorácica del CBNM, oculta a la estadificación convencional. En 3 casos (3,2%) la captación extratorácica correspondió a lesiones premalignas o a un segundo tumor primario. En 12 pacientes (13,1%) el hallazgo correspondía a lesiones benignas, y finalmente en 2 casos (2,2%) no se pudo determinar el origen de la captación.

Conclusiones: La PET/TC indicada en pacientes operables con CBNM potencialmente resecables supone un elemento diagnóstico de utilidad en la detección de metástasis ocultas que afecta a la toma de decisiones terapéuticas.

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Introduction

Lung cancer (LC) is one of the main causes of mortality in the general population of Spain with an incidence of 86.7/100,000 in men and 7.7/100,000 in women, in the year 2000.¹ The non-small cell lung cancer (NSCLC) has, in our environment, a global survival rate of 13% and of 40% at 5 years in those cases that undergo surgical resection.²

Surgical treatment is the best therapeutic option in stages i-ii, and some selected iiiA cases³ without extrapulmonary extension. Unfortunately, at the time of diagnosis NSCLC has a high rate of metastasis, therefore a correct clinical staging is indispensable to determine patient treatment. In a recent series of LC at our centre (2000-2001), 41.3% of the patients had distant metastasis at diagnosis,² at a time when positron emission tomography (PET) was not available for clinical staging.

PET used separately or combined with computed tomography (PET/CT), has been incorporated during recent years to study LC, either to characterise solitary lung nodules,⁴ for mediastinal and extrathoracic NSCLC staging, to assess the response to chemotherapy and radiotherapy used for NSCLC,⁵ and for LC clinical staging. It is superior to other imaging methods such as CT or bone scintigraphy for detecting metastatic disease and is of great usefulness in the staging of mediastinal lymph nodes, due to its high negative predictive value.⁶⁻⁸ It has been reported that PET detects between 10-21% of extrathoracic uptake in patients with NSCLC.^{7,9,10} Extrathoracic uptake with PET can be due to physiological uptake, benign lesions, premalignant lesions, second primary tumours or true metastasis of the original tumour.

The aim of this study is to analyse the frequency and aetiology of PET extrathoracic uptake in a consecutive series of operable patients

with resectable NSCLC, and to assess the influence of this uptake on the final staging and definitive treatment plan for these patients.

Patients and Methods

Study Population

A prospective and concurrent study of all the cases of NSCLC collected between June 2004 and November 2006 that underwent PET/CT for lymph node assessment following our centre's diagnostic-therapeutic protocol for this disease.¹¹

In this 2004 protocol, PET/CT is used before thoracotomy is performed for mediastinal lymph node staging in NSCLC patients who comply with all the surgery criteria and tumour resection.

According to this protocol, only 20% of diagnosed cases reach this phase of the study, since patients with SCLC and NSCLC that have evidence of tumour invasion or extensive regional or distant adenopathy with criteria that do not permit surgery, are patients who have already had other treatments. Surgery is therefore not considered as the best therapy with the intent to cure, whether alone or combined with other treatments.

Finally, in these selected NSCLC cases, that comply with criteria for undergoing surgery and resection, PET/CT was indicated when upper mediastinal adenopathies were detected at 1 cm from the short axis in a spiral CT with intravenous contrast, according to previously published criteria,⁶ since in these patients, systematically, a surgical exploration of the mediastinum was indicated.

Definitions

Extrathoracic uptake is the accumulation of 2-[F-18]-2-deoxy-2-fluoro-D-glucose (FDG) with an intensity greater than is physiological

in each organ studied. FDG uptake in the central nervous system, the renal pelvis, urinary system and myocardium are considered physiological.

The accumulation of 18-FDG in an extrapulmonary location was considered an NSCLC occult metastasis when the patient did not present organ specific symptoms or radiological alterations (on simple X-rays or contrast spiral CT) compatible with distant metastasis prior to the PET/CT and in which we confirmed the NSCLC metastasis using other criteria or procedures.

Those cases that had multiple locations of extrathoracic uptake on PET/CT that suggested metastatic dissemination were interpreted as metastatic. In those patients with a single focal extrapulmonary uptake on PET/CT, we performed cyto-histological studies and when this was not possible we carried out clinical, radiological and analytical follow-up for one year.

Bone uptake was presumed to be metastasis when bone pain was subsequently developed in the uptake area or when a radiological pattern of osteolysis was seen at that location. In cases of nodular uptake in the adrenal gland we carried out cyto-histological studies by fine needle puncture aspiration guided by CT, when these cases were of single uptake and/or nodes >2cm. If no definitive cyto-histological diagnosis was possible, the criterion of malignity was growth seen on images in subsequent studies.

Cases of uptake in atypical zones for LC metastasis were considered as premalignant or second primary tumours, especially in the gastrointestinal tract, and were always confirmed endoscopically. We diagnosed primary digestive involvement when the histological findings confirmed this.

We considered that there was benign uptake when benign lesions were found on cyto-histological study or when there was clinical and radiological stability in the follow-up after one year. Finally, we considered that there was indeterminate uptake in those cases where it was not possible to obtain a representative sample despite a cyto-histological-focused study, or in those cases where death occurred prior to definitive staging or those where subsequent follow-up was not possible.

Table 1
Definitive diagnosis of extrathoracic uptake with PET/CT in our series (n=19)

Etiology	Number of cases (%)
Occult metastasis	7 (7.7%)
Pre-malignant lesions or second primary tumour	3 (3.3%)
Benign lesions	12 (13%)
Indeterminate uptake	2 (2%)
Total	24 (26%)

Table 2
Patients with occult metastasis seen with PET/CT in our series (n=7)

Histology	Tc*	Nc**	PET uptake	Occult metastasis
Epidermoid	T1	N0	Uptake vertebra L-3	Bone metastasis
Large cells	T1	N0	Uptake in nodes in left and right upper lobes and right lower lobe, vertebrae L-3 and D-4, left suprarenal, costal arches	Bone and adrenal metastasis
Large cells	T3	N0	Uptake in both adrenals and right parietal mass	Bone and adrenal metastasis
Adenocarcinoma	T2	N0	Left axillary adenopathy, right adrenal, iliac bone, vertebrae 4-D and 3-L	Adrenal, bone and lymphatic metastasis
Epidermoid	T2	N1	Left adrenal uptake	Adrenal metastasis
Carcinoma	T1	N0	Left adrenal (adenoma), left scapula	Bone metastasis
Large cells	T3	N0	Liver uptake, sacrum	Liver and bone metastasis

*Tc: Tumour (T) clinical classification based on findings after PET/CT.

**Nc: Node (N) clinical classification based on findings after PET/CT.

PET/CT Technical Characteristics

All PET/CT examinations were carried out in the Nuclear Medicine Department of the Hospital Universitario de la Paz, and were reviewed by one single observer. Studies were conducted using combined PET/CT equipment (Discovery LS, General Electric Medical Systems), which has a PET tomograph with 18 detector rings of bismuth germinate crystals (BGO), and a multislice spiral CT with 4 detectors (LightSpeed Plus TC). Both systems are aligned, making it possible to perform sequential PET and CT scans in the same position in a single session. Patients had to be in fasting condition and be well hydrated beforehand. It was confirmed that glycaemia was below 180 mg/dl before the FDG injection. All patients received oral contrast to make it easier to study abdominal structures and subsequently a standard dose of FDG of 370 MBq was given intravenously. The patients had to rest 45-60 min after the radiotracer injection. Urine voiding was necessary before beginning image acquisition. The patients were told they must maintain a gentle breathing pattern throughout the study to prevent respiratory artefacts.

After the topogram was acquired, a low-dose whole-body CT was performed (140 kV; 80 mA) without intravenous contrast. PET study was acquired in 2D mode, with an approximate time of 4 min for each table position (normally 6-7 table positions are required).

The reconstructed images were sent to an Xeleris work station (GE Medical System), where the PET and CT images could be seen as well as simultaneous fusion of coronal, sagittal and transaxial slices. In addition, 3D reconstruction in movement and calculation of measurements and quantifications could be observed.

Results

In this prospective study we included 91 patients with consecutively and sequentially staged NSCLC according to the NSCLC guidelines of our hospital described previously, and in whom a PET/CT was performed. Patient mean age was 66 years (9.65) with 88% males and 12% females.

Of these, 24 patients (26%) had at least one extrathoracic uptake. In Table 1 it is possible to see the final diagnoses, according to previously established definitions, of all the patients with extrathoracic uptake of PET/CT.

The characteristics of the 7 cases finally considered as occult metastasis can be seen in Table 2. Metastasis distribution in these cases was the following: Bone metastasis 5.5% (5 out of 91 patients), adrenal 4.5% (4 out of 91 patients) and central nervous system 1% (1 out of 91 patients). Three cases (3.3%) were detected with premalignant lesions or second primary tumours, all with asymptomatic gastrointestinal uptake. All patients underwent endoscopic examination by means of a colonoscopy. For two of the

Table 3
Relation of all extrathoracic uptakes seen in our study

Patient number	Histology	Tc*	Nc**	Location of extrathoracic uptake	Definitive diagnosis
1	Epidermoid	T1	N0	Uptake 9th left costal arch	Benign uptake
2	Epidermoid	T2	N0	Doubtful rectal uptake	Indeterminate uptake
3	Epidermoid	T1	N0	Uptake vertebra L-3	Metastasis
4	Adenocarcinoma	T2	N0	Submandibular and jugulodigastric uptake	Benign uptake
5	Adenocarcinoma	T2	N2	Submandibular and parotid uptake	Benign uptake
6	Adenocarcinoma	T2	N0	Doubtful left adrenal uptake	Benign uptake
7	Adenocarcinoma	T2	N3	Jugulodigastric and node uptake in the left lower lobe	Benign uptake
8	Large cells	T2	N2	Left submandibular uptake	Benign uptake
9	Adenocarcinoma	T2	N0	Rectosigmoid uptake	Second primary
10	Adenocarcinoma	T1	N0	Sigmoid uptake	Second primary
11	Carcinoma	T2	N2	Right submandibular uptake	Benign uptake
12	Adenocarcinoma	T2	N2	Jugulodigastric and submandibular uptake	Benign uptake
13	Carcinoma	T2	N2	Transverse colon uptake	Indeterminate uptake
14	Adenocarcinoma	T2	N2	Left and right upper lobe node and laterocervical adenopathy uptake	Benign uptake
15	Large cells	T1	N0	Uptake in nodes in left and right upper lobes and right lower lobe, vertebrae D-5 and D-6, left adrenal, costal arches	Metastasis
16	Adenocarcinoma	T2	N0	Left lower lobe node (not assessable) and left adrenal (doubtful)	Benign uptake
17	Large cells	T3	N0	Uptake in both adrenals and right parietal mass	Metastasis
18	Epidermoid	T2	N2	Gastric wall mucosa	Benign uptake
19	Adenocarcinoma	T2	N0	Left axillary adenopathy, right adrenal, iliac bone, vertebrae 4-D and 3-L	Metastasis
20	Epidermoid	T3	N0	Sigmoid uptake	Second primary
21	Epidermoid	T2	N1	Left adrenal uptake	Metastasis
22	Carcinoma	T2	N0	Right parotid uptake	Benign uptake
23	Carcinoma	T1	N0	Left adrenal (adenoma), left scapula	Metastasis
24	Large cells	T3	N0	Liver uptake, sacrum	Metastasis

*Tc: Tumour (T) clinical classification based on findings after PET/CT.

**Nc: Node (N) clinical classification based on findings after PET/CT.

patients the definitive histology was a tubulovillous adenoma with moderate-severe dysplasia and the third patient's final diagnosis was colon adenocarcinoma.

Benign uptake was seen in 12 (13.1%) patients that were interpreted as inflammatory, or because this was seen on the cyto-histological study or because clinical-radiological follow-up was compatible with this condition. Benign uptake in our series was seen in the following cases: 8 cervical (without relapse or growth in more than 12 months' evolution), 2 adrenal (without changes in size seen in 12 months of follow-up), 1 gastric (with a biopsy compatible with antral gastritis) and 1 costal (in a patient with a history of trauma and resolution with fracture callus).

Finally there were 2 uptakes that were considered indeterminate: 1 in the transverse colon, (the study could not be completed because the colonoscopy was incomplete and the patient subsequently died); and 1 rectal (considered inflammatory according to the nuclear medicine report and therefore not subsequently explored).

The summary of all the cases of extrathoracic uptake detected in our series can be seen in Table 3. Among the patients with extrathoracic uptake it is also possible to see that mediastinal lymph node uptakes is not suspected in the TC of 8 patients. In 6 cases mediastinal lymph node involvement was confirmed in the invasive staging of the mediastinum.

Discussion

Once the diagnosis of NSCLC was established, it was possible, according to the clinical status of the tumour and the patient's surgical criteria, to consider different treatments (surgery, radiotherapy, chemotherapy, combinations of treatment, or palliative treatment). In our study, we assessed the probability of detecting occult metastasis using PET/CT in a very select theoretically operable and resectable population after conventional tumour staging studies. Extrathoracic uptake was found in 26% of the patients. Of these, 10 patients (11%) had uptake related to malignant causes, either occult metastasis (7.7%) not detected previously or premalignant lesions, or

second tumours (3.3%). In 12 (13.1%) patient uptake was finally considered secondary to a benign condition.

According to some studies, using PET/CT to stage NSCLC would reduce the number of exploratory mediastinoscopies and thoracotomies by up to 20%,¹² either by detecting occult metastasis or by observing unsuspected lymph node 2-3 involvement from the results of other imaging studies.

In different publications PET/CT is used to study NSCLC and enables occult metastasis to be detected, in 10-20% of patients studied.^{9,12,13} In our study, the percentage of metastasis detected (7.7%) is in the lower range of values published, probably because we used a very select population, with potentially resectable NSCLC, and in an advanced study phase (with previous histological diagnosis, fibrobronchoscopy and thoracoabdominal CT). It is striking that 50% of the patients with occult metastasis present large cell histology, in other series,⁹ the predominant cell type was adenocarcinoma, although in these studies the percentage of women (30%) was considerably higher than in our population (12%).

PET/CT is an imaging technique with great sensitivity for the detection of adrenal metastasis, especially if standardised uptake values with cut-off points above 3.1 are used, with a specificity of 98%, a sensitivity of 92%,^{14,15} and a false negative rate of about 3.8%,¹⁶ especially in adrenal masses with large necrotic lesions. The reported detection of metastatic adrenal nodules using PET/CT is 10.6%¹⁵ in a population with different stages of LC. This represents a higher rate than in our study, which was 4.5%. This difference could be due to the fact that our series included patients with potentially resectable tumours in an immediate presurgical phase and that not all were cases of LC:

PET/CT is also a very useful diagnostic method for the detection of bone metastasis, with greater efficacy than conventional CT in the detection of sternal and vertebral metastasis,¹⁷ and greater sensitivity, specificity, positive and negative predictive value than bone scintigraphy.¹⁸⁻²⁰ In our series bone metastasis was detected in 5.5% of the patients, a lower percentage than in other studies that reported

values of around 10.5%,¹⁹ this can also be explained by the fact that our population was a selected one.

PET/CT has shown greater efficacy in the detection of occult metastasis in LC than other conventional imaging techniques²¹ and it allows clinical staging in 25–40% of patients,²² higher values than those described for other imaging techniques.

The existence of extrathoracic uptake in PET/CT is not specific for tumour extension, since a high percentage of extrathoracic uptake cases were finally found to be benign. As a result, in all cases of extrathoracic uptake it is necessary to confirm malignancy by means of cyto-histological studies whenever possible, by assessing additional X-ray images or by clinical-radiological follow-up compatible in all cases. In our series the percentage of cases with extrathoracic uptake which were finally considered benign (13%) was similar to the number finally considered malignant (11%).

In the 7 cases in which extrathoracic uptake of PET/CT finally corresponded to NSCLC occult metastasis, these were not suspected either clinically or by means of other imaging techniques, and therefore the PET/CT findings meant that patients' clinical staging changed to more advanced stages of the disease, avoiding the performance of thoracotomies that would have finally been superfluous.

On the other hand, 6 patients had gastrointestinal uptake, two uptake cases finally corresponding to premalignant lesions (tubulovillous adenoma) and 1 a primary colon adenocarcinoma. The other 3 gastrointestinal uptake cases were considered benign (antral chronic gastritis in 1 case, and indeterminate colon uptake in 2 cases). These figures are somewhat higher than those described in other PET/CT studies in a series of solitary lung nodules, in which the percentage of unsuspected gastrointestinal uptake was 1.3–3%.^{23–25} PTC/CT in cases of colorectal carcinoma has a high sensitivity (97%) and specificity (76%) both in diagnosis and in follow-up of possible recurrences of this condition.²⁶ These PET/CT findings are of special importance since there are lesions which cannot be seen with an abdominal CT because they are so small, and are not found due to the absence of associated gastrointestinal symptoms.

The existence of second primary tumours in cancer patients that have undergone PET/CT is of about 1–2%,²⁷ this being the most frequent second primary tumour seen with LC. In this sense it is reasonable to investigate single uptake in areas where LC metastasis are not common because they may be a second primary or a false positive tumour.

Using PET/CT to detect metastasis in the central nervous system is not as useful as other imaging techniques, since lesions are hidden by the intense physiological uptake of 18-F-FDG by the brain cortex. Different series describe the low percentage of unsuspected metastasis in the brain (0.4–1.5% of patients)^{28,29} and the high percentage of false negatives. If dissemination to the CNS is suspected, CT with contrast must be performed, or even better, a magnetic resonance image. In our series we located a unsuspected intracranial metastasis (1%), a percentage in agreement with the figures in the literature reviewed.

In conclusion, the results of our study suggest that, PET/CT is a very useful diagnostic element for detecting occult metastasis and can affect decisions with regards treatment in patients with NSCLC who after the diagnostic and staging protocol comply with surgical resection criteria. On the other hand, a high percentage of uptake that can finally be considered benign means that all single uptakes of PET/CT must be examined by means of cyto-histological studies where possible, more specific imaging studies or for those cases in which these are impossible, patient follow-up should include clinical-

radiological study. In our opinion, PET/CT must be performed in all patients with NSCLC who are going to be offered surgery with intent to cure, as long as there is adequate access to this test that it does not involve unacceptable waiting-time.

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