Original article

Is a selective brain $^{18}$F-FDG PET/CT study profitable in patients with small cell lung cancer?


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**A R T I C L E I N F O**

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**A B S T R A C T**

**Aim:** To evaluate the diagnostic yield of a selective brain $^{18}$F-FDG PET/CT in neurologically asymptomatic patients with small cell lung cancer.

**Material and methods:** Twenty-one neurologically asymptomatic patients referred to our service between July 2008 and December 2009 for staging of small cell lung cancer were included in the study. All underwent a standard $^{18}$F-FDG PET/CT study followed by a selective brain PET/CT. The neurological findings were confirmed by CT scan with intravenous contrast, MRI or minimum clinical follow-up of 6 months. The brain PET/CT was considered positive if any alteration was observed in the FDG distribution that was not related with previously known benign lesion in the CT image.

**Results:** Brain metastases were detected in 5 of the 21 patients (23.8%), these being correctly classified in 3 of them by the selective brain PET/CT. The stage was upgraded in one of them with the selective brain study. Only one patient showed a hypermetabolic lesion in the PET images in relationship to the lesions observed in the CT images. Sensitivity, specificity, positive predictive value and negative predictive value were 60, 100, 100 and 88.89%, respectively.

**Conclusion:** Hypometabolic areas in the cerebral parenchyma are frequently associated to metastatic lesions in patients with small cell lung cancer. The selective brain PET/CT in these patients allows correct staging and early treatment of unsuspected metastasis.

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**¿Resulta rentable un estudio selectivo cerebral con $^{18}$F-FDG-PET/TAC en los pacientes con cáncer microcítico de pulmón?**

**R E S U M E N**

**Objetivo:** Evaluar la rentabilidad diagnóstica del estudio selectivo cerebral con $^{18}$F-FDG-PET/TAC en pacientes con cáncer microcítico de pulmón asintomáticos neurológicamente.

**Material y métodos:** Se incluyeron en el estudio 21 pacientes derivados a nuestro servicio entre julio de 2008 y diciembre de 2009, para estadificación, con histología de carcinoma microcítico de pulmón y asintomáticos neurológicamente. A todos ellos se les realizó un estudio $^{18}$F-FDG-PET/TAC estándar y a continuación un estudio selectivo cerebral, y se confirmaron los hallazgos neurológicos mediante TAC con contraste intravenoso, RM o seguimiento clínico mínimo de 6 meses. Un estudio cerebral PET fue considerado positivo si mostraba cualquier alteración en la distribución de la FDG no relacionada con lesiones benignas previas en la TAC cerebral.

**Resultados:** En 5 de los 21 pacientes (23.8%) se detectaron metástasis cerebrales, siendo correctamente diagnosticadas mediante $^{18}$F-FDG-PET/TAC 3 de ellos. En uno de ellos la realización del estudio cerebral incrementó el estadio. Sólo uno de los pacientes mostró hipermetabolismo en la imagen PET en relación con las lesiones cerebrales evidenciadas en la imagen TAC. Se obtuvieron valores de sensibilidad, especificidad, valores predictivos positivo y negativo del 60, 100, 100 y 88,89%, respectivamente.

**Conclusión:** Las áreas hipometabólicas en el parénquima cerebral con frecuencia se asocian a lesiones metastásicas en pacientes con cáncer microcítico de pulmón. La realización de un estudio selectivo cerebral PET/TAC en estos pacientes permite una correcta estadificación y el tratamiento precoz de las metástasis no sospechadas.

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**Introduction**

In the last decades, lung cancer has become one of the neoplastic diseases with the highest incidence in our country (a little more than 23,000 new cases per year), only behind colorectal tumors in a general sense and prostate and breast cancer related to specific pathologies for males and females, respectively. In addition, lung
cancer presents a high mortality (approximately 20,000 individuals per year) with an ascending trend.  

The frequency of metastasis in lung cancer is high, with the localization most often observed being the central nervous system. The probability of the appearance of metastasis varies based on the stage of the disease at diagnosis, being 7.5% for patients in stage I, 18% in stage II and 24% for those in stage III. The histological type is the second most important factor in the development of metastasis, with cerebral metastasis at diagnosis in 15% of the patients with small cell lung carcinoma, rising up to 20% due to the introduction of magnetic resonance imaging (MRI). In the case of non small cell tumors the incidence of the appearance of metastasis is of approximately 40%. With adenocarcinomas presenting a higher percentage of cerebral metastasis than the remaining histologies.  

According to EUROCare-4 the one-year survival of patients with lung cancer is only 36.9%, decreasing to 12% at 5 years and further diminishing to 3–6 months after diagnosis in cases presenting cerebral metastasis.  

With respect to the staging of these patients the usefulness of positron emission tomography with 18F-FDG associated with computerized tomography (18F-FDG PET/CT) is well known and is indicated in the staging and detection of metastasis, the diagnosis of recurrence and monitoring of response to treatment.  

In the specific case of the detection of cerebral lesions, MRI shows the greatest profitability due to the lower sensitivity of 18F-FDG. Nonetheless, the protocol to follow in the detection of cerebral metastasis remains to be established since it varies according to the different groups. Some authors recommend cerebral MRI in patients who are candidates for curative treatment and not in an early stage, while others suggest both cerebral MRI and CT with contrast in patients with advanced stages despite being asymptomatic or that they should be performed only in symptomatic cases or in those receiving chemoradiotherapy.  

In view of the absence of consensus and the important clinical and prognostic implications involved in the detection of cerebral metastatic disease we decided to undertake a selective cerebral study with 18F-FDG-PET/CT in all the patients diagnosed with lung cancer. Due to the greater metastatic aggressiveness and worse prognosis of the patients with small cell cancer we evaluated the diagnostic performance achieved with selective cerebral PET/CT in neurologically asymptomatic patients. Likewise, we attempted to define the presence of any factor to predict the greater probability of cerebral disease with the aim of determining the group at risk to justify more exhaustive cerebral studies.

Material and methods

Patients

We retrospectively analyzed 300 patients referred to our department for suspicion of lung cancer from July 2008 to December 2009, excluding those with absence of histological confirmation or with a follow-up of less than 6 months. Of these 300 patients we only selected those histologically presenting small cell lung carcinoma in whom PET/CT was requested for staging prior to treatment and thus, the final sample included 21 patients (18 males and 3 females) with a mean age of 66.57 years (range: 45–83). All were asymptomatic from a neurological point of view. The mean follow-up was of 10.4 months (range: 3–19). Table 1 shows the clinical characteristics of the patients.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Epidemiologic and clinico-pathologic characteristics of the patients: age range (years).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range (years)</td>
<td>45–83</td>
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<tr>
<td>Mean age (years)</td>
<td>66.57</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>18</td>
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<tr>
<td>Females</td>
<td>3</td>
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<tr>
<td>Staging by CT</td>
<td></td>
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<tr>
<td>Stage I</td>
<td>2</td>
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<tr>
<td>Stage II</td>
<td>13</td>
</tr>
<tr>
<td>Stage III</td>
<td>6</td>
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<tr>
<td>Staging by PET/CT</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>1</td>
</tr>
<tr>
<td>Stage II</td>
<td>7</td>
</tr>
<tr>
<td>Stage III</td>
<td>13</td>
</tr>
<tr>
<td>Cerebral studies</td>
<td></td>
</tr>
<tr>
<td>Normal PET</td>
<td>18</td>
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<tr>
<td>Pathological PET</td>
<td>3</td>
</tr>
<tr>
<td>Patients with cerebral metastasis</td>
<td>5</td>
</tr>
</tbody>
</table>

PET/CT methodology and image evaluation

All the patients underwent 18F-FDG PET/CT study following the standard procedure using hybrid equipment (Discovery DSTE 16, GE Healthcare). Initially a whole-body scan was performed (from the base of the cranium to the upper third of the lower extremities) with acquisition beginning with the transmission study with CT at low doses (120 keV, 80 mA) without intravenous contrast, followed by a three-dimensional (3D) emission scan at 3 min/bed. Posteriorly the patients were submitted to a selective cerebral 3D study with an acquisition time of 10 min/bed, also without intravenous contrast. The PET images were reconstructed using the CT images for enhancement correction and after the use of the iterative reconstruction algorithm. The images of the PET and CT studies and the fusion images of both techniques in axial, coronal and sagittal projection were independently evaluated by at least two experts in nuclear medicine.

The whole-body scans were classified based on the TNM classification determining the change in stage induced by PET/CT in each case.

The selective cerebral studies were evaluated visually, confirming the metabolic alterations by measurement of the Standard Uptake Value of the area of the lesion and the contralateral side and correlating these with the morphologic image obtained. A positive cerebral study was considered with the presence of alterations (hypermetabolism or areas of reduction in metabolism) in the distribution of the radiotracer in the absence of known benign lesions (meningioma, arteriovenous malformation or previous infarction) in the CT. Negative cerebral studies were those with no alterations in the distribution of FDG in the cerebral parenchyma.

Final diagnosis

The final diagnosis was achieved by cerebral MRI with or without intravenous contrast, CT with intravenous contrast or by clinical follow-up of at least 6 months. Patients with negative imaging studies or who were neurologically asymptomatic during the follow-up were classified as free of cerebral disease.

Statistical analysis

Descriptive analysis of the patient data was performed using the Med Calc 11.3.1.0 program. The analyses of sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV)
and statistical precision in the diagnosis of cerebral metastasis were carried out with Epidat 3.1.

Results

Only five patients presented cerebral metastasis during follow-up. Of these three were correctly diagnosed with 18F-FDG-PET/CT. Two were classified as stage IV after the whole-body scan on the detection of metastasis in other localization and one of these went from stage III to stage IV after the cerebral study showed only metastatic disease at a cerebral level.

Two false negatives were observed; in both cases the cerebral metastases were diagnosed 5 months after the staging PET/CT study. One of the patients had been classified as stage III at the time of the PET/CT. In the other patient, who remained neurologically asymptomatic, cerebral metastases were diagnosed (Fig. 1) 5 months after the staging PET/CT study (stage IV for metastasis in the adrenal glands). After the reevaluation PET/CT study for assessment of response to treatment an area of hypometabolism was observed, with posterior confirmation of the lesion by MRI. Due to the absence of neurological manifestations in this case, no other diagnostic tests (cerebral CT with contrast or MRI) have been performed.

Of the three patients correctly classified after the selective cerebral PET/CT study only one showed a hypermetabolic lesion while the second presented two hypometabolic lesions and the third patient showed three hypometabolic lesions and one mixed lesion with areas of hypermetabolism and hypometabolism (Fig. 2). The characteristics of the cerebral lesions of each patient are shown in Table 2. The values of sensitivity, specificity, PPV, NPV and statistical precision with confidence intervals of 95% were 60% (14.6–94.73%), 100% (74.91–100%), 100% (29.24–100%) and 88.89% (65.29–98.62%), respectively. The statistical precision was 7%.

The 18F-DG-PET/CT induced a change in staging with the detection of disseminated disease (stage IV) in 7 patients (33%). In one of these patients lesions were observed in the contralateral lung, four cases showed bone involvement, one presented involvement of the suprarenal glands and the last patient had the previously described cerebral involvement. Cerebral metastasis was found at the time of diagnosis in stage IV in 60% of the patients.

Discussion

The role of 18F-FDG-PET/CT in the staging of lung cancer is well established since, according to the different series, 30% of the cases show metastatic lesions not suspected by other imaging techniques similar to what occurred in 33% of our patients in whom the stage was modified. On the other hand, to evaluate cerebral lesions in these patients, the last guidelines of the National Comprehensive Cancer Network do not recommend the use of 18F-FDG-PET since this radiotracer does not provide high diagnostic performance. Nonetheless, CT and MRI studies are recommended for early diagnosis since 30% of the patients with cerebral metastasis remain asymptomatic in the early stages. This allows the implementation of earlier treatment which carries a reduction in complications and morbidity, with prophylactic cranial radiation being recommended in some cases. Some groups perform cerebral PET studies to confirm single cerebral lesions, considering that patients in stages IIIb or IV with a single metastasis may be candidates for curative rather than palliative treatment. On the other hand, other groups complement the standard 18F-FDG-PET study with extension of a field in which the cerebral parenchyma is acquired since this does not produce significant radiologic overexposure or they perform late cerebral PET images to confirm the presence of cerebral lesions.

The detection of metastatic cerebral disease not suspected by PET/CT has a fundamental connotation in that it allows the implementation of early treatment. This practice may increase both the survival and the quality of life since patients with untreated cerebral metastasis have a very reduced survival (approximately one month after diagnosis).
Table 2
Characteristics and number of cerebral lesions in each of the patients in the selective cerebral PET/CT study and in the conventional imaging techniques performed posteriorly.

CT with intravenous contrast and MRI in the case of patient number 5.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Lesions according to PET/CT</th>
<th>Lesions according to conventional imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Two hypometabolic lesions in the cerebellous region and right temporal region.</td>
<td>Three lesions with perilesional edema, two of which were of approximately 17 mm in the cerebellous region and the right temporal region and one was of 7 mm in the right caudate nucleus.</td>
</tr>
<tr>
<td>2</td>
<td>Four lesions, three of which were hypometabolic in the right cerebellum and the ipsilateral temporal region and one mixed lesion in the left temporal region.</td>
<td>Multiple lesions with edema of different sizes (from 1 to 2 cm) and localizations.</td>
</tr>
<tr>
<td>3</td>
<td>One hypermetabolic lesion in right temporal region.</td>
<td>Right temporal lesion with ring uptake after intravenous contrast of 30 mm.</td>
</tr>
<tr>
<td>4</td>
<td>Normal PET/CT cerebral staging</td>
<td>Right subcentimetric frontoparietal lesion</td>
</tr>
<tr>
<td>5</td>
<td>Normal PET/CT cerebral staging. In the PET/CT of response to treatment we observed a hypometabolic lesion in the right parietal region.</td>
<td>Right parietal lesion of around 20 mm confirmed by MRI.</td>
</tr>
</tbody>
</table>

It is important to note that the greatest incidence of cerebral lesions was found in patients with stage IV (60%) and thus, we suggest that cerebral studies should be performed in all patients presenting this stage.

MRI is the technique with the greatest diagnostic performance in the detection of lesions of the central nervous system. Nonetheless, the different types of imaging may provide valuable information for the diagnosis of cerebral lesions. Therefore, despite the limitation of $^{18}$F-FDG-PET due to the high metabolism at the cortical level, the PET and CT image corregister aids in the interpretation of the PET findings. This corregistered image is particularly useful in hypometabolic lesions, providing a simple definition of its correspondence with areas of perilesional edema such as in the case of cerebral metastasis. Thus, in relation to the metabolic nature of the cerebral metastases, it is important to note that in our series we observed hypometabolism in most of the lesions detected. Indeed, two of the five patients with cerebral metastasis in our series presented a reduction in metabolic activity in the cerebral parenchyma in five lesions, coinciding with areas of edema shown in the localizing CT image, and one of the patients presented a mixed lesion (hypermetabolic and hypometabolic). Moreover, it should be underlined that many pathologies may appear with hypermetabolic...

Fig. 2. Images of CT, PET and fusion PET/CT in a patient with small cell lung cancer (A), stage IV due to lesions in both adrenal glands (B). The patient was neurologically asymptomatic and 15 days after the PET/CT study began with symptomatology (vomiting and headache). The selective cerebral study (C) shows several lesions in both the morphologic and metabolic images. At least two of the lesions demonstrated hypometabolism (white arrows) in the right cerebellum, with another mixed lesion with an area of hypometabolism in the anterior region and increased glycidic activity in the posterior portion in the left temporal region (black arrow).
leading to confusion in the interpretation in the absence of knowledge of previous neurological manifestations of the patient such as acute cerebral ischemia, meningoencephalitis, or infectious diseases, among others.

We are aware that our sample size was small. However, the values of sensitivity and specificity obtained (60% and 100%, respectively), the statistical precision of 7%, and the fact of not selecting the patients, led us to reassess the advantages provided by a protocol of cerebral PET/CT in small cell lung carcinoma for the early diagnosis of cerebral lesions, especially in advanced stages.

Another drawback to take into account is the acquisition of cerebral CT in a non-diagnostic protocol without intravenous contrast. The limited morphological evaluation of cerebral parenchyma did allow diagnosis of the 2 lesions not detected in the staging PET. Despite the lower sensitivity of CT compared with cerebral MRI, we believe that the administration of radiological contrast and the acquisition in the diagnostic protocol for CT may provide better resolution and definition of the lesions detected by PET or may even allow the diagnosis of small lesions without metabolic translation. Indeed, some authors have suggested that the administration of intravenous contrast in the PET/CT study, even at low doses and including a selective cerebral study, may be sufficient to improve the detection of cerebral metastases thereby reducing the radiation received by the patient.42

We consider that the absence of symptoms within the six months following the PET/CT study may be a sufficiently safe parameter for final clinical classification of patients without cerebral imaging studies since this disease, especially in advanced stages, evolves rapidly. Although contradictory, the cerebral PET detected disease during the post-treatment follow-up of one of the patients with initial negative PET five months later, with the patient remaining neurologically asymptomatic.

Conclusion

Although 18F-FDG-PET/CT is not generally recommended in the diagnosis of cerebral metastasis, the use of a selective cerebral study together with the standard study in patients with small cell lung cancer, especially in cases with disseminated disease at other levels, allows more correct staging as well as the detection of unsuspected cerebral metastatic lesions with important prognostic and therapeutic implications. It should be considered that any alteration in the distribution of FDG in the cerebral parenchyma should lead to suspicion of the presence of malignant lesions in this area since the alterations observed in PET images often correspond with areas of cerebral edema and are, therefore, hypometabolic.

References


