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Original Article

The usefulness of ^{18}F-fluorocholine PET/CT in the detection of recurrence of central nervous system primary neoplasms☆

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ABSTRACT

Aim: To study the usefulness of ^{18}F-fluorocholine (FCH) in detecting the recurrence of primary brain tumors.
Materials and methods: A prospective study was conducted on brain PET/CT with FCH for compassionate use in 21 patients with suspected recurrence of a primary brain tumor. The distribution by pathology was: three grade II astrocytomas, three grade III astrocytomas, one grade II oligodendroglioma, three grade III oligodendrogliomas, one grade III oligoastrocytoma, four glioblastoma multiform, one gliomatosis cerebri, and five meningiomas. Studies in which there was a visually significant uptake in the brain parenchyma were classified as positive.
Results: A total of 17 patients were classified as positive, with the results being confirmed by histology (10 cases) or clinical follow-up and imaging, with no false positives or negatives. The mean SUV_{max} for positive patients was 8.02 and 0.94 for the negative ones, which was significantly different ($P = .003$)
Conclusion: PET/CT with FCH shows encouraging results in the evaluation of patients with suspected recurrence of primary brain neoplasms.

Valor de la PET/TC cerebral con ^{18}F-fluorocolina en la detección de recurrencias de neoplasias primarias del sistema nervioso central

Palabras clave:
^{18}F-fluorocolina
Tumor cerebral
Neurooncología
Recidiva
PET/TC cerebral

RESUMEN

Objetivo: Estudiar el impacto clínico en el manejo de los pacientes de la ^{18}F-fluorocolina (^{18}F-COL) en la recurrencia de neoplasias cerebrales primarias.
Material y métodos: Se estudió prospectivamente a 21 pacientes con sospecha de recidiva de neoplasia cerebral primaria mediante PET/TC cerebral con ^{18}F-COL en uso compasivo. La distribución por patología de los pacientes estudiados fue: 3 astrocitomas grado II, 3 astrocitomas grado III, un oligodendroglioma grado II, 3 oligodendrogliomas grado III, un oligoastrocitoma grado III, 4 glioblastomas multiformes, una gliomatosis cerebri y 5 meningiomas. Se consideraron positivos los estudios en los que había una captación visualmente significativa respecto al fondo del parénquima cerebral.
Resultados: Diecisiete de los pacientes fueron positivos, comprobándose dicho resultado por histología (10 de ellos) o seguimiento clínico y por neuroimagen, sin hallarse falsos positivos o negativos. El índice target to backgroud ratio medio para los positivos fue de 8,02 y para los negativos de 0,94, lo que representa una diferencia significativa (p = 0,003).
Conclusión: La PET/TC con ^{18}F-COL presenta resultados alentadores en la valoración de pacientes con sospecha de recidiva.

Introduction

Primary brain tumors are a heterogeneous group of neoplasms with different behaviors and prognosis. They make up a group of infrequent diseases, representing less than 2% of malignant tumors in adults, and having an annual incidence of approximately 5 cases of malignant glioma per 100,000 inhabitants. The most common neoplasms are glioblastomas which are found in 60–70% of the cases, followed by anaplastic astrocytomas (10–15%), and

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anaplastic oligodendrogliomas and anaplastic oligoastrocitomas (10%).[1,2]

The diagnosis of primary neoplasms is challenging with respect to both the evaluation of the naive tumor and that of possible recurrences. This is particularly true in relation to recurrence since magnetic resonance (MR) findings of relapse and radionecreosis may be confused and often overlap[3].

On the other hand, PET/CT studies with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) are relatively limited in the study of these patients due to the elevated normal cortical encephalic metabolism which shows low contrast of the lesion with respect to the background. Although there is an increase in tracer uptake in high grade tumors, low grade brain lesions present little affinity for ^{18}F-FDG,[2] and this can contribute to the characterization of tumor grade. The radiotracer most commonly used for the evaluation of this type of neoplasms is L-[methyl-^{11}C]methionine (^{11}C-MET) since it does not have the limitation of cortical uptake of ^{18}F-FDG because of the little uptake by healthy brain tissue, thereby allowing clear definition of the tumor lesion. ^{11}C-MET plays an important role in the management of primary brain tumors in that, in addition to helping achieve a diagnosis, it allows other actions such as imaging-guided biopsy, the detection of recurrence, evaluation of prognosis and radiotherapy planning.[2,4–6]

Considering the difficulties of the application of ^{11}C labeled radiotracers, the appearance of new fluorinated tracers for PET, which can be used on a large scale in hospitals without a cyclotron, may play a relevant role in the management of these patients. One of these tracers is [^{18}F]-O-(2-fluoroethyl)-L-tyrosine (^{18}F-FET), and similar to ^{11}C-MET, it is based on the metabolism of amino acids[2,7]. Studies comparing this radiotracer with ^{11}C-MET have shown a similar sensitivity and specifity,[2] even with lesser uptake in inflammatory diseases.[8]

Another fluorinated radiotracer is [^{18}F]-6-fluoro-L-3,4-dihydroxyphenylalanine (^{18}F-DOPA). This tracer is usually used to study movement disorders. Structure-wise it is an analog of phenylanine and is therefore actively uptaken by type L amino acid transporters and is metabolized in dopamine.[2] Thus, the uptake of this tracer is increased in different tumors such as gliomas in which the uptake is related to tumor grade.[2,9]

Choline is a molecule which is involved in the formation of the cellular membrane. Its entry in cells is produced by specific transporters, and it is phosphorylated by choline kinase. This phosphorylcholine is transformed into phosphatidylcholine on its incorporation to lecitin and is thus converted into a component of the cell membrane.[2] Neoplasms present a high rate of cellular proliferation leading to the formation of large quantities of cell membrane. This provokes the accumulation of choline in tumor tissue. The abundant presence of choline in MR spectroscopy is of note.[2,10]

Choline was labeled with ^{11}C to obtain carbonocholine (^{11}C-COL) and was later labeled with ^{18}F, producing the synthesis of fluorocholine (^{18}F-COL). The utility of these tracers seems to be related to alterations in the uptake and metabolism of choline which are related to the presence of malignant lesions.[11] Gómez-Río et al.[12] studied the usefulness of ^{18}F-COL in patients with low grade gliomas, demonstrating the capacity of this tracer to define tumor infiltration in white matter and suggesting that ^{18}F-COL may complement SPECT with ^{201}TI since the latter is useful for defining tumor grade. Likewise, ^{11}C-COL is an aggressive marker and may be of use in the monitoring of antiangiogenic therapy.[13–15] In addition, several studies have described the superiority of ^{11}C-COL compared to MR in radiotherapy planning.[16,17] The few studies comparing ^{11}C-COL directly with ^{11}C-MET did not find it to be better in the differential diagnosis of recurrence versus radionecrosis.[18,19] Nonetheless, the main problem continues to be the labeling with carbon which does not allow its distribution to centers without a cyclotron, thereby precluding large scale application.

The biodistribution of ^{18}F-COL in the brain does not relevantly differ compared to ^{11}C-COL. It presents low uptake in the brain cortex and greater concentrations in the venous plexuses and extracranial structures such as the nasal mucosa or the saliva glands.[20] Moreover, ^{18}F-COL does not have the problem of the short half life found in compounds labeled with ^{11}C.

The aim of the present study was to evaluate the usefulness of ^{18}F-COL in detecting the recurrence of primary brain tumors and the impact on the clinical management of these patients. This was a preliminary study analyzing neoplasms with different histologies and grade of differentiation.

Materials and methods

We prospectively studied a series of 21 cases from June 2014 to July 2015 in a pilot study with the aim of obtaining preliminary information for posterior studies.

The cases selected fulfilled the following criteria:

- Previous diagnosis of primary brain tumor.
- Clinical and/or radiological suspicion of recurrence.
- Doubtful MR findings in the evaluation of recurrence.

The patients were evaluated by brain PET/CT with ^{18}F-COL in a Philips Gemini TF. The patients received an intravenous dose of 370 MBq of ^{18}F-COL, and the images were acquired 50 minutes after administration of the radiotracer. Although some studies have reported the possibility of acquiring images with this tracer 5 min after administration,[21] the stability of the biodistribution of ^{18}F-COL during the first hours and the organizational demands of the center established the time of radiotracer incorporation as 50 min.[22] No special preparatory measures were undertaken to perform the imaging studies.

Iterative reconstruction (LOR RAMLA, 3 iterations and 33 subsets) were carried out with a matrix of 128 × 128 pixels of 2 mm in length and 2 mm in thickness. The associated CT was with a low dose with 120 kV and 50 mAs, a slice thickness of 3 mm with an increase of 1.5 mm and field of view of 600 mm according to the specific needs of the equipment for correction of attenuation. A reconstruction of 256 mm with a window of visualization of cerebral parenchyma was considered the most adequate for the neurological study. The diagnosis was made taking into account both the PET/CT images in the 3 spatial axes and fusion with the cerebral MR images using software.

Since this indication is not currently registered, the PET/CT with ^{18}F-COL was performed within the context of compassionate use under the approval of the Spanish Agency of Medication and Health Care Products and after being approved by a multidisciplinary committee.

The presence of high contrast tracer uptake compared to the background was visually evaluated, and it was determined whether this corresponded with the pathological images observed in the fusion with MR by 2 specialists in Nuclear Medicine. Tracer uptake was considered pathological when localized outside the zones of physiological uptake (described previously) and with the presentation of high contrast compared to the background and/or to the contralateral region. The criteria to consider the study as positive was the presence of at least one pathological uptake indicating the presence of tumor tissue. The absence of pathological uptake was classified as a negative study. The lesions were semiquantitatively analyzed by the drawing of regions of interest (ROI) and the measurement of their SUV_{max} in the zones with a pathological appearance as well as zones of contralateral physiological uptake,