Clinical note

Detection of second tumors in $^{11}$C-choline PET/CT studies performed due to biochemical recurrence of prostate cancer$^{\ast}$

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Early localization of biochemical recurrence in patients after radical treatment of prostate cancer is a widely accepted clinical indication of $^{11}$C-choline PET/CT. Its widespread clinical use has prompted the depiction of incidentalomas, unusual sites of metastatic lesions, as well as false positive and negative cases. Over the last 6 years, a total of 454 $^{11}$C-choline PET/CT studies have been performed in our institution to locate biochemical recurrence of patients with prostate cancer. With these studies, a second neoplasm has been found in 7 patients (1.54%): 3 lung, 2 colorectal, 1 esophageal and 1 esophageal junction, respectively. Although the clinical usefulness of this technique for detecting cancer lesions other than prostate origin is known for those patients who undergo this technique in the accepted indication, the diagnosis of a second tumor has a significant impact on their therapeutic management.

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Detección de segundos tumores en estudios de la PET/TC con $^{11}$C-colina realizados por recurrencia bioquímica de cáncer de próstata

R E S U M E N

La aplicación clínica más aceptada de la PET/TC con $^{11}$C-colina es la localización precoz de la recidiva bioquímica en pacientes tras un tratamiento radical de cáncer de próstata. Su uso generalizado ha hecho evidente la existencia de localizaciones infrecuentes de incidentalomas, lesiones metastásicas, así como falsos positivos y negativos en la exploración. En los últimos 6 años, de un total de 454 estudios de la PET/TC con $^{11}$C-colina realizados en nuestro servicio para localizar la recidiva bioquímica de un cáncer de próstata hemos detectado un segundo tumor en 7 casos (1.54%): 3 pulmón, 2 colorrectales, uno de esófago y uno esofagogástrico. Si bien es conocida la utilidad de la PET/TC con $^{11}$C-colina en la detección de otros tipos de tumores diferentes al cáncer de próstata, en los pacientes en los que se realiza la exploración por esta indicación aceptada su diagnóstico muestra un importante cambio en el manejo terapéutico de estos pacientes.

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Introduction

$^{11}$C-choline was initially proposed as a tumor tracer for the study of brain tumors by Hara et al. in 1997. Choline is one of the components of phosphatidylcholine, an essential element of the phospholipids of the cell membranes. Tumor cells present an elevated metabolic rate which increases the uptake of choline in tumor tissue required for the synthesis of phospholipids in the cell membranes. The consumption of choline is associated with cellular proliferation. Nonetheless, other factors affecting the grade of choline uptake remain to be clarified. Thus, their entry into the cell is related to simple diffusion, suggesting its role in tumor perfusion. In addition, the rate of uptake is not affected by the hypoxic/normoxic state as occurs with $^{18}$F-FDG.

Several, mainly preliminary, studies published on the utility of this tracer in different types of tumors including gliomas, lung cancer, esophageal cancer, prostate cancer, gynecological tumors and soft tissue/bone sarcomas have been presented in a recent systematic review.

However, at present the most accepted application of PET/CT with $^{11}$C-choline is in the management of patients with prostate cancer as an alternative to $^{18}$F-FDG due to the low affinity of this tracer by well differentiated tumor processes and its physiological urinary elimination which makes the interpretation of pelvic images difficult. Choline is currently available labeled with $^{11}$C and with $^{18}$F. However, no comparative studies have been performed, although $^{18}$F has an advantage over $^{11}$C in its longer half life (120 min vs. 20 min) thereby allowing its distribution from the cyclotron installation to other PET services. At present, the indications of PET/CT with $^{11}$C-choline in patients with prostate cancer include the staging of patients at medium/high risk and, mainly, early localization of biochemical recurrence.

With more generalized use some studies have described incidentalomas, infrequent localization of metastatic lesions as well as false positive and negative results. In the last 6 years of a total of 454 PET/CT studies with $^{11}$C-choline performed in our...
department for the localization of suspicion of biochemical recurrence of prostate cancer we detected a second tumor in 7 cases (1.54%): 3 in the lung, 2 colorectal, 1 esophageal and 1 esophagogastric.

Clinical cases

Methodology of PET/CT study with $^{11}$C-choline

The methodology of the PET/CT studies with $^{11}$C-choline is conditioned by the short half life of the tracer (20 min). $^{11}$C-choline was synthetized in the cyclotron located in the same installation following the method of Hara et al. All the patients were fasted for 6 h. No oral or endovenous contrast was administered prior to the acquisition of PET/CT. The patients were placed on the tomograph bed for PET/CT. The $^{11}$C-choline was intravenously injected ($656 \pm 119$ MBq), initiating the acquisition of images, the low dose CT for correction of attenuation and whole body PET 5 min after the injection. The acquisition began at the pelvis and continued in the caudocranial direction.

Case 1

A 67-year-old patient with a history of adenocarcinoma of the prostate and treated with radiotherapy 3 years before, presented a progressive elevation in PSA serum values (5.2 ng/ml).

PET/CT study with $^{11}$C-choline showed a metabolically active image in the sigmoid colon presenting parietal thickening and an increase in density of the perisigmoid fat planes suggesting a neoplastic process. In addition, a deposit of $^{11}$C-choline was observed in the mid-basal region of the left prostatic gland suspicious of active tumor recurrence (Fig. 1).

A colonoscopic study was performed confirming the presence of a tumoral process, and the patient underwent surgery due to the absence of suspicious images of metastasis in the $^{11}$C-choline study and in an enhanced-contrast CT (T2N1M0). A control study and possible treatment of the suspicious image of left prostate recurrence remains outstanding.

Case 2

A 71-year-old patient with a history of adenocarcinoma of the prostate treated with prostatectomy 4 years before (postsurgical PSA 4.16 ng/ml) followed by radiotherapy (ended 2 years before) presented a progressive serum elevation in PSA level (post-radiotherapy: 0.12 ng/ml; currently 2 ng/ml).

PET/CT study with $^{11}$C-choline showed a mass in the upper lobe of the left lung with irregular increased uptake of the tracer and deposits of the tracer with slightly lower intensity on both sides of the mediastinum and in the subcarinal area corresponding to lymph nodes of less than 1 cm in size in the CT. No other metabolically active lesions were observed in the pelvic cavity, in the infradiaphragmatic lymph node stations or in the bone structures (Fig. 2).

In view of these findings a FNAP of the left pulmonary mass was performed confirming the presence of pulmonary adenocarcinoma. The lesions were then characterized by PET/CT with $^{18}$F-FDG showing greater glycidic activity of these lesions but with no evidence of other metabolically active lesions. An EBUS was carried out confirming the pulmonary metastatic origin (T2N3M0), and chemotherapy treatment was initiated with partial response at the third month.

Case 3

A 75-year-old patient had a history of adenocarcinoma of the prostate treated with prostatectomy 6 years before. Biochemical recurrence was treated with radio- and brachytherapy 4 years beforehand and the patient currently presented mild, albeit persistent, elevation of PSA serum values (0.3 ng/ml).

The PET/CT study with $^{11}$C-choline demonstrated intense uptake of the tracer in the middle third of the esophagus with concentric thickening of the esophageal walls and extension to periesophageal fat planes. Large hypermetabolic adenopathies were observed in the posterior paraesophageal region and in the tracheoesophageal sulcus. Intense uptake of $^{11}$C-choline was also found in the left sacral region with normal CT. No other active images were observed in the pelvic cavity (in this sense, it should be noted the detection of early activity in the urinary bladder) or in the infradiaphragmatic lymph node stations (Fig. 3).
Fig. 2. A. Uptake of $^{11}$C-choline in the left apical pulmonary mass (SUV max. 3.9). B–D. Deposits of the tracer in the right paratracheal region (SUV max. 2.2), in the right hilum (SUV max. 2.5), in the subcarinal area (SUV max. 2.6) and in the left paraesophageal region adjacent to the inferior vena cava (SUV max. 2.1). E. All these lesions were evident with a higher grade of metabolic activity in the PET/CT study with $^{18}$F-FDG.

Fig. 3. A. Intense radiotracer uptake (SUV max. 5.3) in the middle third of the esophagus with concentric thickening of its walls of approximately 6 cm and with extension to the periesophageal fat planes. B and C. Hypermetabolic adenopathies of significant size in the posterior paraesophageal region (SUV max. 2.9) and in the tracheoesophageal sulcus (SUV max. 2.5). Pulmonary physiologic activity (SUV max. 0.9) and mediastinum (SUV max. 1.3). D. Intense uptake of $^{11}$C-choline in S3 (SUV max. 14) compatible with M1, and normal CT. Physiologic activity in the right sacral wing (SUV max. 1.6).

An endoscopy showed an adenocarcinoma of the esophagus and the posterior paraesophageal adenopathy puncture confirmed the esophageal tumor origin. The sacral lesion was characterized as solitary bone metastasis by MR. To differentiate whether it is secondary to the prostate or esophageal process, the bone lesion puncture determined its esophageal origin. The patient initiated chemotherapy treatment but presented radiological progression at one month.

**Discussion**

Previous reports have shown that the presence of synchronous tumors or the appearance of a second tumor in oncologic patients is frequent and probably multifactorial. Thus, the U.S. National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program has reported multiple neoplasms in 13.1% of cancer males and 13.7% in women.

In our series we detected a second tumor in 1.54% of the cases of biochemical recurrence of prostate cancer: 3 of the lung, 2 colorectal, 1 esophageal and 1 esophagogastric.

One recent systematic review analyzed the utility of PET/CT studies with choline in other tumors appearing with prostate cancer: extensive references were available in gliomas given the absence of brain physiologic activity and the possibility of differentiation of tumor grade but with few comparative studies with $^{11}$C-methionine; in esophageal cancer diagnostic efficacy was
reported in mediastinal staging similar to that of $^{18}$F-FDG; in lung cancer the results were likewise good but the comparative studies with $^{18}$F-FDG were controversial; promising preliminary results were obtained in hepatocarcinoma, bone/soft tissue sarcomas, breast cancer and gynecologic tumors; in head and neck tumors as well as in urinary bladder cancer there is limited experience.

Even fewer references are available in colorectal cancer since despite the presence of a dysregulation in the phosphorylation of choline, the physiological uptake of the tracer in the intestinal loops, predominantly in the small bowel makes the interpretation of the images difficult.\(^\text{10}\)

The incidental diagnosis of tumor lesions logically has an important clinical impact.\(^\text{9}\) Firstly, since early detection allows more radical treatment with improvement in survival as in our case in which we detected adenocarcinoma of the sigma. Secondly, in the case of presenting another tumor as in the case in which we found squamous carcinoma of the lung and adenocarcinoma of the esophagus, the management of the patient should initiate with treatment of these due to their worse prognosis compared to recurrence of prostate cancer.

Nonetheless, all deposits of $^{11}$C-choline should be evaluated knowing the physiological distribution of the tracer and the variants of normality as well as considering the possibility of false positive results and, depending on their localization, if they are suspicious of metastatic or primary lesions.\(^\text{7,8}\) The integrated equipment provides morphologic information and improves the diagnostic performance of the study while always taking into account that, given the possible implications, any lesion with uptake must be confirmed in order to implement the most adequate therapeutic approach.\(^\text{7}\)

Briefly, in the interpretation of PET/CT studies with $^{11}$C-choline we should always take into account the possibility of detecting a second tumor with important impact on the therapeutic management of these patients.

**Conflict of interest**

The authors have no conflicts of interest to declare.

**References**