Evaluation of efficacy and clinical impact of $^{18}$F-FDG-PET in the diagnosis of recurrent medullary thyroid cancer with increased calcitonin and negative imaging test

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A B S T R A C T

\textbf{Aim:} To evaluate the efficacy and clinical impact of the $^{18}$F-FDG-PET in the diagnosis of suspicion of recurrence of medullary thyroid cancer (MTC) in patients with elevated serum calcitonin and negative imaging test.

\textbf{Material and methods:} We performed a retrospective study of 31 consecutive cases from February 2001 to October 2007 of 17 women and 14 men, mean age 56.2 years (range: 26–88), with anatomo-pathological diagnosis of MTC and suspicion of recurrence due to abnormal elevation of calcitonin and negative imaging tests. All the patients underwent whole body $^{18}$F-FDG-PET scan with a dedicated PET or PET-CT 60 min after intravenous injection of 333–434 MBq of $^{18}$F-FDG. Results were confirmed by pathology study in 45.2\% of the patients and by clinical follow-up with a mean of 4 years (range: 16 months–8 years).

\textbf{Results:} Sensitivity was 88\%, specificity 84.6\%, positive predictive value (PPV) 88\%, negative predictive value (NPV) 84.6\% and diagnostic accuracy 87\%. The results of the $^{18}$F-FDG PET modified the therapeutic strategy in 14 cases (45.2\%). A comparison was made of the mean values of calcitonin using the Student’s t-test between positive PET studies for the disease and negative ones. No significant differences were found ($p = 0.3$).

\textbf{Conclusions:} In patients with MTC and suspected recurrence with elevated calcitonin and negative imaging test, the $^{18}$F-FDG PET is the best test for the diagnosis of occult recurrence in MTC with elevated calcitonin and negative imaging techniques with elevated clinical impact. It facilitates the therapeutic management of the patients with MTC recurrence, and should be included in the diagnosis algorithm in these patients.

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\textbf{Evaluation of the efficacy and the impact clinical of the PET-$^{18}$F-FDG in the diagnostic of recurrence of medullar tiroides with calcitonina elevada and pruebas de imagen negativas}

\textbf{Resumen}

\textbf{Objetivo:} Evaluar la eficacia y el impacto clínico de la PET-FDG en el diagnóstico de sospecha de recurrencia de carcinoma medular de tiroides (CMT), en pacientes con calcitonina elevada y pruebas de imagen negativas.

\textbf{Material y métodos:} Estudiamos retrospectivamente a 31 pacientes consecutivos de febrero de 2001 a octubre de 2007; 17 mujeres y 14 hombres con una edad media de 56,2 años (range: 26–88), diagnóstico anatomopatológico de carcinoma medular de tiroides y sospecha de recurrencia por elevación patológica de calcitonina y pruebas de imagen negativas. A todos los pacientes se les realizó PET/PET-CT corporal 60 min post-inyección intravenosa de 333–434 MBq de $^{18}$F-FDG. Los resultados se confirmaron mediante anatomía patológica en el 45,2\% de los pacientes y por seguimiento clínico/radiológico en el 54,8\% durante un período de seguimiento medio de 4 años (range: 16 m–8 años).

\textbf{Resultados:} Se obtuvo una sensibilidad del 88\%, especificidad del 84.6\%, valor predictivo positivo del 88\%, valor predictivo negativo del 84.6\% y exactitud diagnóstica del 87\%. Los resultados de la PET-FDG modificaron la actitud terapéutica en 14 casos (45.2\%). Se compararon las medias de los valores de calcitonina entre PET positivos para enfermedad y negativos, mediante la prueba de la $t$ de Student no encontrando diferencia significativa ($p = 0.3$).

\textbf{Conclusiones:} La PET-$^{18}$F-FDG es la prueba idónea para el diagnóstico de recurrencia oculta en CMT con calcitonina elevada y técnicas de imagen negativas, con elevado impacto clínico facilitando el manejo terapéutico de los pacientes con recurrencia de CMT, debiendo ser incluida en el algoritmo diagnóstico de estos pacientes.

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Introduction

Medullary thyroid carcinoma (MTC) is a relatively uncommon neuroendocrine tumor derived from parafollicular thyroid C cells from the neural crest and which secrete calcitonin and other tumor markers such as the carcinoembryonic antigen, the vasoactive intestinal polypeptide and somatostatin which may used for the diagnosis and follow up of MTC.

This type of cancer represents 3–5% and 8–10% of the thyroid tumors and has two forms of presentation: sporadic (75–80%), most frequently occurring in the 6th and 7th decades of life and familial (20–25%) with an early presentation (3rd decade) and being well associated with multiple MEN2A and MEN2B type endocrine neoplasms or as isolated familial MTC.1,2 Both presentations are characterized by a relatively slow tumor growth with early metastatic lymph node involvement.3 Thus, at the time of the initial diagnosis 22–50% of the patients have cervical and mediastinal metastasis, with distant metastasis in 2–33%, localized particularly in the lung, bone, liver and, less frequently, in the brain.2,4

MTC is responsible for up to 13.4% of all the deaths related to thyroid cancer, with survival rates of 40–50% at 10 years and of 20% in patients with distant metastasis. The prognosis of these patients is worse than for those with differentiated thyroid cancer due to early metastasis and the lack of effective systemic therapy.5,6

Surgery is the main and only effective treatment, with total thyroidectomy plus cervical lymph node dissection being the treatment of choice. Treatment of recurrence is resection or local irradiation. In addition to surgical treatment, early diagnosis of recurrence and locoregional and/or distant relapse is crucial in the therapeutic management and prognosis of these patients.7,8 Early diagnosis is the most important prognostic factor in patients with MTC recurrence, allowing surgery to be performed before the appearance of distant metastasis.9

Calcitonin is the most specific tumor marker for the early diagnosis and post-surgical follow up of MTC. An elevated calcitonin serum level, measured at 8–12 weeks post-surgery, indicates disease persistence or recurrence. Calcitonin levels may be undetectable in patients who have undergone extensive surgery and do not present metastasis in the lymph nodes in the neck, with the concentrations being elevated in two-thirds of the patients with cervical lymph node involvement and abnormally high in 100% of the cases with metastatic MTC.1,10 Multiple European studies have demonstrated that routine measurement of calcitonin serum levels in patients with thyroid nodules is effective for the detection of clinically occult MTC.5–8 However, some authors have reported false positive results (in cases of renal insufficiency or with the presence of other neuroendocrine tumors, small cell lung carcinoma, pancreatitis, etc.) or false negative calcitonin levels in the detection of MTC.1,3,10,11

The diagnosis of recurrence or distant metastasis and their localization continues to be difficult. Morphological imaging techniques such as echography (ECO), computed tomography (CT), magnetic resonance (MR) and several scintigraphic procedures (18F-FDG-PET-CT) are performed in patients with elevated calcitonin levels to localize the responsible tumor tissue, but many of these techniques continue to be negative. Morphological imaging techniques are limited by post-treatment tissue distortion (surgery or radiotherapy) and thus, the use of FDG-PET has been implemented in the search for occult lesions based on the fact that the metabolic changes precede the structural changes.1

There is now evidence that 18F-FDG-PET is a better and more sensitive technique for the localization of lymph node tumor involvement and distant metastasis and therefore has an important role in the post-surgical follow up of MTC.8,9 Physiological uptake of FDG is very low in the lower neck region and the upper mediastinum, thereby facilitating the clinical evaluation of local recurrence and regional lymph node metastasis. The metabolic imaging findings shown by PET may precede the morphological changes observed with CT or MR by several years or months. FDG-PET detects metabolic activity in the tissues which compose the residual mass and thus, the presence of viable tumor tissue.

The aim of the present study was to evaluate the efficacy and clinical impact of 18F-FDG-PET in the diagnosis of suspected MTC recurrence in patients with elevated calcitonin levels and negative imaging tests.

Materials and methods

Patients

We performed a retrospective study in 31 consecutive patients from February 2001 to October 2007. Seventeen were women and 14 men with a mean age of 56.2 years and a range of 26–88 years with a histological diagnosis of MTC. All patients had undergone total thyroidectomy and in 14 (45.2%) cervical lymph node emptying was performed. The patients were referred to our Nuclear Medicine Unit for presenting a progressive pathological elevation and/or maintenance of serum calcitonin values (mean: 841.79 pg/ml; range: 59–2500 pg/ml) and negative imaging tests.

Serum calcitonin levels were determined in all the patients two months after surgery and every six months thereafter by radioimmunometric assay (IRMA) until October 2006 (26 patients) and/or chemoluminescence (CIL) after November 2006 (5 patients). The reference values for the determinations were 0–50 pg/ml with a sensitivity of 1.5 pg/ml by IRMA and 5–18 pg/ml for CIL.

Blood was extracted from all the patients to determine serum calcitonin levels the same day the PET was carried out.

A second PET was carried out during the follow up in 14 patients (9 PET and 5 PET-CT), with a third PET in 5 of these patients (PET-CT in 3) and a fourth PET in two (PET-CT in both). The performance of PET or PET-CT depended on the availability of equipments in the Nuclear Medicine Unit. Until May 2007 we used a dedicated PET; subsequently, studies were performed using a hybrid PET-CT equipment.

Written informed consent was not required for this study. Oral informed consent was obtained according to the Order of 8th of July 2009/BOJA No. 152, pp. 77–79, which includes measures of radiological protection, information on reporting management and providing the opportunity to solve any doubts.

Positron emission tomography

The 18F-FDG-PET studies were performed in a PET ECAT Exact HR+ tomography (Siemens®) and the PET-CT study was carried out in a high sensitivity and high resolution hybrid Biograph 16 model tomography (Siemens®) integrating a PET system of 24,336 lutetium oxyorthosilicate (LSO) detectors and a helicoidal 16-slice CT (Somatom Sensation 16).

Image acquisition was performed 60 min post-intravenous injection of 333–434 MBq (9–12 mCi) of 18F-FDG according to the weight of the patient. The study was carried out following glycaemia determination and the administration of 50 mg of oral terazepam and furosemide (0.25 mg/kg of weight) and intravenous hydration (250 cm³ of saline serum). The images were acquired from the vertex to the proximal third of the thigh. PET scan was obtained in 2D and 3D with and without correction of attenuation; images in coronal, axial, and sagittal slices were reconstructed applying an iterative algorithm (2 iterations/8 subsets). A low dose CT (without oral or intravenous contrast) was acquired for the PET-CT scan; PET in 3D was performed with and without correction of attenuation,
with iterative reconstruction (4 iterations/8 subsets) in coronal, axial and sagittal planes.

Fourteen patients underwent a second PET or PET-CT (5 PET-CT) during the follow up, with a third PET in 5 of these patients (3 PET-CT) and a fourth PET in two (both PET-CT).

Image interpretation

The studies were qualitatively evaluated by two experts in nuclear medicine analyzing the emission images with and without correction of attenuation. In the PET-CT studies the fusion PET-CT images were analyzed with knowledge of the clinical and radiological data leading to the request, with deposits of abnormal radiotracer uptake not corresponding to physiological activity being interpreted as pathological. In the cases of doubtful interpretation, a normal or pathological decision was resolved by consensus of the experts in nuclear medicine. All the cases were semiquantitatively evaluated by the determination of the standardized uptake value (SUV). Tumor localization, number and size were determined.

Confirmation of results

The results of the PET studies were classified as true positives for local recurrence or locoregional or distant metastasis, if confirmed by either of the following criteria: firstly, positive histological results for the presence of disease and secondly, the detection of lesions by conventional images techniques and evolution. The images were classified as false positive when the apparent anomalies in tracer uptake were not confirmed by either of the above two criteria and as false negatives with images without pathological uptake but with confirmation of the clinical presence of disease on posterior surgical resection and histological evaluation.

The results were confirmed by histology or clinical and radiological follow up during a minimum period of 16 months.

Statistical analysis

We performed the statistical analyses using the SPSS 16.0 program to analyze the quantitative variables of the serum calcitonin levels in pg/ml using the Levene's test for equality of variances. The means of calcitonin were compared applying the Student's t-test, considering a p value <0.05 as statistically significant.

Results

Of the 31 patients, 14 were diagnosed with MTC associated with multiple endocrine neoplastic syndromes, 13 MEN2A (three multicentric and one with diagnosed pheochromocytoma) and one MEN2B (associated with neuromas). Of the 17 remaining patients, 3 had histological confirmation of multicentric MTC.

The results were confirmed by histology in 14 patients (45.2%) and clinical and radiological follow up in 17 patients (54.8%) during a mean follow up of 4 years with a range of 16 months–8 years.

FDG-PET detected pathological lesions in 18/31 patients (58%), with confirmation of the presence of disease in 16 true positives (TP). No pathological deposits of the radiotracer were found in 13/31 (42%) of the patients, confirming the absence of disease in 11 true negatives (TN) (Table 1). In our series the sensitivity (S) was 88%, the specificity (Sp) 84.6%, the PPV was 88% and the NPV was 84.6% with a diagnostic precision of 87% (Table 2).

On analysis of the results of the FDG-PET, the presence of disease was confirmed in 16 of the 18 positive FDG-PET (TP), with no evidence of disease in the two false positives. Histological confirmation was obtained in 12/16 patients. The other 4 were confirmed by clinical follow up of 1–7 years. All showed disease progression and one died. In the two false positive cases, the FDG-PET findings were not confirmed by morphological CT studies, which were negative. One 52-year-old patient presented serum calcitonin levels at the lower limit of pathological values (59 pg/ml) determined by IRMA prior to undergoing the FDG-PET and mediastinal lymph node involvement was observed on PET. After clinical/radiological follow up of 2.5 years the patient remains asymptomatic, with normal calcitonin values and no evidence of disease by imaging tests. Another patient of 88 years of age presented pathological calcitonin levels of 2018 pg/ml prior to PET which diminished to 1046 pg/ml at the time of the test in which cervical lymph nodes were observed. After 4 years of clinical/radiological follow up the patient remains asymptomatic with no evidence of disease by imaging tests.

The results were confirmed in 11 of the 13 patients in whom FDG-PET did not detect disease: in 4, CT did not detect any findings and the calcitonin levels normalized during follow up, remaining asymptomatic and disease-free with a clinical/radiological follow up of 1.5–5 years. In the remaining 7 patients no findings were observed in the conventional imaging tests performed (CT and ECO), remaining asymptomatic and with no evidence of locoactive disease over a clinical/radiological follow up of 1.7–8 years. A second PET was carried out in 3 of these patients and it continued to be negative. Two of these patients underwent surgery for pheochromocytoma.

In the two false negative cases, one woman and one man of 52 years and 47 years of age, respectively, the calcitonin values leading to the performance of FDG-PET were above the limits of normality at 400 and 1500 pg/ml, respectively. The PET was negative in both cases, with calcitonin levels of 681 pg/ml and 1530 pg/ml respectively at the time FDG-PET was performed. The woman underwent scintigraphy with 123I-MIBG and the man a CT showing right and bilateral cerebral adenopathies, respectively. Both patients underwent lymph node cervical dissection with the histological study showing metastasis of MTC. At the time of this study the woman has had a clinical/radiological follow up of 3 years during which she has received a second and third PET which were negative, with calcitonin values of 168 pg/ml and 99 pg/ml, respectively. Two years after surgery the man presented a progressive elevation of pathological calcitonin levels of up to 5175 pg/ml, showing disease progression with distant metastasis (hepatic, pulmonary and bone) in the imaging techniques, leading to palliative chemotherapy.

Of the 18 patients with confirmed disease, the 18F-FDG-PET/PET-CT was positive in 16 (TP) and was negative in two (FN). Locoregional recurrence was diagnosed in 13 cases (72%) (11 TP + 2 FN) and distant metastasis in the remaining 5 patients (28%) (TP) (Fig. 1). The lesions in the patients with locoregional recurrence were localized in the anteroinferior cervical region, in both cervical lymph node chains and in the left supraclavicular fossa (Fig. 2).

Table 1 Results of the PET-FDG in patients with MTC referred for suspicion of recurrence and/or metastasis with a pathological elevation in the serum calcitonin levels and negative imaging tests.

<table>
<thead>
<tr>
<th>Confirmation of disease</th>
<th>Disease free</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET-FDG+</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>PET-FDG−</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>18 (58%)</td>
<td>13 (42%)</td>
</tr>
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</table>

Table 2 The sensitivity (S), specificity (Sp), positive predictive value (PPV) negative predictive value (NPV) and diagnostic precision obtained in this series of patients.

<table>
<thead>
<tr>
<th>S</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
<th>Diagnostic precision</th>
</tr>
</thead>
<tbody>
<tr>
<td>88%</td>
<td>84.6%</td>
<td>88%</td>
<td>84.6%</td>
<td>87%</td>
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The localizations of distant metastasis in 5 PET positive patients were distributed in the extracervical lymph node chains in 2 cases, in the liver in 3, in the bone in 3 and in the lung in 2 (Figs. 3 and 4).

In one of the patients PET detected a second lung tumor which was resected with histological results of large cell lung cancer. The mean of the serum calcitonin levels in the PET positive patients was 682.82 pg/ml and 493.92 pg/ml in the PET negative patients, obtaining a P = 0.3. Thus, no statistically significant differences were found between the calcitonin values of the PET positive and PET negative patients (Fig. 5).

Clinical impact

The results of the \(^{18}\)F-FDG-PET/PET-CT modified the therapeutic strategy in 14 of the 16 TP patients, facilitating radical intention-to-cure surgery in 10 patients with locoregional lymph node metastases.

In the 4 remaining patients identification of locally advanced, disseminated disease led to the initiation of less radical and palliative therapies, with one patient undergoing surgery plus adjuvant radiotherapy and another surgery plus palliative radiotherapy; the third patient received surgery plus palliative chemotherapy and the fourth underwent palliative telecobaltotherapy and died during the follow up period.

The global clinical impact of \(^{18}\)F-FDG-PET/PET-CT was of 45.2% on modifying the therapeutical approach in 14 of the 31 patients studied.

Discussion

These tumors usually present local recurrence or metastasize near the neck with a good prognosis and elevated survival if effectively treated with resection or local irradiation of all the recurrences developing during the evolution of the disease.

The follow up of these patients is based on the monitoring of serum calcitonin levels and imaging studies of the region of the body in which recurrence or the presence of metastasis is suspected. Morphological imaging techniques are limited by the tissue distortion presented after surgery or radiotherapy. PET is able to detect the metabolic activity localizing viable tumor tissue and has the advantage that whole body studies may be performed and the images are not affected by surgery performed a few months previously. The S of FDG-PET in the literature is of 70–96%, being 50–80% for radiography, CT and MR and 25–33% for \(^{111}\)In-Pentetreotide, DMSA and MIIBG. On comparison with conventional imaging methods, FDG-PET shows a greater S and Sp thereby justifying its routine use in MTC.

Studies evaluating the clinical utility of FDG-PET are limited by the small number of patients analyzed. In a study including 20 patients, the group of Brandt-Mainz et al. found a S of 76%, and in a multicenter study Diehl et al. reported a S of 78% in 55 patients. In another multicenter study, Oudoux et al. found a global S of 76%, being 83% in cervical metastasis, 85% in the mediastinum, 75% in the lung, 60% in the liver and 67% in bone. In a group of 40 patients, Szakáll et al. the rate of detection of lymph node metastasis was 95%. To the contrary, De Groot et al. described a S of only 41%. The results of our series of patients showed a S of 88%, a Sp of 84.6%, and a diagnostic precision of 87%. Different studies have demonstrated the utility of FDG-PET in patients with elevated calcitonin levels in the detection of cervical, supraclavicular and mediastinal tumoral lesions and in the detection of distant metastasis and may be used as a guideline for planning the most appropriate surgery in each case, thereby avoiding unnecessary surgery of cervical and mediastinal lymph nodes. FDG-PET also allows identification of the patients who will benefit from radical intention-to-cure to less radical surgery and those who will not benefit from surgery. In our study the results of the FDG-PET studies led to intention-to-cure surgery in 10/31 patients (32.2%). Another three patients underwent surgery and were treated with adjuvant radiotherapy, chemotherapy and palliative radiotherapy and another patient received palliative telecobaltotherapy. The global clinical impact was 45.2%.

Histological confirmation of all the lesions detected by PET/PET-CT or conventional images methods was not obtained for ethical reasons.
reasons. Clinicoradiological follow up of at least 16 months (mean of 4 years) was performed in the cases without histological confirmation.

Of the two FN cases in our study, one presented small-sized hepatic metastasis during the immediate follow up with conventional imaging techniques (CT) and the other showed a small-sized lesion in the right cervical region in \(^{123}\)I-MIBG scan. The limitation of maximum spatial resolution with PET in small-sized lesions should be taken into account.

In a small number of cases \((n = 5)\) PET-CT was carried out, representing an important aid in the localization of pathological deposits of FDG uptake and in the identification of malignant or non malignant deposits such as those reported in other studies published.\(^2,3\)

In opposition to the results described in the literature in regard to the relationship between serum calcitonin levels and the positivity of PET,\(^2,15,16\) we did not find significant differences on comparing the means of the serum calcitonin levels between the PET positive and PET negative patients. In the literature we found reports of hypercalcitoninemia with etiologies different from MTC, describing diseases related to the thyroids such as lymphocytic thyroiditis and micropapillary thyroid carcinoma as well as diseases not related to the thyroids such as small cell lung carcinoma, different neuroendocrine tumors, chronic renal insufficiency, pernicious anemia, the Zollinger Edison syndrome and pancreatitis.\(^18\)

The utility of PET/PET-CT studies with \(^{18}\)F-FDOPA in the detection of neuroendocrine tumors including MTC should be highlighted, despite its not very extended use, being especially useful in differentiated tumors which, in turn, present less uptake of FDG.\(^19\)

The use of FDG-PET presents a series of limitations such as the spatial resolution of the tomography in small-sized lesions as well as the low rate of proliferation of some endocrine tumors which may cause normal FDG uptake in tumoral tissue. The results of the PET were not compared with the findings of the conventional imaging techniques since the nuclear physicians knew the results of these techniques when PET was performed.

**Conclusions**

The use of \(^{18}\)F-FDG-PET in our study presented an elevated S of 88%, being ideal for the detection of residual disease, occult recurrence or metastasis in patients with MTC with elevated calcitonin levels and negative imaging techniques after thyroidectomy. This has an important clinical impact of 45.2%, thereby allowing modification of the therapeutic management of the patients with recurrence of MTC and avoiding unnecessary surgery and identifying the patients who may benefit from radical intention-to-cure or less radical surgery and/or complementary therapies.
Conflict of interests

The authors declare no conflict of interests.

References