Original article

Comparison of $^{99m}$Tc-sestamibi and $^{11}$C-methionine PET/CT in the localization of parathyroid adenomas in primary hyperparathyroidism


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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 usefulness of $^{11}$C-methionine PET/CT (MET) in the localization of the parathyroid adenomas and to compare the results with those obtained with the conventional technique in double-phase $^{99m}$Tc-sestamibi scintigraphy (MIBI). We evaluated the optimal timing to acquire MET images.

Material and methods: A prospective study that included 14 patients (mean age: 65.5 ± 9.7 years) with primary hyperparathyroidism (PH) who underwent surgery was performed. Mean serum iPTH was 215.8 ± 108 pg/mL and serum calcium 10.8 ± 0.9 mg/dL. MIBI (planar and SPECT) was obtained 10 min and 2–3 h after injection of 740 MBq (20 mCi) of $^{99m}$Tc-sestamibi. MET was obtained 10 min and 40 min after injection of 740 MBq (20 mCi) of $^{11}$C-methionine. MIBI and MET images were visually evaluated and compared. A score for 10 min and 40 min MET images from 0 (no abnormal uptake) to 3 (intense uptake) was assigned.

Results: MIBI and MET were positive and concordant in 11/14 patients and in 10 of them the parathyroid adenoma was correctly localized. In 3/14 MIBI was positive and MET negative (MIBI correctly localized the parathyroid adenoma in 2 of them). According to the timing of MET imaging acquisition, the 10 min and 40 min acquisition showed the same score in 10 patients, it was higher at 10 min acquisition in 3 and in 1 the parathyroid adenoma was only detected at 40 min acquisition.

Conclusion: MIBI remains the technique of choice for the localization of parathyroid adenomas in patients with PH. MET may play a complementary role in selected patients. Delayed acquisition should be included in the MET protocol when the early acquisition is negative.

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Comparación del $^{99m}$Tc-sestamibi y $^{11}$C-metionina PET/CT en la localización del adenoma de paratiroides en el hiperparatiroidismo primario

R E S U M E N

Objetivos: Evaluar la utilidad de la $^{11}$C-metionina PET/CT (MET) en la localización de adenoma de paratiroides comparado con la técnica convencional en doble fase con $^{99m}$Tc-sestamibi (MIBI). Evaluar el tiempo adecuado para la adquisición de imágenes MET.

Material y métodos: Este estudio prospectivo incluyó 14 pacientes (edad: 65.5 ± 9.7 años) con hiperparatiroidismo primario (HPTP) sometidos a cirugía. La iPTH fue de 215.8 ± 108 pg/mL y el calcio sérico 10.8 ± 0.9 mg/dL. El MIBI (planar, SPECT) fue realizado a los 10 min y 2–3 horas tras la inyección de 740 MBq (20 mCi) de MIBI. La MET fue realizada 10 min y 40 min tras la inyección de 740 MBq (20 mCi) de MET. Las imágenes fueron evaluadas visualmente y comparadas. Las imágenes con MET a 10 min y 40 min fueron valoradas según el grado de captación (0 [ninguna captación] a 3 [intensa]).

Resultados: MIBI y MET fueron positivos y concordantes en 11/14 pacientes, en 10 de ellos el adenoma de paratiroides fue correctamente localizado. En 3/14 el MIBI fue positivo y la MET negativa (el MIBI localizó correctamente 2). Con respecto al tiempo de adquisición imágenes MET a los 10 min y 40 min se observó la misma puntuación en 10 pacientes, fue mayor a los 10 min en 3 y un paciente sólo fue positivo a los 40 min.

Conclusiones: El MIBI continúa siendo la técnica de elección para la localización del adenoma de paratiroides en pacientes con HPTP. La MET podría tener un papel complementario en pacientes seleccionados. La adquisición tardía de la MET debería ser incluida cuando la imagen precoz sea negativa.

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Introduction

Primary hyperparathyroidism (PH) is characterized by the increased production of parathyroid hormone (PTH) and is the most often cause of hypercalcemia. It is caused by a solitary parathyroid adenoma in 80–85% of cases, by hyperplasia in 15% and by
carcinoma in approximately 1% of cases.\textsuperscript{1,2} The diagnosis of PH is established by biochemical data (elevated serum PTH and calcium levels) and the treatment of choice is surgical resection. Currently, and, in order to reduce the extent and duration of the intervention and the post-operative morbidity, a minimal invasive surgery focused in the resection of the enlarged gland is the ideal approach.\textsuperscript{3} However, the success of the surgical procedure depends on the accurate preoperative localization of the abnormal glands. The anatomical imaging techniques (ultrasonography, computerized tomography and magnetic resonance imaging) show low sensitivity.\textsuperscript{4-6}

The improvement of the nuclear medicine imaging techniques has greatly contributed to the development of the minimally invasive surgery and, in this context, double-phase \textsuperscript{99m}Tc-sestamibi scintigraphy (MIBI) is a widespread technique generally applied for the preoperative localization of the gland responsible of the PH with sensitivities up to 90\%\textsuperscript{7,8} specially when SPECT and SPECT/CT is applied.\textsuperscript{9-11}

Other radiotracers have been used for the localization of parathyroid adenomas. Methionine labeled with \textsuperscript{75}Selenium was introduced in 1964 and was the first radiotracer used for in vivo imaging of the hyper functioning parathyroid glands.\textsuperscript{12,13} However, suboptimal results were obtained due to the physical characteristics of the \textsuperscript{75}Selenium and the imaging technology used.

The introduction of the new PET instrumentation along with the general acceptance of the technique in oncology raised the possibility of evaluating new PET radiotracers for the preoperative localization of the parathyroid adenoma.

The first PET radiotracer used for this purpose was the \textsuperscript{18}F-fluorodeoxyglucose (FDG), widely applied in oncological processes. Only a few studies applying FDG in PH have been published\textsuperscript{14,15} and only in one of them a direct comparison with MIBI was performed showing a higher sensitivity but a lower specificity for FDG.\textsuperscript{16}

Although methionine was previously applied for the detection of parathyroid adenomas, the availability of methionine labeled with \textsuperscript{11}Carbon deserves a new evaluation of that radiotracer.

The first approaches to \textsuperscript{11}C-methionine-PET were done in the mid-1990s, with contradictory results. Hellman et al. described low sensitivity probably related to the heterogeneity of the population evaluated\textsuperscript{17} and Beggs and Hain reported a greater sensitivity in a selected group of patients with negative conventional imaging techniques.\textsuperscript{18}

More recently, the hybrid PET/CT technology has been included to the diagnostic arsenal available for the preoperative study of patients with hyperparathyroidism. However, only a few reports using \textsuperscript{11}C-methionine PET/CT (MET) have been published, although based in different designs, populations and methodologies.\textsuperscript{19-21} In this context, a preoperative evaluation of the contribution of MET compared to MIBI in the parathyroid localization is still needed.

Another interesting issue concerns the acquisition protocol of images. For MIBI, this aspect has been previously assessed in detail; however, for MET only a few authors investigated this issue that should be evaluated in a deep way.

Our aim was to evaluate the usefulness of MET in the localization of pathological parathyroid glands in patients with PH and to compare the results with those obtained with MIBI. Also, we evaluated the optimal timing of MET imaging.

**Material and methods**

**Patients**

This prospective study included 14 patients (10 women, mean age: 65.5 ± 9.7 years) with biochemical evidence of PH and underwent surgical treatment. The mean serum intact parathyroid hormone (iPTH) was 215.8 ± 108 pg/mL (normal range, 10–55) and the mean serum calcium was 10.8 ± 0.9 mg/dL (normal range, 8.1–10.4). In all patients a preoperatively MIBI and MET were performed. The interval between both scans was 25.2 ± 46.3 days. Nine patients had concomitant multinodular goiter and in 2 patients a previous surgery was performed and showed recurrent PH. An additional thyroid scan with \textsuperscript{99m}Tc-perchtenenate using a pin-hole collimator was acquired if necessary.

Written informed consent for MET scan was obtained in all patients. Surgery and histopathological analysis were performed in the 14 patients; in all of them a parathyroid adenoma was found and 2 of them showed a concomitant differentiated thyroid cancer.

**Double-phase \textsuperscript{99m}Tc-sestamibi scintigraphy protocol**

MIBI was acquired after intravenous injection of 740 MBq (20 mCi) of \textsuperscript{99m}Tc-sestamibi (Cardiolite, Bristol-Myers Squibb, Munich, Germany; labeling efficiency more than 95\%), using a double-headed Siemens E.cam gammacamera equipped with low-energy, parallel hole high-resolution collimators. Anterior planar images (matrix: 128 × 128 and 10 min/image) of the neck and thorax at 10 min and 2–3 h after injection were acquired. Also, an early SPECT was acquired immediately after the early planar image (matrix: 128 × 128, 64 projections, 20 s/projection).

**\textsuperscript{11}C-methionine PET/CT protocol**

The \textsuperscript{11}CO\textsubscript{2} was produced in a PETtrace cyclotron (General Electric, Uppsala, Sweden) by the nuclear reaction \textsuperscript{14}N(p,\alpha) \textsuperscript{11}C. The \textsuperscript{11}C-methionine was synthesized in a Tracerlab FX\textsubscript{N} module (General Electric, Uppsala, Sweden) by direct methylation of precursor L-Homocysteine thiolactone hydrochloride (ABX, Germany).

MET was acquired 10 min and 40 min after intravenous injection of 740 MBq (20 mCi) of \textsuperscript{11}C-methionine, using a Biograph LSO Pico3D Siemens equipment. First, a non-contrast low dose CT for attenuation correction and anatomical localization was performed. Then, PET scan was acquired early at 10 min and delayed at 40 min after injection, including the neck and thorax (two beds, 3 min/bed in the early scan and 4 min/bed in the delayed scan).

**Image analysis**

A separate visual analysis of MET and MIBI images was done by two specialists in nuclear medicine, blinded to clinical and laboratory data.

First of all, MIBI and MET images were classified into negative and positive for parathyroid adenoma and, if positive, the localization of the adenoma was specified. The results obtained with both techniques were compared with the histopathological result. Then, MET images at 10 min and 40 min were evaluated separately, by grading from score 0 (no abnormal uptake) to 3 (intense uptake suggesting a parathyroid adenoma) and both results were compared.

**Results**

In Table 1 we describe the MIBI and MET results in the 14 patients. MIBI and MET were positive in 11 of the 14 patients (78.6\%). A parathyroid adenoma was correctly localized by both studies in 10 of these 11 patients (90.9\%) (Fig. 1) and incorrectly in 1 (9.1\%). One of these 10 parathyroid adenomas correctly localized was found in an ectopic retro-esophageal location (Fig. 2). On the other hand, MIBI was positive and MET negative in 3 of the 14 patients (21.4\%), in 2 of them MIBI correctly localized the parathyroid adenoma (Fig. 3) but in 1 the localization was incorrect.
Fig. 1. (a) Axial, sagittal and coronal $^{99m}$Tc-MIBI-SPECT views show an abnormal uptake below the left thyroid lobe, (b) axial, sagittal and coronal PET and (c) fused $^{11}$C-methionine PET/CT views show the same abnormal uptake corresponding to a left inferior parathyroid adenoma successfully excised (arrows).

Fig. 2. (a) Axial, sagittal and coronal views of $^{99m}$Tc-MIBI-SPECT, (b) PET and (c) fused $^{11}$C-methionine-PET/CT show an abnormal focal uptake localized in the retro-esophageal region corresponding to an ectopic parathyroid adenoma (arrows). Also, a diffuse and higher uptake was seen in the enlarged thyroid gland.
Table 1
MIBI and MET results in 14 patients and surgical localization of the parathyroid adenoma.

<table>
<thead>
<tr>
<th></th>
<th>No. patients</th>
<th>Correct localization</th>
<th>Incorrect localization</th>
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<tr>
<td>MIBI+ and MET+</td>
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<td>10</td>
<td>1</td>
</tr>
<tr>
<td>MIBI+ and MET−</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>12</td>
<td>2</td>
</tr>
</tbody>
</table>

MIBI 99mTc-sestamibi scintigraphy; MET, 11C-methionine PET/CT.

The sensitivity achieved for the correct localization of the pathological gland was 100% for MIBI and 76.9% for MET and the positive predictive value was 85.7% and 90.0%, respectively (Table 2).

We also analyzed the results obtained for MET according to the timing of imaging. In 10/14 patients (71.4%) both acquisitions (early at 10 min and delayed at 40 min) showed the same score (in 3 of them the score was 0 and in 7 it was 3). In the other 4 patients (28.6%) the score was different, in 3 the score was higher in the early acquisition and in 1 the parathyroid adenoma was only detected in the delayed acquisition (Table 3).

Discussion

The results reported in this paper correspond to the evaluation of an old molecule, methionine, previously applied labeled with 75Selenium and using old imaging technology like rectilinear scanners and gammacameras. However, in our case the label of the same molecule with a positron emitter isotope like 11Carbon along the introduction of a new imaging technology like PET/CT offers a new framework for a new radiotracers 11C-methionine. Its application for the localization of parathyroid adenoma, however, offers a difficult challenge as there is already a well established cheap and accurate technique like MIBI. Therefore, such a sophisticated technique like PET/CT should justify its use in the clinical setting.

Table 3
MET score, grading from 0 to 3, at the early (10') and delayed (40') acquisition.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Early acquisition</th>
<th>Delayed acquisition</th>
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<tbody>
<tr>
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MET, 11C-methionine PET/CT.
Although some studies have been published using $^{11}$C-methionine as a radiotracer, most of them used PET technology\textsuperscript{17,18,22-25} and in only a few studies PET/CT was applied, and only in one of them the design was prospective and a comparison of MET and MIBI results for the accurate preoperative localization of parathyroid adenomas was specifically addressed.\textsuperscript{26} Our results showed a sensitivity of 100\% for MIBI in the localization of parathyroid adenomas, higher to those obtained by Tang et al.\textsuperscript{26} However, our sensitivity for MET was lower (76.9\% vs. 92\%). These results could be related to different causes, such as the acquisition protocols used, the sample size and the different population included.

MIBI and MET correctly localized the parathyroid adenoma in 10 patients. One of these 10 parathyroid adenomas was correctly localized, both for MIBI and MET, in the retro-esophageal space corresponding to an ectopic parathyroid gland (Fig. 2). In this patient, the anatomic information provided by the CT component of the PET/CT was essential to address surgery. In two of these 10 patients a parathyroid adenoma was excised in a previous successful surgery, however several months later the hyperparathyroidism recurred with high PTH and calcium serum levels, and a new sestamibi scintigraphy was requested. MIBI and MET scans correctly localized a new parathyroid adenoma that was successfully excised, with normal iPTH after one year of follow-up.

One of the 14 patients was MIBI and MET positive at the same localization. However, this finding was not confirmed during surgery, and a contra-lateral parathyroid adenoma was excised with normalization of the iPTH level. One explanation for this false result is that the excised parathyroid adenoma had a small size (1.2 cm $\times$ 0.7 cm $\times$ 0.4 cm) and weight (190 mg). It is well known that the size and weight of the parathyroid adenoma may affect the accuracy of the preoperative localization with MIBI.\textsuperscript{27} A correlation between $^{11}$C-methionine using PET and the weight and size of the parathyroid adenoma was also reported and a weight of 200 mg and a diameter of 7.5 mm have been suggested as the minimum required for its detection.\textsuperscript{22,25} For the abnormal uptake detected on the contralateral side of the neck by both radiotracers, the very likely explanation is that the patient had several nodules involving both thyroid lobes (identified in a previous ultrasound neck study and $^{99m}$Tc-pertechnetate thyroid scintigraphy) and also a Hashimoto’s thyroiditis. This is not a new finding as lymphocytic thyroiditis has been reported as the cause of false positive results for MIBI and FDG.\textsuperscript{15} According to some authors, any inflammation could also be the cause of MET uptake and should be taken into account when interpreting parathyroid images.

Three of the 14 patients were MIBI positive and MET negative and, in 2 of them MIBI correctly localized the parathyroid adenoma. In the other one the abnormal MIBI uptake was contralateral to the parathyroid adenoma, that is, in the other side of the neck; in this sense, the MIBI scan was false positive. The iPTH and calcium levels after surgery and during the follow-up remained normal.

Although there are many studies which approached in depth the MIBI acquisition protocol\textsuperscript{16,28-31} the topic did not deserve the same interest when it applies to MET. Sundin et al. studied the kinetics of $^{11}$C-MET and found that it is taken up by parathyroid adenomas that reach the peak of activity in the first minute post injection and decline over the next 5 min to half of the activity.\textsuperscript{22} These results were reproduced in other groups.\textsuperscript{24,26} The image quality is dependent on many factors such as the amino acid influx into the stimulated parathyroid tissue, the ratio target tissue/background and the histopathological features of the parathyroid lesions. In our study, we compared the MET results obtained with both acquisitions, at 10 min (early) and 40 min (delayed), in order to evaluate the diagnostic efficacy. The early and delayed acquisitions showed the same score in most of the patients (10 of 14). Only in 4 of the 14 patients the intensity of the uptake showed some differences between both acquisitions as in 3 it was one grade higher at the early acquisition. The other patient only showed uptake at the delayed acquisition and, therefore, although the acquisition at 10 min allows a more confident report, the delayed should be also included in the MET protocol.

In conclusion, MIBI remains the technique of choice for the localization of parathyroid adenomas in patients with PH. MET may have a complementary role in selected patients in whom MIBI fails to correctly localize the parathyroid adenoma. The delayed acquisition should be included in the MET protocol when the early acquisition is negative.

Conflict of interest

The authors declare no conflict of interest.

References


