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Diagnostic efficacy and discriminatory capacity of positron emission tomography combined with axial tomography of adrenal lesions☆

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ABSTRACT

Introduction: The usefulness of 18fluorodeoxyglucose positron emission tomography combined with axial tomography (PET-CT) in diagnosing whether adrenal tumours are benign or malignant is assessed.
Material and methods: A retrospective study conducted between June 2005 and May 2009 on a consecutive series of patients on whom a PET-CT scan was performed to study suspected malignant adrenal disease. Focal uptakes were assessed, along with the maximum standard uptake value (SUV), and the ratio of the maximum adrenal/hepatic value. The sensitivity, specificity, positive and negative predictive value of the test, the maximum adrenal uptake values and the ratio for those where the diagnostic yield was maximum.
Results: Fifteen patients were included. The final diagnosis showed malignancy in eight and seven were benign. Ten patients had adrenal uptake: three in benign lesions and seven in neoplasias, with a mean uptake value of 6.3 (3.2 in benign lesions and 9.0 in malignant lesions). The mean adrenal/hepatic ratio was 1.8 (0.9 in benign and 2.6 in malignant lesions). When the presence of adrenal uptake is associated with a final diagnosis of malignancy, we obtained a sensitivity of 87.5%, a specificity of 57.1%, and a positive and negative predictive value of 70% and 80%, respectively. An SUV cut-off value of 6, or an adrenal/hepatic uptake ratio of 2, gave a sensitivity of 75%, a specificity of 100%, and a positive and negative predictive value of 100% and 77.7%, respectively.
Conclusions: PET-CT has a high ability to discriminate between benign and malignant lesions in the adrenal disease studied.

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Efectividad diagnóstica de la tomografía por emisión de positrones con [18]fluorodeoxiglucosa asociada a tomografía axial en la discriminación de benignidad o malignidad de las lesiones suprarrenales

Palabras clave:
Glándulas suprarrenales
Tumores de las glándulas suprarrenales
Tomografía por emisión de positrones
Pruebas diagnósticas
Sensibilidad
Especificidad
Valor predictivo positivo
Valor predictivo negativo

R E S U M E N

Introducción: Se analiza la utilidad de la tomografía por emisión de positrones asociada a la tomografía axial computarizada (PET-TAC) en el diagnóstico de benignidad o malignidad de lesiones suprarrenales.

Material y métodos: Estudio retrospectivo, entre junio de 2005 y mayo de 2009, de una serie consecutiva de pacientes a los que se les realizó una PET-TAC para el estudio de patología suprarrenal con sospecha de malignidad. Se valoraron la presencia de captaciones focales, su valor estándar de máxima captación (SUV), y la ratio del valor máximo suprarrenal/hepático. Se analizó la sensibilidad, especificidad, valor predictivo positivo y negativo de la prueba, y los valores de captación máxima adrenal y la ratio para los que la rentabilidad diagnóstica fue máxima.

Resultados: Se incluyeron 15 pacientes. El diagnóstico final reveló malignidad en ocho y benignidad en siete. Diez pacientes presentaron captación suprarrenal: tres en lesiones benignas y siete en neoplasias, con un valor de captación medio de 6,3 (3,2 en benignas y 9 en malignas). La ratio media suprarrenal/hepático fue de 1,8 (0,9 en lesiones benignas y 2,6 en malignas). Cuando se relaciona la presencia de captación suprarrenal con el diagnóstico final de malignidad, obtuvimos una sensibilidad del 87,5%, especificidad del 57,1%, valor predictivo positivo del 70% y negativo del 80%. Un valor de corte de SUV de 6, o una ratio de captación suprarrenal/hepática de 2, proporciona una sensibilidad de 75%, especificidad de 100%, valor predictivo positivo de 100% y negativo de 77,7%.

Conclusiones: La PET-TAC posee una alta capacidad para discriminar entre benignidad o malignidad en la patología adrenal estudiada.

Introduction

Since the start of 1980s, the availability of computerised axial tomography (CAT) and magnetic resonance imaging (MRI) has meant that adrenal pathology is characterised better, and "incidental" lesions are detected more frequently during the study of other pathologies. As in occurs when locating other lesions, the distinction between benign and malignant is a critical issue.[1]

Adrenal *incidentalomas* are detected in 0.4%-0.5% of patients who undergo abdominal CAT scans. Most of these lesions are benign and non-functioning. This represents 70%-94% of adrenal lesions identified in patients with no history of cancer, and 7%-68% of those detected in patients with cancer. The diagnostic possibilities of these processes are numerous, with cortical adenomas being the most common condition. Metastases are detected in up to 21% of patients with adrenal lesions who have no prior history of tumours, and in 32%-73% of those who have this antecedent.[2]

The first step when finding an adrenal lesion is to perform a large enough biochemical study to rule out endocrine hypersecretion (hypercortisolism, hyperaldosteronism, phaeochromocytoma). There is abundant literature on imaging techniques that can be used for characterising these lesions,[3] including CAT, MRI, scintigraphy, tomography (*single photon emission tomography* with CAT: SPECT/CT) and positron emission tomography (PET) with or without CAT.

CAT scan is the technique that usually reveals the existence of an adrenal *incidentaloma*. Characteristics related to the uptake, retention, and the intravenous contrast medium washout are important to distinguish whether these lesions are benign or malignant.[4] Today's MRI provides better spatial resolution and discriminative power similar to CAT scaners.[5] Scintigraphy with ^{131}I-19-iodocholesterol, and with metaiodobenzylguanidine (MIBG) has allowed for the functional study of cortical and medullary tumours, respectively.[6] Uptake of these tracers in a adrenal mass suggests a benign tumour while a space-occupying lesion without uptake would potentially be malignant. Technical limitations of planar scintigraphy related to the lack of spatial resolution have improved with the application of SPECT technology and its association with the anatomical information provided by CAT.[7]

The 18F-fluorodeoxyglucose (^{18}F-FDG) is a radiolabeled glucose analogue, which identifies tissues, such as tumours, with an increased metabolic activity for glucose.[1,8] PET has been used with this tracer to identify primary or metastatic malignant tumours of the adrenal gland.[1,2,9,10] Its diagnostic performance is enhanced when used in conjunction with axial tomography.[11] Other radiolabeled molecules have been used, such as ^{11}C-epinephrine, ^{11}C or ^{18}F-hydroxy-epinephrine, ^{18}F-fluorodopamine, ^{18}F-dihydroxyphenylalanine, and somatostatin analogues such as octreotide or pentetreotide. All of these substances have a high sensitivity for detecting tumours derived from the adrenal medulla, but are less capable of discriminating between benign and malignant lesions compared with ^{18}F-FDG.

The aim of this study is to analyse how useful ^{18}F-FDG PET/CT scan is in distinguishing between benign and malignant adrenal lesions that are suspected of being malignant due to lesion characteristics observed in other diagnostic imaging techniques or from the patient history.

Patients and method

Patients

This is a retrospective analysis of a series of patients with adrenal lesions suspected of malignancy who underwent a PET-CT scan as part of their diagnostic study. The analysis was conducted in a university hospital during the period between June 2005 and March 2009. We included patients with extra-adrenal neoplasms who had adrenal lesions detected through other imaging tests during their extension study or follow-up. Furthermore, we included patients with primary adrenal lesions that were suspected of malignancy due to their size (greater than 6cm), their clinical behaviour, hormonal hypersecretion biochemical data, and imaging test data (heterogeneous pattern, irregular edges, and suspicion of local infiltration or metastatic spread). The search was conducted in the adrenal pathology database maintained by the endocrine surgery section of the hospital's general surgery department.

The following data was assessed: age, sex, past medical history, results of other imaging techniques, indication and results of the PET-CT, preoperative and final diagnosis based on the histopathological study after adrenalectomy, and patient progression data. Exclusion criteria included contraindications to PET-CT (uncontrolled diabetes mellitus, patient refusal to undergo procedure, pregnancy and breastfeeding) and patients where there was no evidence for a definite diagnosis of the lesion.

PET-CT scan

The scan was conducted in accordance with our hospital's protocol. A 370 MBq dose of ^{18}F-FDG was administered intravenously. Patients were requested to avoid solid foods for at least 6 hours prior to the procedure and to be under conditions of overhydration. Images were acquired in a Siemens Biograph® 16 PET-CT scanner (Knoxville, Tennessee) after 45-60min of sensorimotor rest. The original images were reconstructed topographically using iterative algorithms (OSEM, 2 iterations, 8 subsets) after attenuation correction and were presented in orthogonal planes (axial, coronal and sagittal) along with CT fusion images of the areas of interest.

Image analysis

Two nuclear medicine specialists (ARF and RSS), who were unaware of the definite diagnosis, analysed and reached consensus on the presence of focal uptake in the adrenal gland in all the cases. In addition, they calculated the maximum standard uptake value (SUV) of the adrenal lesion, analysing its central area if uptake was homogeneous, or the most uniform zone if it was heterogeneous. Lastly, with the aim of improving the objectivity and reproducibility of the decision, the relationship between maximum SUV (SUVmax) of the adrenal lesion and SUVmax of the liver was quantified. This was obtained from an area of the parenchyma of the right lobe that was homogeneous and free of visible tumour disease.

Data analysis

All numerical variables are expressed as arithmetic means (standard deviation). All positive PET lesions that were ultimately benign were considered false positives, with malignant tumours the true positives. Negative PET lesions that were ultimately benign were considered true negatives and were considered false negatives if they were ultimately malignant. We calculated the sensitivity (S), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) for the test for deetecting malignant adrenal disease. These were calculated qualitatively (presence or absence of adrenal uptake) and quantitatively (adrenal SUVmax value and adrenal SUVmax/liver SUVmax ratio).[9,10]

The differences in proportions of enhancing lesions in adrenal masses in PET that were ultimately benign or malignant were analysed using Fisher's exact test. The mean differences (adrenal SUVmax and adrenal/liver SUVmax ratio) were tested using the U statistic of the nonparametric Mann-Whitney test. The discriminative power of the quantitative assessment of the PET-CT was determined using receiver-operating characteristic curves (ROC) that compare the sensitivity of the test against the inverse of its specificity for all possible cutoff values of adrenal SUVmax and the adrenal/liver SUVmax ratio.[12] We analysed the values for which the diagnostic yield was highest. The statistical analysis was done with SPSS v.15.0 software package (SPSS Iberia, Madrid, Spain).

Results

During the period between June 2005 and March 2009, 15 patients of the 44 who underwent surgery for adrenal masses were included in the study. The anatomical and clinical characteristics and the results of the series' PET-CT are summarised in Table 1. The mean age of patients in the series was 53.6 (14) years with a male to female ratio of 2:1. Six patients were indicated for a PET-CT after the follow-up of a previously treated extra-adrenal neoplasm: two squamous cell carcinomas of the lung, an osteosarcoma, a ductal carcinoma of the breast, carcinoma of the kidney and a rectal mucinous adenocarcinoma. For two patients, the adrenal mass was discovered in an extension study of an extra-adrenal primary neoplasm (a gastric adenocarcinoma and a pancreatic gastrinoma) and for the seven remaining it was discovered as a result of suspicion of an adrenal primary neoplasm.

Table 1 – Anatomical/clinical characteristics of patients and results of the PET-CT

Patient	Age	Sex	Clinical presentation	Lesion size, cm	Clinico-pathologic diagnosis	CAT	Adrenal uptake	Adrenal SUVmax	ASUVmax/LSUVmax ratio
1	51	F	Hormonal hyperfunction	5	B (Phaeoc)	NP	Positive	3.8	1.3
2	52	F	Follow-up of extra-adrenal neoplasm	2	B (adrenal cyst)	NP	Negative	2.7	0.8
3	70	M	Hormonal hyperfunction	2	B (Phaeo)	F	Positive	4.2	1.4
4	68	M	Tumour syndrome	3	B (Adenoma)	SB	Positive	5.4	1.2
5	40	M	Hormonal hyperfunction	5	B (Adenoma)	SB	Negative	3.9	1.0
6	55	F	Follow-up of extra-adrenal neoplasm	3	B (Adenoma)	SB	Negative	1.1	0.3
7	64	M	Hormonal hyperfunction	12	B (Phaeo)	SM	Negative	1.3	0.4
8	36	F	Extra-adrenal neoplasm extension study	4	MN (metastasis of pancreatic gastrinoma)	SM	Positive	3.0	1.1
9	48	M	Follow-up of extra-adrenal neoplasm	2	MN (carcinoma metastasis in the lung)	SM	Positive	7.9	2.2
10	35	M	Tumour syndrome	18	MN (adrenal carcinoma)	SM	Positive	9.7	3.5
11	73	M	Tumour syndrome	10	MN (adrenal carcinoma)	SM	Positive	16.3	3.9
12	43	M	Hormonal hyperfunction	5	MN (adrenal carcinoma)	SM	Positive	10.4	2.8
13	72	M	Extra-adrenal neoplasm extension study	7	MN (gastric carcinoma metastasis)	SB	Positive	10.0	2.8
14	29	F	Tumour syndrome	11	MN (osteosarcoma metastasis)	SM	Negative	3.7	1.1
15	68	M	Follow-up of extra-adrenal neoplasm	5	MN (rectal carcinoma metastasis)	SB	Positive	11.3	3.9

ASUVmax indicates maximum adrenal standard uptake value; B, benign; CAT, computerised axial tomography; F, female; LSUVmax, maximum liver standard uptake value; M, male; MN, malignant neoplasm; NP, not performed; Phaeo, phaeochromocytoma; SB, suspicion of benignity; SM, suspicion of malignancy; SUVmax, maximum standard uptake value.

An abdominal CAT was performed on 13 patients with a sensitivity of 75% for detecting malignancy and a specificity of 60%. Ultrasound, which was performed in six cases, showed sensitivity for malignancy detection of 60% and a specificity of 100%. Scintigraphy with MIBG and MRI were both performed on only four occasions on patients with lesions that were ultimately benign.

Thirteen patients underwent surgery. Twelve adrenalectomies and one biopsy, in the case of an unresectable adrenal carcinoma, were performed. Two patients did not undergo surgery due to extra-adrenal metastatic spread (an adrenal carcinoma and a poorly differentiated non-microcytic lung carcinoma). The preoperative diagnosis in six cases was adrenal metastases, phaeochromocytoma and adrenal carcinoma on four occasions, and *incidentaloma* in the last patient. The final diagnosis, from the histopathology or evolution, showed malignancy in eight cases: three adrenal carcinomas and five metastatic lesions. Seven patients had benign lesions: three adenomas, three phaeochromocytomas and one adrenal endothelial cyst.

There was adrenal uptake in PET-CT in 10 patients: three in lesions that were benign in the end and seven in malignant neoplasms. Table 2 shows the results of the qualitative study, analysing the presence of adrenal uptake, which obtained a sensitivity of 87%, a specificity of 57% and a positive and negative predictive value of 70% and 80%, respectively. The study of the proportion of enhancing and non-enhancing lesions between ultimately benign or malignant masses did not reveal significant differences (*P*=.11, Fisher's exact test).

The average adrenal SUVmax was 6.3 (4) with the average in benign lesions being 3.2 (1) and 9 (4) in malignant tumours. These differences were statistically significant (*P*=.02, Mann-Whitney test). The average adrenal/liver SUVmax ratio was 1.8 (1) with the average in benign lesions being 0.9 (0.4)

Table 2 – Analysis of the presence or absence of adrenal uptake in the PET-CT

	Benign lesions	Malignant lesions	Total
Presence of adrenal uptake	3	7	10
Absence of adrenal uptake	4	1	5
Total	7	8	15

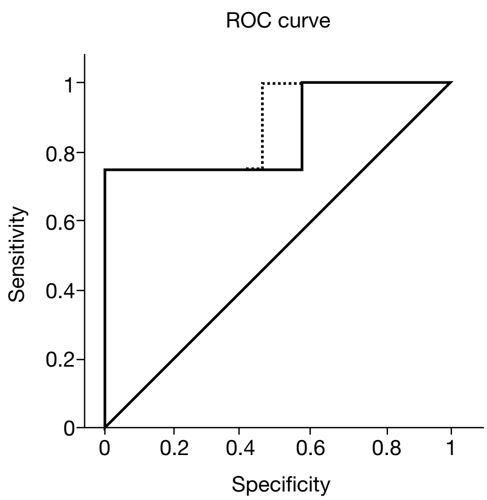

Figure 1 – ROC curves generated for the adrenal SUVmax and adrenal/liver SUVmax ratio parameters. ROC indicates receiver-operating characteristic curves.

and 2.6 (1) in malignant tumours. These differences were also statistically significant (P=.01, Mann-Whitney test). No patient with a lesion that was ultimately malignant had an adrenal uptake that was less than the liver uptake.

By quantitatively assessing this uptake using adrenal SUVmax, we obtained an ROC curve (Figure 1, solid line) with good discrimination between benign and malignant lesions and an area under the curve of 0.85 (95% confidence interval: 0.65-1.06). The adrenal/liver SUVmax ratio analysis (Figure, dashed line) improved this discrimination, with an area under the curve of 0.89 (95% confidence interval: 0.72-1.06). A SUV cutoff value of 6 or an adrenal/liver SUV ratio of 1.8 gave a sensitivity of 75%, a specificity of 100%, and a positive and negative predictive value of 100% and 78%, respectively. The six lesions with values greater than these cutoff points were ultimately malignant. The two malignant lesions that did not exceed these cutoff points were a cystic metastasis of pancreatic gastrinoma and a metastatic lesion of skeletal osteosarcoma, which in the histological study revealed a degree of cell necrosis greater then 90%.

Discussion

In adrenal pathology, it is very important to have reliable imaging techniques for diagnosis that distinguish a lesion's benign or malignant nature. Decisions can, therefore, be made on treatment options, prioritisation on waiting lists for surgery, preoperative preparation, operative session scheduling, surgical approach to employ, etc. Several publications have described procedures to achieve these findings, by CAT and MRI, based on the lipid content of the lesions suggested by their attenuation levels in the CAT and the diminution of signal intensity in the MRI.[10] Although many were well classified, the differences in equipment, calibration, patients' build or physique and lipid content of lesions explain why 12% of tumours that were ultimately malignant were incorrectly classified as benign by CAT and MRI in the Kim et al. study.[13]

Another popular diagnostic technique that should be included in the action algorithms would be inpercutaneous CT-controlled fine needle aspiration cytology (FNAC),[14] or more recently performed with endoscopic ultrasound,[15] in a transgastric position to approach the left adrenal or transduodenal to approach the right. This technique is not without risks,[16] and should not be performed in cases of suspected phaeochromocytoma due to the risk of triggering an adrenergic crisis. In our opinion, FNAC should be now indicated in suspected adrenal metastases in patients with previous history of cancer and an adrenal mass with a low uptake value in PET-CT.

Unlike these techniques, PET is a functional study that detects the metabolism of glucose, which is increased in malignant lesions. The simultaneous use of CAT improves the ability to locate the uptakes. This is difficult for adrenal lesions while only using PET.[9,17] Both in primitive adrenal lesions[9,11] and metastases,[18] PET-CT has been shown in previous studies to have a high discriminative power for determining benignity or malignancy. This power is even greater if a quantitative analysis of uptakes obtained through the SUVmax value is performed. When the interindividual variability is reduced, the benefit is at its highest if the results are weighted against the background uptake via the adrenal/liver SUVmax ratio.[9,17,18] Both in these studies and in our series, these indicators have provided uptake threshold values. All lesions with values above these thresholds were found to be malignant in the end. Therefore, an adrenal/liver SUVmax ratio of 1.45 can distinguish adenomas versus adrenocortical carcinomas in the study by Groussin et al.[9] with a ratio of 1.8 for primitive adrenal gland tumours in the study by Tessonnier et al.[11] With regard to adrenal metastases, Okada et al.[17] found that a value of 1.8 for this ratio had the greatest discriminant value, and Brady et al.[19] reported that no adrenal metastases of lung cancer in their series showed a ratio lower than 2.5. All of this makes this technique a very useful tool to distinguish whether an adrenal lesion is benign or malignant prior to surgery.

This study has several limitations: it was carried out in a single centre, it had a retrospective and non-systematic nature, and there was possible bias in patient selection since it was more diverse than in other groups. However, we believe that the consistency of the results when compared with other studies and the high discriminative power validate our results. We believe that a prospective multicentre study should be designed to further evaluate its usefulness, using the adrenal/liver SUV ratio as a discriminant variable as it has a lower interindividual and intercentre variability. This study, with a greater number of specific cases, would be able to analyse its validity for different types of benign and malignant adrenal lesions (adenomas, phaeochromocytomas, metastases and adrenal carcinomas) and with tracers other than FDG. It would also help identify subgroups of patients with adrenal *incidentalomas* (with or without prior history of cancer) who can be recommended surgical treatment or follow-up with imaging tests.

As a final point, we would like to emphasize the interest of adding PET-CT to the preoperative study protocol of adrenal pathology because of its high discriminative power for determining whether a lesion is benign or malignant. Based on our results and the literature review, we believe that it should be indicated in suspected malignant lesions as well. These suspicions include: patients with a history of cancer, clinical data suggestive of malignancy (pain or abdominal mass, acute onset of symptoms, fever and compressive syndrome), the size of the lesion, the presence of hormonal hypersecretion, or suspicious data in the conventional imaging techniques for diagnosis. These indications should not conflict with the conventional role of CAT, which is essential for the early detection and characterisation of incidentalomas and functioning adrenal masses.

Conflict of interest

The authors affirm that they have no conflicts of interest.

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