Original Article

# Role of $^{18}$F-FDG PET/CT in the differential diagnosis of primary benign and malignant unilateral adrenal tumors

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**Background:** This retrospective study was performed to estimate the clinical role of whole-body positron emission tomography/computed tomography (PET/CT) using 2-[$^{18}$F] fluoro-2-deoxy-D-glucose (FDG) in the differential diagnosis of primary benign and malignant unilateral adrenal tumors.

**Methods:** A total of 64 patients (31 male, 33 female; age range: 3–76 years, mean: 48.5) with a confirmed unilateral adrenal tumor underwent $^{18}$F-FDG PET/CT examination for diagnosis and staging. The whole-body $^{18}$F-FDG PET/CT examination excluded metastasis, and all patients were confirmed by operation and biopsy pathology. Their clinical data and pathological results were collected. On visual analysis of PET/CT imaging, adrenal uptake was based on a three-scale grading system. The region of interest (ROI) was delineated in the liver and the renal lesion site. Standardized uptake value (SUV) measurements were determined on a standardized reconstruction, and the maximum values ($SUV_{max}$) of the lesion and liver were measured. The ratio of tumor to the liver was defined as T/L. Visual interpretation, $SUV_{max}$-receiver operating characteristics (ROC) method, and T/L-ROC method were used to analyze the diagnostic accuracy.

**Results:** A total of 64 lesions (48 benign, 16 malignant lesions) were detected. The visual analysis found that 100% of Grade I cases were benign, 90.9% of Grade II cases were benign, and 65.1% of Grade III cases were benign. The $SUV_{max}$ of malignant lesions (10.0±5.8) was higher than that of benign lesions (5.4±5.3, P<0.05). The T/L was 3.39±1.79 for malignant lesions and 1.99±2.09 for benign lesions (P<0.05). In the differentiation of primary benign and malignant unilateral adrenal tumors, the sensitivity, specificity, and accuracy of the $SUV_{max}$-ROC method (cut-off value =5.65) were 81.25%, 72.91%, 75.00%, and the positive and negative predictive values were 50.00% and 92.11%, respectively. The sensitivity, specificity, and accuracy of the T/L-ROC method (cut-off value =1.52) were 93.73%, 62.50%, 70.31%, and the positive and negative predictive values were 46.88% and 96.77%, respectively.

**Conclusions:** $^{18}$F-FDG PET/CT improved diagnostic accuracy in differentiating primary benign and malignant unilateral adrenal tumors. There was a high negative predictive value, and for positive prediction, other tracer imaging is needed for differential diagnosis.

**Keywords:** $^{18}$F-FDG; positron emission tomography/computed tomography (PET/CT); differential diagnosis; primary adrenal tumor

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## Introduction

Up to 5% of adrenal masses are identified incidentally on abdominal computed tomography (CT) imaging (1), and most of them are benign adenomas in patients without a primary malignancy (2). Although CT and magnetic resonance imaging (using adrenal lesion-specific techniques) are classically utilized in the evaluation of incidental adrenal lesions, 2-[$^{18}$F] fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)/CT is emerging as an adjunctive imaging test for distinguishing benign from malignant adrenal nodules (3-6). PET/CT is an imaging technology that combines functional qualitative and anatomic localization and is widely used to diagnose adrenal diseases.

Discrimination of benign adrenal lesions from malignant masses is very important for choosing the appropriate treatment approach and assessing prognosis. The application of PET/CT for adrenal tumors includes tumor localization and qualitative diagnosis and locating the primary focus of metastatic tumors. Early $^{18}$F-FDG PET/CT studies (2,7-10) reported high sensitivity, specificity, and accuracy for detecting metastatic adrenal lesions. When patients with unilateral adrenal tumors undergo a PET/CT examination and have malignant tumors and metastases from other parts of the body excluded, the differential diagnosis of benign and malignant tumors becomes critical, and few relevant reports.

Our goal was to evaluate 18F-FDG PET/CT's value in the differential diagnosis of benign and malignant tumors in patients with unilateral adrenal masses, where other malignant tumors have been excluded.

## Methods

### *Patients*

Between January 2018 and December 2019, 26,264 $^{18}$F-FDG PET/CT examinations were evaluated retrospectively. A total of 64 patients (31 male, 33 female; age range: 3–76 years, mean: 48.5) with a confirmed unilateral adrenal tumor underwent $^{18}$F-FDG PET/CT examination for diagnosis and staging. The whole-body $^{18}$F-FDG PET/CT examination excluded metastasis, and all patients were confirmed by operation and biopsy pathology. Their clinical data and pathological results were collected. The inclusion criterion was a primary unilateral adrenal tumor without metastasis, and the exclusion criteria were a history of malignancy and metastasis or bilateral adrenal tumors. The Ethics Committee approved the study of the Chinese PLA General Hospital. Informed patient consent was not required.

### *Imaging protocol*

All patients were instructed to fast for at least 4–6 h, and rested for 10–15 min in a quiet environment before an injection of 2.96–4.44 MBq/kg FDG. Blood glucose was controlled within 6.5 mmol/L. PET/CT scanning was performed 60 min after injection, using an integrated scanner (Siemens Biograph 64 PET/CT, Germany). Whole-body CT scanning was performed without intravenous contrast administration, with parameters of 120 kV, 100 mA, the pitch of 0.9, and section thickness of 5 mm. The CT images were used for subsequent PET attenuation correction. After unenhanced CT scanning, PET scanning was performed immediately, and images were acquired from the skull base to the upper thigh with a 2-min acquisition per bed position using a three-dimensional acquisition mode. The point diffusion method (turex) was used for the PET reconstruction, with 3 iterations and 21 subsets. The image matrix was 172 mm × l72 mm, 4-mm half-height and width Gaussian filtering, plus scattering correction.

### *Image analysis*

After receiving other imaging examinations (e.g., ultrasound, CT, MRI), the patient was found to have adrenal space occupying lesion, and then PET/CT examination was recommended. The PET/CT scans were reviewed by two experienced nuclear medicine doctors who did not know either the other imaging results or the clinical information. The region of interest (ROI) was delineated in the liver and the renal lesion site, and the maximum standardized uptake values ($SUV_{max}$) of the renal lesion and liver were measured on a standardized reconstruction. Discrepancies between the two readers, measuring 50% of the larger measurement, were reviewed by a third reviewer. The two most similar $SUV_{max}$ measurements were then used for calculations. On visual analysis of PET/CT images, adrenal uptake was based on a three-scale grading system (2): (I) Grade I: intensity less than that of the liver; (II) Grade-II: intensity equal to that of the liver; (III) Grade III: intensity higher than that of the liver. The ratio of tumor to the liver was defined as T/L. For the visual interpretation, $SUV_{max}$-receiver operating characteristics (ROC) and T/L-ROC methods were used to analyze the diagnostic accuracy.

### *Statistical analysis*

SPSS22.0 was used to analyze the data. Measurement data were expressed as the mean ± standard deviation of the mean (SD). With surgery or biopsy pathology as the gold standard, the patients were divided into benign and

 

**Table 1** Pathologic findings (N=64)

| Lesion type | Pathology | No. of patients | Location | $SUV_{max}$ |
|---|---|---|---|---|
| Benign (n=48) | Pheochromocytoma | 21 | L [9], R [12] | 2.3–25.7 |
| | Adenomas | 13 | L [5], R [8] | 1.5–6.1 |
| | Ganglioneuroma | 6 | L [2], R [4] | 1.5–4.2 |
| | Myelolipoma | 2 | L [2] | 1.6, 2.2 |
| | Calcifying fibrous tumour | 1 | R [1] | 4.3 |
| | Hemangioendothelioma | 1 | L [1] | 4.7 |
| | Hemangioma | 1 | L [1] | 2.2 |
| | Neurogenic tumor | 1 | R [1] | 9.6 |
| | Angiogenic tumor | 1 | L [1] | 1.5 |
| | Schwannoma | 1 | L [1] | 5.6 |
| Malignant (n=16) | Cortical adenocarcinoma | 12 | L [7], R [5] | 3.1–23.9 |
| | Leiomyosarcoma | 3 | L [2], R [1] | 5.1, 5.7, 7.3 |
| | Ewing's sarcoma | 1 | L [1] | 12.4 |

L, left adrenal; R, right adrenal.

**Table 2** Grades of uptake for benign and malignant

| Grade | I (%) | II (%) | III (%) |
|---|---|---|---|
| Benign | 10/10 (100.0) | 10/11 (90.9) | 28/43 (65.1) |
| Malignant | 0/10 (0.0) | 1/11 (9.1) | 15/43 (34.9) |

malignant groups. $SUV_{max}$-ROC method and T/L-ROC method were used to evaluate the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of unilateral adrenal primary tumor diagnosis.

## Results

### *Pathologic findings*

All 64 patients had histopathologically proven adrenal lesions. A total of 64 lesions included 48 benign lesions (left adrenal gland: 22; right adrenal gland: 26) and 16 malignant lesions (left adrenal gland: 10; right adrenal gland: 6) (*Table 1*). Among the benign lesions, pheochromocytoma was the most common, in addition to rare tumors such as ganglioneuroma, hemangioendothelioma, and hemangioma. Cortical adenocarcinoma was the most common of the malignant tumors, which included leiomyosarcoma and Ewing's sarcoma.

### *PET/CT findings*

The visual analysis found that 100% of Grade I cases were benign, 90.9% of Grade II cases were benign, and 65.1% of Grade III cases were benign (*Table 2*). One malignant adrenal lesion (cortical adenocarcinoma) was Grade II.

The $SUV_{max}$ of the malignant lesions (10.0±5.8) was higher than that of the benign lesions (5.4±5.3, $P<0.05$) (*Table 3*). The average size of malignant adrenal lesions was 83.4±27.4 mm, and that of benign lesions was 62.1±33.5 mm ($P<0.05$) (*Table 3*). The T/L of malignant lesions was 3.39±1.79, and that of benign lesions was 1.99±2.09 ($P<0.05$).

In the differentiation of primary benign and malignant unilateral adrenal tumors, the sensitivity, specificity, and accuracy of the $SUV_{max}$-ROC method (cut-off value =5.65) were 81.25%, 72.91%, 75.00%, and the positive and negative predictive values were 50.00% and 92.11%, respectively (*Table 4*). The sensitivity, specificity, and

**Table 3** Size and $SUV_{max}$ values for adrenal benign and malignant lesions

| Lesion type | Parameter | Size (mm) | $SUV_{max}$ |
|---|---|---|---|
| Benign (n=48) | Mean | 62.1 | 5.4 |
| | SD | 33.5 | 5.3 |
| | Minimum | 23.0 | 1.5 |
| | Maximum | 157.0 | 25.7 |
| Malignant (n=16) | Mean | 83.4 | 10.0 |
| | SD | 27.4 | 5.8 |
| | Minimum | 49.0 | 3.1 |
| | Maximum | 126.0 | 23.9 |
| Total (n=64) | Mean | 67.4 | 6.6 |
| | SD | 33.2 | 5.7 |
| | Minimum | 23.0 | 1.5 |
| | Maximum | 157.0 | 25.7 |

SD, standard deviation; $SUV_{max}$, maximum standardized uptake value.

**Table 4** Differentiation between adrenal benign and malignant lesions using maximum standardized uptake value, and tumor/liver standardized uptake value ratios

| | Sensitivity (%) | Specificity (%) | Accuracy (%) | Positive predictive value (%) | Negative predictive value (%) |
|---|---|---|---|---|---|
| $SUV_{max}$ >5.65 | 81.25 | 72.91 | 75.00 | 50.00 | 92.11 |
| T/L $SUV_{ratio}$ >1.52 | 93.73 | 62.50 | 70.31 | 46.88 | 96.77 |

$SUV_{max}$, maximum standardized uptake value; T/L, tumor maximum standardized uptake value/liver maximum standardized uptake value.

accuracy of the T/L-ROC method (cut-off value =1.52) were 93.73%, 62.50%, 70.31%, and the positive and negative predictive values were 46.88% and 96.77%, respectively (*Table 4*). ROC curves generated from $SUV_{max}$ and T/L are illustrated in *Figures 1,2*, respectively.

## Discussion

In patients with incidentally discovered adrenal nodules, so-called adrenal "incidentaloma", FDG PET/CT is emerging as a useful test to distinguish benign from malignant etiology (11). Several reports have documented the effectiveness of standalone $^{18}$F-FDG PET/CT in differentiating benign from malignant adrenal lesions (2,7-10); however, most of those patients had primary cancer. $^{18}$F-FDG PET/CT could be used to stratify patients with a higher risk of malignancy for surgical intervention while recommending surveillance for adrenal masses with low malignant potential (11). Our retrospective study used $^{18}$F-FDG PET/CT to assess the characteristics of primary benign and malignant unilateral adrenal tumors.

Although metastases comprise most malignant adrenal lesions, less common primary adrenal malignancies, such as adrenocortical carcinoma, primary adrenal lymphoma, melanoma, malignant pheochromocytoma, and angiosarcoma, are also occasionally found (11). We reported leiomyosarcoma and Ewing's sarcoma in this study. Benign lesions include adrenocortical adenoma, benign pheochromocytoma, myelolipoma, ganglioneuroma, adrenal cyst, adrenal hemorrhage, and granulomatous disease (11). In addition to these benign lesions, we reported calcifying fibrous tumor, hemangioendothelioma, hemangioma, neurogenic tumor, angiogenic tumor, and schwannoma.

Most benign adenomas show adrenal FDG uptake equal to or less than the liver background (11). However, in our study, 38.5% (5/13) of the benign adenomas had a higher FDG uptake than that of the liver. The main reason for that finding may be that these were atypical adenomas and

 

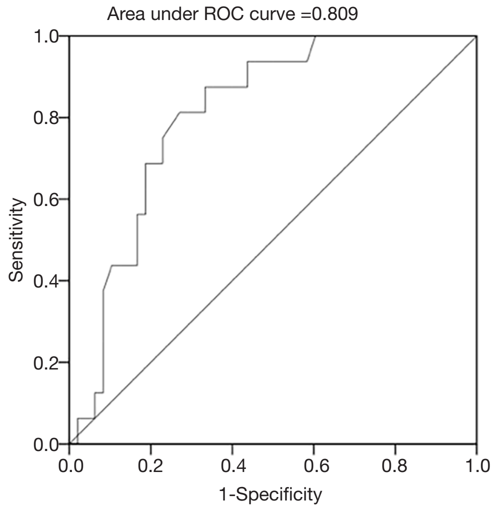


**Figure 1** Receiver operating characteristics (ROC) generated from $SUV_{max}$ information. Using $SUV_{max}$ cut-off value of 5.65 gave sensitivity of 81.25%, specificity of 72.91%, accuracy of 75.00%, negative predictive value of 92.11%, and a positive predictive value of 50.00%.

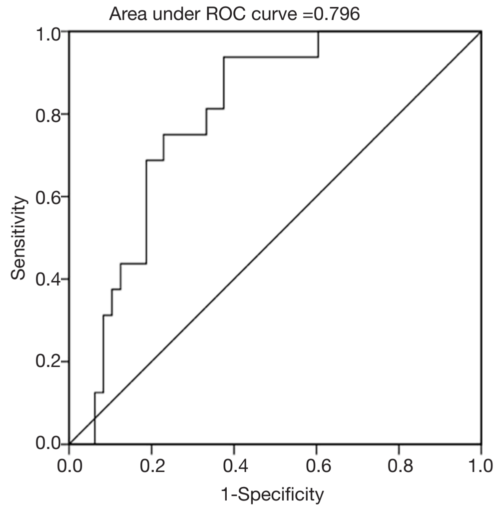


**Figure 2** Receiver operating characteristics (ROC) generated from T/L information. Using T/L cut-off value of 1.52 gave sensitivity of 93.73%, specificity of 62.50%, accuracy of 70.31%, negative predictive value of 96.77%, and a positive predictive value of 46.88%. T/L, tumor to liver ratio.

pheochromocytoma. The SUV and T/L of most benign lesions were small, but for a few benign lesions they were large, even higher than those of the malignant lesions (*Table 1*), which led to an increase in the standard deviation of SUV and T/L for benign lesions. On visual analysis, we found that 95.3% (20/21) of the lesions in Grade I and Grade II were benign. Therefore, when the adrenal lesions are Grade I and Grade II, the mass is likely to be benign. Among the malignant lesions, 93.4% (15/16) were Grade III. Among the benign lesions, 58.3% (28/48) were Grade III, and 74.2% (16/21) of pheochromocytoma and 46.2% (6/13) of adenomas were Grade III. Therefore, when the adrenal lesions are Grade III, the malignant tumor should be differentiated from pheochromocytoma and adenoma.

The diagnostic performance of the $SUV_{max}$-ROC and T/L-ROC methods were similar. Both methods had high sensitivity and negative predictive value but low specificity and positive predictive value. When the $SUV_{max}$-ROC method's cut-off value is >5.65, or the cut-off value of the T/L-ROC method is >1.52, it may help differentiate malignant tumor from pheochromocytoma by combining $^{18}$F-FDG PET/CT with 6-l-$^{18}$F-fluoro-dihydroxyphenylalanine ($^{18}$F-DOPA). $^{18}$F-DOPA is approved in several EU countries for the diagnosis and staging of phaeochromocytoma (12). Therefore, $^{18}$F-FDG combined with $^{18}$F-DOPA should assist in the differential diagnosis of pheochromocytoma from a malignant adrenal tumor. However, sometimes even combination imaging has difficulty differentiating malignant adrenal tumors from adenomas, so pathologic confirmation is essential.

## Conclusions

The advantage of $^{18}$F-FDG PET/CT is to exclude malignant tumors from other parts of the body. $^{18}$F-FDG PET/CT had a high negative predictive value in differentiating primary benign and malignant unilateral adrenal tumors, which means adrenal lesions with low FDG uptake are likely to be benign. Although the positive predictive value of $^{18}$F-FDG was not high, $^{18}$F-FDG combined with $^{18}$F-DOPA can assist the differential diagnosis of malignant adrenal lesions and pheochromocytoma.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.

org/10.21037/qims-20-875). The authors have no conflicts of interest to declare.

*Ethical Statement:* All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of the Chinese PLA General Hospital. Individual consent for this retrospective analysis was waived.



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