Does $^{18}$F-FDG PET/CT add diagnostic accuracy in incidentally identified non-secreting adrenal tumours?

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Abstract

Purpose The widespread use of high-resolution cross-sectional imaging such as computed tomography (CT) and magnetic resonance imaging (MRI) for the investigation of the abdomen is associated with an increasing detection of incidental adrenal masses. We evaluated the ability of $^{18}$F-fluorodeoxyglucose positron emission tomography to distinguish benign from malignant adrenal masses when CT or MRI results had been inconclusive.

Methods We included only patients with no evidence of hormonal hypersecretion and no personal history of cancer or in whom previously diagnosed cancer was in prolonged remission. PET/CT scans were acquired after 90 min (mean, range 60–140 min) after FDG injection. The visual interpretation, maximum standardised uptake values (SUVmax) and adrenal compared to liver uptake ratio were correlated with the final histological diagnosis or clinico-radiological follow-up when surgery had not been performed.

Results Thirty-seven patients with 41 adrenal masses were prospectively evaluated. The final diagnosis was 12 malignant, 17 benign tumours, and 12 tumours classified as benign on follow-up.

The visual interpretation was more accurate than SUVmax alone, tumour diameter or unenhanced density, with a sensitivity of 100% (12/12), a specificity of 86% (25/29) and a negative predictive value of 100% (25/25).

The use of 1.8 as the threshold for tumour/liver SUVmax ratio, retrospectively established, demonstrated 100% sensitivity and specificity.

Conclusion FDG PET/CT accurately characterises adrenal tumours, with an excellent sensitivity and negative predictive values. Thus, a negative PET may predict a benign tumour that would potentially prevent the need for surgery of adrenal tumours with inconclusive conventional imaging.

Keywords Adrenal incidentaloma · Tumour · FDG · PET/CT

Introduction

Incidentally identified adrenal tumours—adrenal “incidentalomas”—are found in up to 5% of abdominal CT scans [1]. Most adrenal incidentalomas are benign non-secreting
tumours even in patients with a known primary malignancy [2, 3]. When adrenal metastases do occur, they are principally related to lung, breast and kidney malignancies and malignant melanomas [2, 3]. Lymphomas represent up to 75% of bilateral adrenal tumours. Overall, adrenocortical carcinomas represent up to 5% of adrenal tumours, with a prevalence that is closely proportional to tumour size (<4 cm: 2%; 4–6 cm: 6%; >6 cm: 25%) [4].

On encountering an adrenal incidentaloma, the first step involves an accurate assessment for clinical or biochemical evidence of hormonal hypersecretion. A thorough clinical history and examination, coupled with blood and urine biochemical investigations, enable the exclusion of pheochromocytomas, Conn’s or Cushing’s syndromes. Tumours found to be hypersecreting require surgery, usually in the form of a laparoscopic adrenalectomy.

In the absence of hypersecretion, a radiological evaluation of malignancy risk is required, which typically begins with an unenhanced CT scan of the abdomen. Some adrenal masses such as myelolipomas, lipid-rich adenomas and adrenal cysts have reassuringly typical benign imaging features. The criteria used to classify adrenal tumour malignancy risk on CT and MRI include unenhanced CT attenuation, enhancement washout on CT or decrease of signal intensity on chemical shift MRI [5–15]. However, despite the optimal use of the best available imaging technology, CT and MRI alone or in combination fail to characterise some adrenal lesions. The options in such cases are varying degrees of intervention ranging from fine-needle aspiration cytology or biopsy to surgery, depending on the size of the lesion [16].

Several studies of FDG PET/CT have shown promising results in the differentiation of benign from malignant adrenal tumours [17–26]. However, these series have involved only patients with a known primary malignancy, and data are more limited on adrenal tumours in non-cancer patients, where conventional imaging has been unhelpful [17, 27].

The purpose of this study was to evaluate the value of FDG PET/CT in predicting the benign or malignant nature of non-secreting adrenal tumours when conventional imaging alone had failed.

### Material and methods

#### Patients

We prospectively evaluated patients with incidental adrenal tumours referred between 2005 and 2007. Inclusion in this study required:

1. The presence of a single or bilateral adrenal tumour
2. No biochemical evidence of hormonal hypersecretion
3. No categorical benign feature on conventional imaging (CT and/or MRI) according with widely accepted criteria (unenhanced density <10 HU in homogeneous tumour; washout calculation on delayed enhanced CT; decrease of signal intensity on chemical shift MRI)
4. The absence of a personal history of cancer or a disease-free interval of at least 5-year post-therapy

Patients with positive FDG PET/CT were referred for surgical treatment.

Patients with negative FDG PET/CT were either referred for surgical treatment or followed up with conventional imaging (CT or MRI) for a minimum of 6 months. For this group, the surgical decision was decided by the surgeon according with the size of the tumour, patient preference, patient age and comorbidities.

The final diagnosis of malignancy (“gold standard”) was based on histological confirmation, when available, or on the follow-up.

#### 18F-FDG PET/CT scan

Patients fasted for at least 6 h before the tracer injection (4 MBq/kg), and scanning began at 60 min post-injection (mean 90 min; range 60–140). 3D images were acquired from the skull base to the upper thigh using a GE Discovery ST PET/CT hybrid scanner (General Electrics Medical System). CT was performed first, from the head to the upper thigh, with 140 kV, 80 mA, and a 5-mm-section thickness, which matched the PET section thickness. Immediately after CT, a PET emission scan that covered the identical transverse field of view was obtained. Acquisition time was 3 min per table position. PET image datasets were reconstructed iteratively (OSEM algorithm) using CT data for attenuation correction. Co-registered images were displayed on a workstation (Xeleris; GE Healthcare), with 3D representation and axial, coronal, and sagittal slices.

#### Image interpretation and quantitative measurements

All PET/CT scan interpretations were performed independently by two experienced nuclear medicine physicians. The physicians were blinded to the reports of other imaging studies, including nuclear and conventional morphologic imaging.

#### Visual analysis

They individually graded each adrenal tumour between probably benign or malignant. Equivocal tumours were classified as probably malignant. The visual analysis was the main criterion and was used for the prospective evaluation. Qualitative comparison of the adrenal FDG
uptake with the liver FDG uptake was undertaken, whereby the PET/CT image was considered positive if FDG uptake in the adrenal tumour appeared visually markedly higher than the liver and negative if it appeared visually less, equal, or slightly higher than that of the liver.

Quantitative analysis

These criteria were retrospectively evaluated.

A region of interest (ROI) was drawn on the tumour. We tried to use a large enough region to cover more than half of the adrenal mass but avoided peripheral areas of the adrenal mass to avoid partial volume effect. A large ROI was also drawn on a large homogeneous liver region (segment VIII). Activity counts in the ROIs were normalized to injected doses per kilogram of patient body weight [maximum standardised uptake value (SUVmax)]. Then, we measured SUVmax in the ROI on PET images. Maximum diameter (millimeters) and unenhanced attenuation (Hounsfield Units) were assessed on co-registered CT images. A ratio of SUVmax tumour on SUV max liver was calculated.

Average measurements (mean values between both physicians) were used for the statistical analysis.

Statistical analysis

Visual analysis, tumour SUVmax, maximum diameter, unenhanced attenuation value and tumour/liver SUVmax ratios were compared between benign and malignant tumours using Mann-Whitney tests (SPSS 15.0 for Windows.) A p value of less than 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were performed to estimate the ability of quantitative variables to discriminate between malignant and benign tumours.

Results

Patients and tumours

We included 37 patients (15 women, 22 men; mean age, 58 years) with 41 adrenal tumours. Twelve of the tumours were classified as malignant (22%) and 29 as benign (78%). Histology was obtained in 17 benign tumours and all malignant tumours (Table 1). The 12 other tumours were classified as benign on the basis of absence of change in imaging features (size and tumour tissue component) during the follow-up (mean 13.3 months; 6–28).

Visual analysis

Histological diagnosis were obtained for all patients but one with positive FDG PET/CT.

For the negative FDG PET/CT, we had histological diagnosis for 17 patients (17 tumours) and follow-up for 11 patients (12 tumours).

The sensitivity, specificity, positive predictive value, negative predictive value (NPV) and accuracy were 100% (12/12), 86% (25/29), 75% (12/16), 100% (25/25) and 90% (37/41), respectively. Both physicians were in agreement in all cases. There was no false negative result. Based on visual analysis, 4/29 benign lesions were falsely classified as positive findings: three were histologically benign and one did not increase in size after 11 months follow-up. In these cases, tumour/liver SUVmax ratios were 1.66, 1.7, 1.67 and 1.56, respectively. SUVmax were 3.5, 3.9, 3.6 and 4.2, respectively. Unenhanced attenuation density values were 22, 30, 32 and tumour sizes ranged from 18 to 33 mm.

Examples of true negative, true positive and false positive results are seen in Fig. 1.

Additional value of quantitative analysis

Tumour characteristics are summarised in Table 2. Benign tumours had smaller sizes (p=0.001), lower CT density (p=0.005), a lower SUVmax (p<0.001) and lower tumour/liver SUVmax ratio (p<0.001). The tumour/liver SUVmax ratio was the most accurate parameter to distinguish the nature of tumours (Fig. 2). When the tumour/liver SUVmax ratio was 1.8, the sensitivity and specificity reached to 100% (Fig. 3). The maximal benign ratio was 1.7, whilst the minimal malignant ratio was 1.98. No overlap was observed between benign and malignant

Table 1 Adrenal tumour classification according to the final diagnosis

<table>
<thead>
<tr>
<th>Patients</th>
<th>Tumours</th>
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<tbody>
<tr>
<td>Benign</td>
<td></td>
</tr>
<tr>
<td>Histologically proven</td>
<td>17</td>
</tr>
<tr>
<td>Adenoma</td>
<td>12</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>1</td>
</tr>
<tr>
<td>Ganglioneuroma</td>
<td>1</td>
</tr>
<tr>
<td>Calcified cystic mass</td>
<td>1</td>
</tr>
<tr>
<td>Haematoma</td>
<td>1</td>
</tr>
<tr>
<td>Cavernous angioma</td>
<td>1</td>
</tr>
<tr>
<td>Stable tumour (median follow: 13 month)</td>
<td>11</td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
</tr>
<tr>
<td>Non-secreting adrenal carcinoma</td>
<td>3</td>
</tr>
<tr>
<td>B-lymphoma</td>
<td>2</td>
</tr>
<tr>
<td>Hodgkin disease</td>
<td>1</td>
</tr>
<tr>
<td>Metastasis from primary lung carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Metastasis from poorly differentiated carcinoma of unknown origin</td>
<td>1</td>
</tr>
</tbody>
</table>

Italics were used to distinguish histologically-proven benign tumours from those defined by the follow-up only.
tumours. There was no significant difference concerning the measurements between the two physicians. The mean differences for tumour SUVmax, liver SUVmax and ratio were 0.08 (±0.24), 0.13 (±0.12) and 0.05 (±0.15), respectively. The mean size was 45 mm for all tumours. No personal history of liver disease was present in our population.

Additional information provided by PET/CT scan

In addition to the adrenal tumour metabolic characterisation and therefore risk of adrenal malignancy, PET/CT scans allowed the incidental diagnosis of two previously unidentified unknown lung neoplasms, two B lymphomas and one Hodgkin’s lymphoma.

Discussion

With the increasing use of abdominal cross-sectional imaging, adrenal masses are a frequent incidental finding. Most of these lesions are benign even when of large dimensions. Tumours considered of indeterminate nature on conventional imaging represent a troublesome group since at present, size alone predicts the likely clinical behaviour. Radiologically guided biopsies are unreliable and may be associated with complications. Costly repetitive follow-up is therefore required. To avoid this would require the development of a diagnostic test that reliably differentiates benign from malignant adrenal tumours.

FDG PET offers the opportunity to assess tumour glucose avidity and metabolism. The FDG uptake reflects right adrenal tumour (34 HU) corresponding with adrenocortical carcinoma (adrenalectomy). The tumour/liver SUVmax ratio was 4.8. There is a central hypometabolism corresponding with necrosis (Weiss score=3). G, H, I False-positive FDG PET/CT findings in a 62-year-old woman. Axial FDG PET/CT images show increased uptake (G) of FDG (SUVmax=3.9) in 33-mm soft-tissue-attenuation left adrenal tumour (30 HU; H) corresponding with lipid-poor adenoma (adrenalectomy). The tumour/liver SUVmax ratio was 1.7.
many complex features, including metabolic switch from aerobic to anaerobic metabolism, which is characteristic of cancer cells, named the Warburg effect [28]. Whilst the value of PET/CT in adrenal tumours has been assessed in patients with malignancy, there is no previously published data on the ability of PET/CT to classify adrenal tumours’ malignancy risk in patients without known malignancy.

Within the limitations of this study caused by its limited numbers and the presence of histological proof in only 58%, minimal follow-up of only 6 months, our findings suggest that FDG PET/CT predicts benign behaviour with a sensitivity and NPV of 100% (12/12 and 25/25, respectively), both with visual analysis or tumour/liver SUVmax ratio. When visual analysis alone was used, four false positive results were identified. Retrospectively, the calculation of the tumour/liver SUVmax ratio was therefore a valuable additional criterion that complemented the visual analysis in such cases. A cut-off value of 1.8 for the tumour/liver SUVmax ratio provided 100% accuracy. However, SUVmax alone appeared to be less accurate than visual analysis. We noted that the minimal malignant SUVmax (1.06) was lower than the minimal benign SUVmax (1.3), reflecting the limitations of SUVmax.

Overall, therefore, a negative FDG PET/CT scan appears to be a valid predictor of benign behaviour. These preliminary findings may in first instance offer patients reassurance for tumour diagnosis but may in the future also allow a reduction in the intensity of the conventional radiological follow-up protocols currently adopted. It might avoid surgery or delay it, in case of negative FDG PET/CT scan. If surgical indication was maintained (patient’s demand, increase in tumour size, large tumours), surgery could be performed with minimally invasive surgical approach. This approach might be particularly valid in terms of its cost effectiveness and accurate management of patients.

Placing our findings into context with previous studies is troubled by the fact that these have invariably involved patients with proven or suspected cancer. In such cases, the sensitivity and specificity ranged from 95% to 100% and 80% to 100%, respectively. FDG PET/CT in known cancer patients is helpful since it enables the appropriate treatment strategy by improving the accuracy of staging and therefore improving prognostic accuracy and allowing the optimisation of the treatment pathway.

The investigation of the additional value of FDG PET/CT in the diagnosis of indeterminate adrenal masses has been previously documented [27] with varied opinions. In the study of Caoli et al., 43 of 47 adenomas were diagnosed with unenhanced CT, leaving 16 indeterminate tumours (12 non-adenomas and four lipid-poor adenomas), providing sensitivity and specificity of 91% (43/47) and 100% (12/12) for diagnosing adenoma. With qualitative and quantitative results, FDG PET/CT results corresponded to a sensitivity and specificity of 51% and 100%, respectively, when using threshold <1 (activity in adrenal mass <liver), leading to the conclusion that unenhanced CT was better than FDG PET for diagnosing adenomas [19]. In another study, 19/32 tumours were diagnosed as benign based on a low CT attenuation (<10 HU), and in the 13

<table>
<thead>
<tr>
<th>Table 2 Features of adrenal tumours</th>
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<tbody>
<tr>
<td>Benign</td>
</tr>
<tr>
<td>------------------------------------</td>
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<tr>
<td>Max diameter (mm)</td>
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<tr>
<td>CT density (HU)</td>
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<tr>
<td>Tumour SUVmax</td>
</tr>
<tr>
<td>SUVmax Ratio (tumour/liver)</td>
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<tr>
<td>Liver SUVmax</td>
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Statistical comparison between benign and malignant tumours (statistically significant difference when $p<0.05$).
remaining tumours (that were all benign), FDG PET/CT was negative in 11 cases. The two false positives on visual and quantitative analysis (moderate uptake greater than liver) were classified accurately as adenomas by enhanced CT and calculation of washout [18]. Metsers et al. found 107 benign tumours with 72 lipid-rich adenomas, 28 lipid-poor adenomas, six myelolipomas and one cyst. When using a SUV cut-off of 3.1 for differentiating benign from malignant tumours, they observed an overall sensitivity and specificity of 98.5% and 92%, respectively (eight false positives and one false negative). The specificity reached 93% in lipid-poor adenomas considered alone (two false positive and one false negative) [26]. Jana et al. have compared CT and FDG PET/CT in 80 cancer patients and observed a sensitivity and specificity of 88% and 96%, respectively, in patients with indeterminate adrenal tumours (42/80) on CT [17]. Yun et al. meanwhile have reported that FDG PET/CT accurately diagnosed all lesions among indeterminate adrenal lesions [25].

Low attenuation on CT is widely thought to reflect a highly probable benign behaviour. Our series included six tumours of <10 HU. They were classified “non typical” with conventional imaging because of either heterogeneity, absence of washout or chemical shift. FDG PET/CT was negative for these tumours, and they all corresponded with adenomas. It is our view that FDG PET/CT is unlikely to be of additional benefit if the attenuation on CT is less than 10 HU in a homogeneous tumour.

There was no pheochromocytoma in our study since all had been excluded by meticulous biochemical work-up. However, it is well known that these tumours are FDG avid [29], especially tumours that carry succinate dehydrogenase mutations [30] and that false positives corresponding to a pheochromocytoma may occur [20].

In our study, the median size of tumours was relatively large at 36 mm for benign tumours and 63 mm for malignant tumours. This is probably because patients were referred after an initial selection with endocrine surgeons, endocrinologists and nuclear physicians. This point is important because SUV could be underestimated in small tumours due to partial volume effect and thus providing false negative results [20, 25]. Other potential false negative results include low-FDG avid tumours (such as renal cancer, endocrine tumours) and necrotic tumours [20, 25, 26].

Previous studies found that using liver activity as a threshold, rather than SUVmax alone or background activity, improved their ability to correctly classify adrenal tumours [18–20, 25]. Our findings suggest that using a threshold of 1.8 allows 100% accuracy. Interestingly, Black et al. found no false negative result, but there were two false positive tumours, with uptakes moderately greater than liver (1.45 and 1.47). The lowest malignant ratio was 1.53 so that a cut-off of 1.5 correctly classified all adrenal tumours. Caoili et al. found two false positives among the 16 indeterminate tumours. Tumour uptake was moderately greater than liver, with 1.1 and 1.4 for ratio with liver. Larger and prospective studies are needed for confirming 1.8 threshold in our patient population and for evaluating if this ratio value is altered by the time point of acquisition of PET.
In our study, SUVmax was less accurate than visual analysis and ratio analysis. Previous studies found that visual analysis was more specific than SUV analysis for the evaluation of an adrenal mass [18, 19]. Similarly, we found that adenomas cannot be distinguished by SUV measurements of the adrenal mass alone. However, this is not surprising, given the nature of SUV, which is dependent on many factors [31–33] and might be “normalized” by the use of a ratio.

Conclusion

Incidental adrenal tumours are common. Within the limitations of this preliminary study, FDG PET/CT appears to provide additional information to conventional imaging in classifying the clinical nature of indeterminate adrenal tumours. Tumour/liver SUVmax ratio could be helpful in cases of doubtful visual uptake. Larger prospective studies are needed to assess the reliability of these findings and potential clinical use.

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References


