ORIGINAL ARTICLE

Preoperative characterization of indeterminate large adrenal masses with dual tracer PET-CT using fluorine-18 fluorodeoxyglucose and gallium-68-DOTANOC: initial results

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PURPOSE
We aimed to evaluate the usefulness of dual tracer positron emission tomography-computed tomography (PET-CT) with flourine-18 fluorodeoxyglucose (^{18}F-FDG) and gallium-68 [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid]-1-NaI^3-octreotide (^{68}Ga-DOTANOC) in preoperative characterization of large indeterminate adrenal masses.

MATERIALS AND METHODS
Ten patients (four males, six females; median age, 35 years) with indeterminate, large ($\geq$4 cm) adrenal masses were included in this prospective study. All patients underwent both ^{18}F-FDG PET-CT and ^{68}Ga-DOTANOC PET-CT within one week. Images were evaluated both visually and semi-quantitatively, with standardized uptake value (SUV_{max} and SUV_{ratio} (SUV_{max} of tumor/SUV_{max} of mediastinum). Based on differential uptake pattern on ^{18}F-FDG and ^{68}Ga-DOTANOC, lesions were classified as cortical (^{18}F-FDG>^{68}Ga-DOTANOC), medullary (^{68}Ga-DOTANOC>^{18}F-FDG), or indeterminate (^{18}F-FDG=^{68}Ga-DOTANOC). Histopathology was taken as reference standard. Receiver operating characteristic (ROC) analysis was performed to find a cut-off of SUV_{max}) and SUV_{ratio} to differentiate cortical and medullary lesions.

RESULTS
On histopathology, eight lesions were adrenocortical carcinomas, one was benign pheochromocytoma, and one was malignant pheochromocytoma. Visually, ^{18}F-FDG PET-CT was positive in all ten lesions, while ^{68}Ga-DOTANOC PET-CT was positive in two, both of which were pheochromocytomas. On SUV_{max} based analysis, nine lesions were cortical and one was medullary. On ROC analysis, a SUV_{max} cut-off of > 2.3 was obtained for ^{18}F-FDG PET-CT and 3.6 for ^{68}Ga-DOTANOC PET-CT for differentiating adrenal cortical and medullary lesions. The cut-off for SUV_{ratio} was 4.5 on ^{18}F-FDG PET-CT and 11.1 on ^{68}Ga-DOTANOC PET-CT.

CONCLUSION
These preliminary results demonstrate that dual tracer PET-CT using ^{18}F-FDG and ^{68}Ga-DOTANOC could be informative in the preoperative characterization of large indeterminate adrenal masses.

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O f the various neoplasms affecting the adrenal gland, the most important prognostically is primary adrenal cancer (adrenocortical carcinoma) (1). Morphologic imaging approaches, such as computed tomography (CT) and magnetic resonance imaging (MRI), are excellent methods to delineate the various adrenal neoplasms, including adrenal carcinomas, with a high degree of accuracy. Large tumor size, heterogeneous contrast enhancement, relative percentage washout of less than 40%, and tumor calcification point towards a primary adrenocortical malignancy (2–4). Despite the reliable features of CT and MRI, in some cases the nature of the adrenal mass remains difficult to determine, particularly when the lesion size is large (5, 6). The negative predictive value is unacceptably low even for biopsy and cannot be relied on to rule out malignancy (7). The value of biopsy, however, remains significant for the diagnosis of metastatic carcinoma in patients with a non-adrenal primary malignancy (7).

Positron emission tomography (PET) with flourine-18 fluorodeoxyglucose (^{18}F-FDG) is another important imaging modality often used to determine the nature of an adrenal lesion. It has an excellent negative predictive value in the identification of adrenocortical carcinomas and may be of help in avoiding unnecessary surgery in patients with non-secreting equivocal tumors at CT scanning (5). Gallium-68 [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid]-1-NaI^3-octreotide (^{68}Ga-DOTANOC) is tracer for somatostatin receptor scintigraphy, which provides advantages of better resolution and quantification of PET technology. ^{68}Ga-DOTANOC PET-CT has already been proven to be of great value in neuroendocrine tumors and has shown promising results for pheochromocytoma (8).

In few instances, pheochromocytomas can also be very large in size and show necrosis. In these cases, it might be difficult to differentiate it from adrenocortical carcinoma. As hypertension can be present in both cases, clinical differentiation may not be possible. Though biochemical assays are generally very useful in such instances, in some cases, serum catecholamines may be elevated even in patients with adrenal adenomas or adrenocortical carcinoma. Also, certain lesions such as adrenal adenoma and pheochromocytoma can often be ^{18}F-FDG avid to a variable degree, compromising the predictive value of ^{18}F-FDG PET (9). Therefore, the purpose of the present study was to evaluate adrenal masses that were described as probably malignant on both CT and MRI with ^{18}F-FDG PET-CT. ^{68}Ga-DOTANOC PET-CT was also used in addition to ^{18}F-FDG PET-CT to determine what additional role ^{68}Ga-DOTANOC PET-CT can play in the characterization of such masses.

Materials and methods

This prospective study was approved by the institutional review board. Ten consecutive patients with large adrenal mass (≥4 cm) in whom the origin of adrenal mass (cortical vs. medullary) could not be established after conventional biochemical and radiological evaluation were included in the study. All patients underwent ^{18}F-FDG PET-CT and ^{68}Ga-DOTANOC PET-CT with an up to one week interval (range, 3–7 days). Written informed consent was obtained from all patients.

The ^{18}F-FDG PET-CT was acquired on a dedicated PET-CT system (Biograph 2, Siemens Medical Systems, Erlangen, Germany). Patients fasted for six hours before the study. A dose of 370 MBq (10 mCi) of FDG was injected intravenously, and imaging was acquired 45 to 60 min later from the base of the skull to mid-thigh. Oral contrast was used. No intravenous contrast was used. CT acquisition was performed on spiral dual slice CT with a slice thickness of 4 mm and a pitch of 1. Imaging was acquired using a matrix of 512×512 pixels and pixel size of 1 mm. PET data were acquired using a matrix of 128×128 pixels with a slice thickness of 1.5 mm. CT based attenuation correction of the emission images was employed. PET images were reconstructed by iterative method ordered subset expectation maximization (two iterations and eight subsets). After completion of PET acquisition, the reconstructed attenuation corrected PET images, CT images, and fused images of matching pairs of PET and CT images were available for review in axial, coronal, and sagittal planes, as well as in maximum intensity projections (MIP), three-dimensional cine mode. ^{68}Ga-DOTANOC synthesis was performed as previously detailed by Zhernosekov et al. (10). For ^{68}Ga-DOTANOC PET-CT, fasting was not mandatory. A dose of 132 to 222 MBq (4–6 mCi) of ^{68}Ga-DOTANOC was injected intravenously. After a 45 to 60 min uptake period, the patients were taken for PET-CT. The rest of the acquisition parameters were similar to ^{18}F-FDG PET-CT.

The images were analyzed by two experienced nuclear medicine physicians who were blinded to the clinical details. The largest dimension of the adrenal mass was measured on CT. The uptake in adrenal mass was evaluated both qualitatively and quantitatively (standardized uptake value, SUV_{max}). For both ^{18}F-FDG PET-CT and ^{68}Ga-DOTANOC, PET-CT mediastinal blood pool was taken as reference standard. SUV_{ratio} (SUV_{max} of tumor/ SUV_{max} of mediastinum) was also calculated for both ^{18}F-FDG PET-CT and ^{68}Ga-DOTANOC PET-CT. Liver was not taken as reference standard because of heterogeneous physiological uptake of both tracers. Lesions were classified based on the differential uptake pattern on ^{18}F-FDG and ^{68}Ga-DOTANOC PET-CT as cortical, medullary, or indeterminate (^{18}F-FDG> ^{68}Ga-DOTANOC, cortical; ^{68}Ga-DOTANOC>[18]F-FDG, medullary; ^{18}F-FDG= ^{68}Ga-DOTANOC, indeterminate). All patients underwent surgical removal of the mass, and histopathology was taken as a reference standard.

Because of small sample size, continuous variables were expressed as median and interquartile range. Spearman's rank correlation (two tailed) was used to establish a relation between size of the mass and SUV_{max} (if any), because of lack of normally distributed data. Receiver operating characteristic (ROC) analysis was performed to find a cut-off of SUV_{max} and SUV_{ratio} (SUV_{max} of tumor/ SUV_{max} of mediastinum) to differentiate cortical and medullary tumors. All the data analyses were performed using a commercially available software (Statistical Package for Social Sciences, version 11.5, SPSS Inc., Chicago, Illinois, USA).

Results

Characteristics of the ten patients included in the study are presented in the Table. Six patients were female and four were male, and the median age was 35 years (interquartile range, 30–55 years). The median size of tumor was 6.5 cm (interquartile range, 4.4–10 cm). Based on reference standard, eight masses were cortical (adrenocortical carcinoma), and two were medullary (one benign pheochromocytoma and one malignant pheochromocytoma).

Table. Patients' characteristics

Patient number	Age (years)	Gender	CT	Size (cm)	^{18}F-FDG PET-CT	^{18}F-FDG SUV_{max}	^{68}Ga-DOTANOC PET-CT	^{68}Ga-DOTANOC SUV_{max}	Final diagnosis
1	70	Female	Right adrenal mass	13×7	Positive	16.3	Negative	3.6	Adrenocortical carcinoma
2	22	Female	Right adrenal mass	14×11	Positive	6.5	Negative	1	Adrenocortical carcinoma
3	30	Male	Left adrenal mass	4.4×3.5	Positive	4	Negative	1.7	Adrenocortical carcinoma
4	35	Female	Left adrenal mass	7×5	Positive	7.5	Negative	1	Adrenocortical carcinoma
5	43	Male	Right adrenal mass	7×6	Positive	8.2	Negative	1	Adrenocortical carcinoma
6	35	Female	Right adrenal mass	6×6	Positive	3	Negative	1	Adrenocortical carcinoma
7	24	Male	Right adrenal mass	4×3	Positive	12.5	Positive	5	Malignant pheochromocytoma
8	56	Male	Right adrenal mass	10×7	Positive	2.3	Positive	7	Pheochromocytoma
9	32	Female	Left adrenal mass	5×4	Positive	8.9	Negative	1	Adrenocortical carcinoma
10	55	Female	Left adrenal mass	4×3	Positive	3.2	Negative	1.2	Adrenocortical carcinoma

CT, computed tomography; ^{18}F-FDG, flourine-18 fluorodeoxyglucose; ^{68}Ga-DOTANOC, gallium-68-labelled [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid]-1-NaI[3]-octreotide; PET-CT, positron emission tomography-computed tomography; SUV_{max}, maximum standardized uptake value.
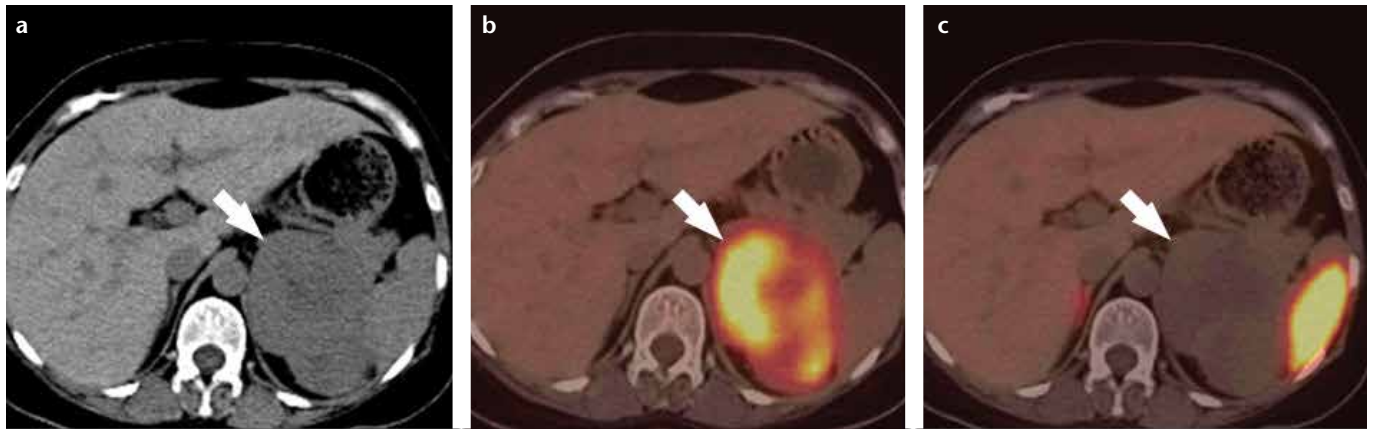
Figure 1. a–c. A 35-year-old female with indeterminate left adrenal mass. Transaxial noncontrast CT **(a)** image reveals a 7×5 cm well-defined left adrenal mass *(arrow)* without calcification. Transaxial ^{18}F-FDG PET-CT image **(b)** shows intense uptake of radiotracer (SUV$_{max}$, 7.5) in the mass along with areas of necrosis *(arrow)*. No significant uptake tracer was noted on transaxial ^{68}Ga-DOTANOC PET-CT **(c, arrow)**. The diagnosis was adrenal cortical tumor on dual tracer PET-CT. The final histopathological diagnosis was adrenocortical carcinoma.

Findings of qualitative PET-CT image analysis are detailed in the Table. ^{68}Ga-DOTANOC PET-CT was visually interpreted as positive in two patients (20%), and both patients were found to have pheochromocytoma on histopathology. ^{18}F-FDG PET-CT was visually interpreted as positive in all 10 patients, including both pheochromocytomas (Figs. 1–3).

Quantitative findings of PET-CT are detailed in the Table. The median SUV$_{max}$ of adrenal lesions on ^{18}F-FDG PET-CT was 7 (interquartile range, 3.2–8.9). The median SUV$_{max}$ on ^{68}Ga-DOTANOC PET-CT was 1.1 (interquartile range, 1–3.6). In nine patients, SUV$_{max}$ on ^{18}F-FDG PET-CT was more than that on ^{68}Ga-DOTANOC PET-CT, including in one patient with malignant pheochromocytoma. In the patient with benign pheochromocytoma, SUV$_{max}$ on ^{68}Ga-DOTANOC PET-CT was more than ^{18}F-FDG PET-CT (7 vs. 2.3, respectively). The quantitative analysis was able to correctly characterize nine of ten lesions (90% accuracy). In one patient with malignant pheochromocytoma, ^{18}F-FDG uptake was more than ^{68}Ga-DOTANOC uptake, and hence falsely characterized as cortical lesion. No significant correlation was seen between SUV$_{max}$ and tumor size on ^{18}F-FDG ($\rho = 0.024$; $P = 0.946$) or ^{68}Ga-DOTANOC PET-CT ($\rho = -0.143$; $P = 0.693$). On ROC analysis, a SUV$_{max}$ cut-off of >2.3 (sensitivity, 100%; and specificity, 50%) on ^{18}F-FDG PET-CT and >3.6 (sensitivity, 100%; and specificity, 100%) on ^{68}Ga-DOTANOC PET-CT was observed for differentiating cortical and medullary tumor. The median SUV$_{ratio}$
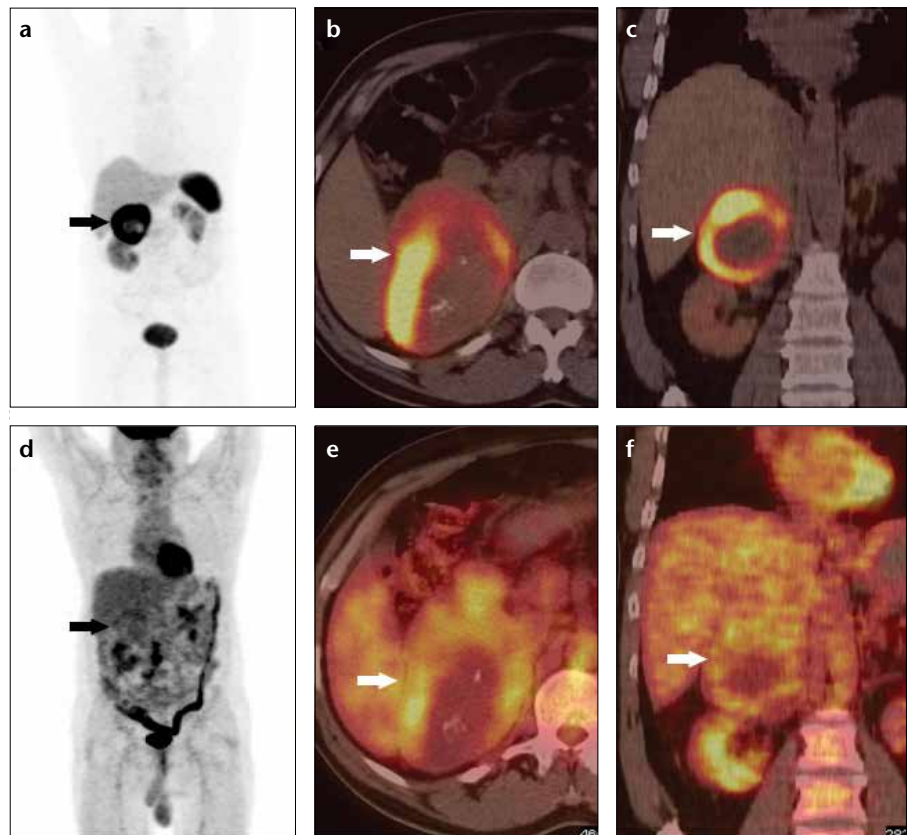

Figure 2. a–f. A 56-year-old male with indeterminate right adrenal mass. Maximum intensity projection (MIP) ^{68}Ga-DOTANOC PET-CT **(a)** image reveals a large focus of tracer uptake in the right suprarenal region *(arrow)*. Transaxial **(b)** and coronal **(c)** PET-CT images show intense ^{68}Ga-DOTANOC uptake in the mass *(arrows)* with central necrosis and areas of calcification (SUV$_{max}$, 7). Mild uptake of tracer (SUV$_{max}$, 2.3) was noted on ^{18}F-FDG PET MIP image **(d)** as well as transaxial **(e)** and coronal **(f)** PET-CT images *(arrows)*. The diagnosis of adrenal medullary tumor was made on dual tracer PET-CT. The final histopathological diagnosis was a pheochromocytoma.

for ^{18}F-FDG PET-CT was 7.8 (range, 3.3–13.6) and that for ^{68}Ga-DOTANOC PET-CT was 1.4 (range, 0.1–50.9). On ROC analysis, a SUV$_{ratio}$ cut-off of ≤4.5 (sensitivity, 100%; and specificity, 100%) on ^{18}F-FDG PET-CT and ≤11.1 (sensitivity, 87.5%; and specificity, 100%) on ^{68}Ga-DOTANOC PET-CT was observed.

Discussion

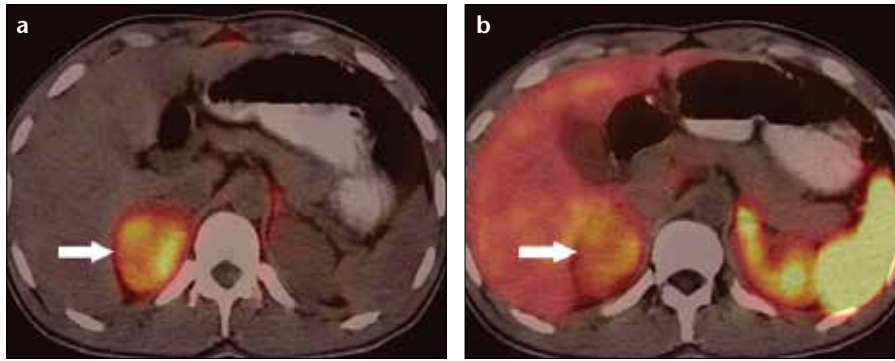Adrenal masses often pose diagnostic problems regarding characterization of

Figure 3. a, b. A 24-year-old male with indeterminate right adrenal mass. Transaxial ^{18}F-FDG PET-CT image **(a)** shows a 4×3 cm right adrenal mass *(arrow)* with intense tracer uptake (SUV$_{max}$, 12.5). Transaxial ^{68}Ga-DOTANOC PET-CT image **(b)** also showed increased uptake of tracer in the mass *(arrow)* (SUV$_{max}$, 5). The diagnosis on dual tracer PET-CT was adrenal cortical tumor. The final histopathological diagnosis was a malignant pheochromocytoma.

their nature. Imaging abilities of CT and MRI in the assessment of adrenal masses are not without pitfalls (5, 6). The role of ^{18}F-FDG PET in the detection of malignant adrenal mass has been previously described, and the common consensus is that ^{18}F-FDG PET has an excellent diagnostic performance in differentiating adrenal lesions detected on CT or MRI (7). Most of the literature describes a role for ^{18}F-FDG in defining an adrenal lesion as benign or malignant in patients with known primary malignancy (9), or evaluating the nature of adrenal incidentalomas. To our knowledge, only one study has evaluated the role of ^{18}F-FDG PET in the identification of adrenocortical carcinomas among indeterminate adrenal tumors at CT scanning (5). The authors concluded that it has an excellent negative predictive value in the identification of adrenocortical carcinomas among indeterminate adrenal masses at CT. The role of ^{18}F-FDG PET in the evaluation of pheochromocytomas has been previously described and the literature supports its success in this capacity (11). In the present study, ^{18}F-FDG PET-CT showed very high tracer uptake in the malignant adrenocortical carcinomas and pheochromocytomas; however, its uptake in a case of benign pheochromocytoma was much lower. On quantitative analysis, a SUV$_{max}$ of >2.3 was found to differentiate cortical and medullary tumors with high sensitivity (100%). No significant correlation was seen between SUV$_{max}$ and tumor size. A SUV$_{ratio}$ cut-off of 4.5 was accurate in differentiating cortical and med-

ullary tumors (sensitivity 100%; and specificity,, 100%) on ^{18}F-FDG PET-CT. Moreover, in these patients, no other metastatic sites were seen on ^{18}F-FDG PET-CT, thereby accurately staging the disease.

^{68}Ga-DOTANOC is a fast emerging tracer and initial results have supported it in the evaluation of patients with neuroendocrine tumors (NETs), including adrenal medullary tumors (8). It targets the somatostatin receptors 2, 3, and 5 (SSTR-2, -3, -5), which are often expressed in such tumors (11). However, its role in the evaluation of indeterminate adrenal lesions has not been previously described. In the present study, no significant ^{68}Ga-DOTANOC uptake was seen in any of the adrenal lesions that were found to be adrenocortical carcinoma at histopathology. This is to be expected, as adrenocortical carcinomas are tumors of epithelial origin and not known to express SSTR. However, increased uptake of ^{68}Ga-DOTANOC were observed in the tumors that were eventually found to be of adrenal medullary origin. Thus, ^{68}Ga-DOTANOC can play an important role in ruling out adrenocortical malignancy in cases where the diagnosis remains doubtful even after a battery of investigations. On ^{68}Ga-DOTANOC PET-CT, a cut-off SUV$_{max}$ of 3.6 could differentiate cortical and medullary lesions with high sensitivity and specificity (100%). A SUV$_{ratio}$ cut-off of 11.1 (sensitivity, 87.5%; and specificity, 100%) on ^{68}Ga-DOTANOC PET-CT was observed for differentiating cortical and medullary tumors. In addition, ^{68}Ga-DOTANOC PET-CT ruled

out any other SSTR expressing tumor (pheochromocytomas/paragangliomas, etc.), thereby impacting surgical strategy. However, no significant correlation was seen between SUV$_{max}$ and tumor size.

On combined dual tracer PET-CT, one of the lesions was falsely categorized as cortical and later found to be medullary. This tumor was histopathologically malignant pheochromocytoma. Pheochromocytomas, particularly malignant pheochromocytomas, are known to concentrate ^{18}F-FDG, and this should be kept in mind when interpreting such a case.

To our knowledge, there has been no systematic study evaluating the combined use of ^{18}F-FDG and ^{68}Ga-DOTANOC PET-CT in the characterization of indeterminate malignant adrenal masses. The current results are encouraging. The findings reported in this study can be of immense value, as cytological and histopathological analysis of an adrenal mass is often not clear until surgery is undertaken, and any prior knowledge regarding the nature of the lesion can lead to a significant change in management and prognosis.

The study has several limitations. First, the sample size was very small. This is because large adrenal masses are usually characterized on conventional imaging and from biochemical marker levels, hence few remain indeterminate. Second, although histopathology was available in all patients, levels of glucose transporters and SSTR expression in tumors were not available. Assessment of imaging characteristics of PET-CT would have given greater insights into biology of these tumors. Finally, because of the smaller sample size, the power of the study was limited and the reliability of the results of statistical analysis was reduced. These preliminary results should be interpreted in light of small sample size, and a larger multicenter study will better address these shortcomings.

In conclusion, these encouraging preliminary results demonstrate that dual tracer PET-CT using ^{18}F-FDG and ^{68}Ga-DOTANOC might help in the preoperative characterization of large indeterminate adrenal masses. A secondary gain of using dual tracers in the evaluation of such patients is accu-

rate staging of the patient in which the mass is an adrenocortical carcinoma (^{18}F-FDG PET-CT), and detection of extra-adrenal lesions if the diagnosis is an adrenal medullary tumor (^{68}Ga-DOTA-NOC PET-CT).

Conflict of interest disclosure

The authors declared no conflicts of interest.

References

1. Bilimoria KY, Shen WT, Elaraj D, et al. Adrenocortical carcinoma in the United States: treatment utilization and prognostic factors. Cancer 2008; 113:3130–3136. [CrossRef]
2. Copeland PM. The incidentally discovered adrenal mass. Ann Surg 1984; 199:116–122. [CrossRef]
3. Slattery JM, Blake MA, Kalra MK, et al. Adrenocortical carcinoma: contrast washout characteristics on CT. AJR Am J Roentgenol 2006; 187:21–24. [CrossRef]
4. Ng L, Libertino JM. Adrenocortical carcinoma: diagnosis, evaluation and treatment. J Urol 2003; 169:5–11. [CrossRef]
5. Nunes ML, Rault A, Teynie J, et al. 18F-FDG PET for the identification of adrenocortical carcinomas among indeterminate adrenal tumors at computed tomography scanning. World J Surg 2010; 34:1506–1510. [CrossRef]
6. Krestin GP, Steinbrich W, Friedmann G. Adrenal masses: evaluation with fast gradient-echo MR imaging and Gd-DTPA-enhanced dynamic studies. Radiology 1989; 171:675–680.
7. Yun M, Kim W, Alnafisi N, Lacorte L, Jang S, Alavi A. 18F-FDG PET in characterizing adrenal lesions detected on CT or MRI. J Nucl Med 2001; 42:1795–1799.
8. Naswa N, Sharma P, Nazar AH, et al. Prospective evaluation of (68)Ga-DOTA-NOC PET-CT in phaeochromocytoma and paraganglioma: preliminary results from a single centre study. Eur Radiol 2012; 22:710–719. [CrossRef]
9. Kumar R, Xiu Y, Yu JQ, et al. 18F-FDG PET in evaluation of adrenal lesions in patients with lung cancer. J Nucl Med 2004; 45:2058–2062.
10. Zhernosekov KP, Filosofov DV, Baum RP, et al. Processing of generator-produced 68Ga for medical application. J Nucl Med 2007; 48:1741–1748. [CrossRef]
11. Shuklin BL, Thompson NW, Shapiro B, Francis IR, Sisson JC. Pheochromocytomas: imaging with 2-[fluorine-18] fluoro-2-deoxy-D-glucose PET. Radiology 1999; 212:35–41.