Original article

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The role of fluorodeoxyglucose-positron emission tomography/computed tomography in differentiating between benign and malignant adrenal lesions

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Objectives This retrospective study was designed to investigate the clinical role of whole-body positron emission tomography/computed tomography (PET/CT) by using 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG), for the evaluation of adrenal lesions and to find the best index to distinguish benign from malignant lesions in various cancer patients.

Materials and methods A total of 81 patients (55 male and 26 female, age range: 31–81 years, mean: 61.5) who had confirmed primary malignancies (lung cancer in 47 patients, gastrointestinal malignancies in 13 patients, malignant melanoma in one patient, renal cell cancer in three patients, mesothelioma in two patients, breast carcinoma in nine patients, cervical cancer in one patient, ovarian cancer in two patients, pheochromocytoma in one patient, unknown primary in two patients) underwent PET/CT examinations for cancer screening, staging, restaging, and detection of suspected recurrence. Of the 81 patients, 104 adrenal lesions (34 benign and 70 malignant adrenal lesions) were shown by CT. On visual analysis of PET/CT imaging, adrenal uptake was based on a three-scale grading system. For final assessment standards of references for adrenal malignant lesions was based on biopsy ($n=2$), interval growth, or reduction after chemotherapy. An adrenal lesion, which remained unchanged on clinical and imaging follow-up of at least 7 months (mean follow-up time 19.31 months $\pm$ 6.46, range 7–30 months), was decided as a benign lesion.

Results In adrenal malignant lesions maximum standardized uptake value (SUV_{max}) (8.82 $\pm$ 4.47) was higher than that of adrenal benign lesions (3.02 $\pm$ 1.15, $P<0.0001$). In the differentiation of adrenal benign and malignant lesions, a CT threshold of 10 Hounsfield units corresponded to a sensitivity of 64.7%, specificity of 98.6%, and accuracy of 87.5%. An SUV_{max} cut-off value of 2.5 corresponded to a sensitivity of 100%, specificity of 38.2%, and accuracy of 80%. An SUV_{max} cut-off value of 4.2 corresponded to a sensitivity of 88.6%, specificity of 88.2%, and accuracy of 88.5%. The ratio of tumor SUV_{max} to liver SUV_{mean} was 3.61 $\pm$ 1.77 for adrenal malignant lesions whereas it was 1.20 $\pm$ 0.38 for adrenal benign lesions ($P<0.0001$). T/L SUV ratio cut-off value of 1.8 corresponded to a sensitivity of 87%, specificity of 91%, and accuracy of 88.5%. T/L SUV ratio cut-off value of 1.68 corresponded to a sensitivity of 90%, specificity of 91.1%, and accuracy of 90.4%.

Conclusion 2-[^{18}F]fluoro-2-deoxy-D-glucose-PET/CT improves the diagnostic accuracy in the differentiation of benign from malignant adrenal lesions in various cancer patients. Combined information obtained from PET/CT (SUV_{max}, T/L SUV ratio, visual analysis) and unenhanced CT (size, Hounsfield units measurement) is recommended for better differentiation. *Nucl Med Commun* 32:106–112 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

The adrenal gland is one of the most common sites of metastases after the lungs, liver, and bone. Incidental adrenal masses could be identified on abdominal computed tomographic (CT) imaging up to 5% [1]. Although most of these lesions are benign adenomas, in cancer patients accurate characterization of adrenal lesions is essential for staging. For benign adrenal adenomas, a CT density cut-off value of 10 Hounsfield units (HU) is widely accepted [2–4]. Abnormal gland size, lesion shape, and internal density characteristics (necrotic or homogeneous) on CT and delayed enhanced CT can be useful in the characterization of adrenal masses. However, the differentiation of benign versus malignant lesions is still a diagnostic dilemma, especially in cancer patients, and when CT scanning is used alone, it is not efficient in the differentiation of these lesions.

PET/CT as a new imaging modality in most cancer patients may be valuable in this matter. PET/CT provides both metabolic and anatomical information and maximum standardized uptake value (SUV_{max}) is the best index to assess disease activity.

An earlier study reported a 89% sensitivity and 94% specificity with an SUV_{max} cut-off value of 2.5 in 35 adrenal lesions of 30 patients [5]. However, the study population number was limited. In another study, a 1.8 threshold value for tumor/liver (T/L) SUV_{max} ratio showed the best sensitivity and specificity [6]. Several methods including SUV_{max} value, T/L SUV ratio, visual analysis, size, and HU values on CT scanning have been used to discriminate benign adrenal lesions versus malignant masses. To the best of our knowledge, no studies have compared all these methods. Therefore, the aim of our study was to compare all these methods, to investigate the best SUV_{max} value and T/L SUV ratio thresholds in various cancer patients by using FDG-PET/CT and to find the best index for differentiation of adrenal benign and malignant lesions.

Materials and methods

Patients

Between January 2008 and August 2010, 3819 PET/CT examinations were evaluated retrospectively. Patients with adrenal lesions on CT imaging provided by PET/CT were selected. A total of 81 patients (55 males and 26 females, age range: 31–81 years, mean: 61.5) who had confirmed primary malignancies underwent PET/CT examinations for cancer screening, staging, restaging, and detection of suspected recurrence. FDG-PET/CT indications and primary malignancies of 81 patients are summarized in Table 1. Our institutional review board did not require informed consent for a review of the patients' records and images.

Imaging protocol

All patients fasted for at least 6 h before an FDG injection of 370 MBq (10 mCi). PET/CT scans were obtained 60 min after injection using an integrated scanner (Siemens, Biograph True Point 6 PET/CT, Germany). A whole-body CT scan was performed without intravenous contrast administration with 130 kV, 50 mAs, a pitch of 1.5, a section thickness of 5 mm, and a field of view of 70 cm. A PET scan was performed immediately after an unenhanced CT scan, and acquired from the skull base to the upper thigh with a 3-min acquisition per bed position using a three-dimensional acquisition mode.

Table 1 ^{18}F-FDG PET/CT indications

Primary lesion	No. of patients
Lung cancer	47
Gastrointestinal malignancies	13
Malignant melanoma	1
Renal cell cancer	3
Mesothelioma	2
Breast carcinoma	9
Cervical cancer	1
Ovarian cancer	2
Pheochromocytoma	1
Unknown primary	2

CT, computed tomography; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; PET, positron emission tomography.

Diagnostic criteria for benign and malignant adrenal lesions

In this study, histopathology and follow-up information after PET/CT scanning served as the standard of reference. The mean follow-up period was 19.31 ± 6.46 months (range: 7–30 months). For final assessment, the standards of references for adrenal malignant lesions were based on biopsy ($n = 2$), interval growth, or reduction after chemotherapy. A mass was considered malignant if follow-up CT scans showed a 30% decrease in the longest diameter (partially response) or disappearance (complete response) after chemotherapy or a 20% increase in the longest diameter (progressive disease) on follow-up CT imaging. These criteria were based on Response Evaluation Criteria In Solid Tumors criteria [6,7]. An adrenal lesion remained unchanged on clinical and imaging follow-up for at least 7 months (mean follow-up time 19.31 months ± 6.46, range: 7–30 months) was decided as a benign lesion.

The references for diagnosis of benign adrenal lesions on CT imaging were HU measurement, diagnosis of a benign lesion (≤ 10), and imaging follow-up. Diagnosis of adrenal malignant lesions was based on two of the following three criteria: more than or equal to 4 cm, HU more than or equal to 30, and delayed contrast enhancement.

Image analysis

CT scans were reviewed by a radiologist with 10 years' experience on abdominal imaging who had no knowledge of either the other imaging results or the clinical information. The PET/CT images were qualitatively evaluated and retrospectively assessed in consensus by three nuclear medicine physicians (readers A, B, and C with 5, 4, and 2 years of experience on PET/CT, respectively). PET images were viewed in the coronal, axial, and sagittal sections. The degree of uptake intensity on transaxial PET/CT images was visually rated taking liver as a reference area based on a three-scale grading system:

(1) Grade I: intensity lower than liver
(2) Grade II: intensity equal to the liver
(3) Grade III: intensity higher than that of the liver.

All adrenal lesions detected on the CT portion of PET/CT imaging were measured on the CT scan as the longest diameter on transaxial images. Density was measured on CT scan using a region of interest (ROI) on CT. SUV_{max} of adrenal lesions were calculated on PET/CT fusion images by using a similar ROI. Both ROIs included at least two-thirds of the adrenal lesions. Partial volume effect was minimized in this way. The regions were drawn by generating sphere circles. The quantitative uptake values of FDG (SUV_{max}) in the adrenal ROIs were semiautomatically calculated using a workstation (Siemens). SUV_{mean} from the liver were also obtained from the ROI placed over the homogenous distribution of radioactivity in the right lobe of the liver that was free of metastasis and tumor SUV_{max}/liver SUV_{mean} ratios were calculated.

An SUV_{max} cut-off value of 2.5 and 1.8 as the threshold for T/L SUV ratio was used for the differentiation of adrenal benign and malignant lesions according to earlier reports [5,8]. In addition, an analysis of the receiver operating characteristics (ROC) curve to determine the best diagnostic value of the SUV_{max} and T/L SUV ratio was used.

Statistical analysis

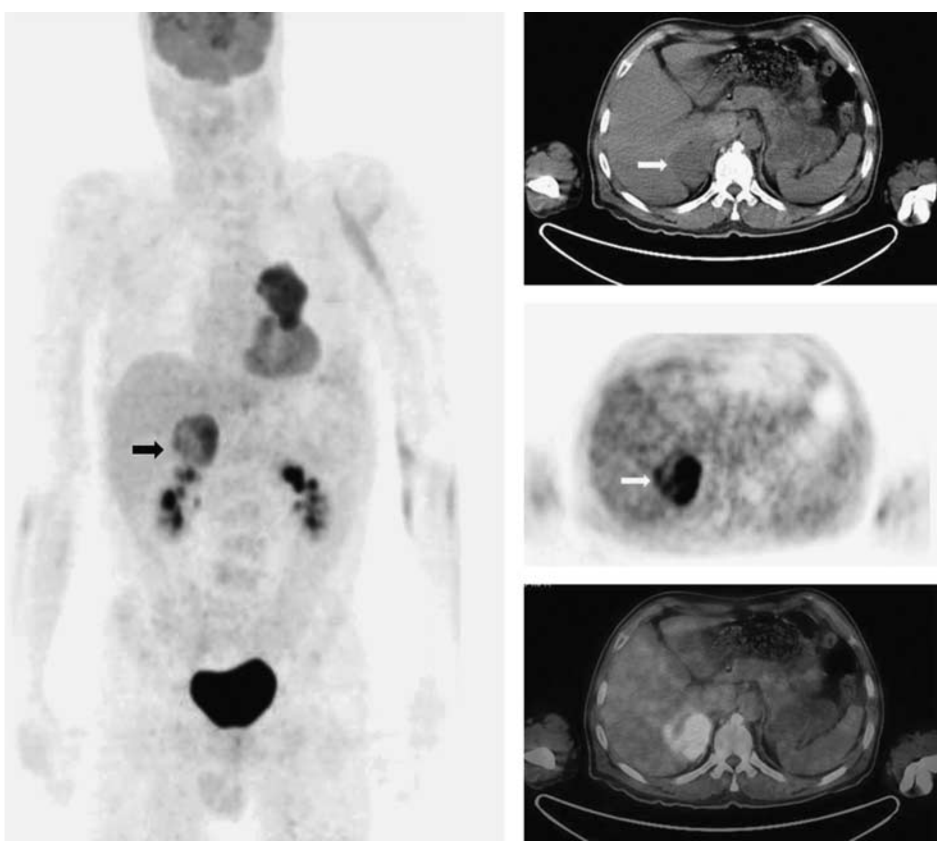
Patient groups were compared with regard to tumor size, density on CT (HU), T/L SUV ratio, and SUV_{max} using independent *t* tests. The values are expressed as mean ± standard deviation. Statistical analysis was carried out with SPSS software (SPSS Inc., Chicago, Illinois, USA). A *P* value of less than 0.05 was considered statistically significant.

ROC curves were drawn to determine the cut-off values. The best HU, SUV_{max} and T/L SUV cut-off values to differentiate benign from malignant adrenal lesions were determined. The McNemar test was used to compare the areas under the ROC curve and a *P* value of less than 0.05 was considered to show a significant difference. Sensitivity, specificity, and positive and negative predictive values were calculated using formulas based on an earlier report [9].

Results

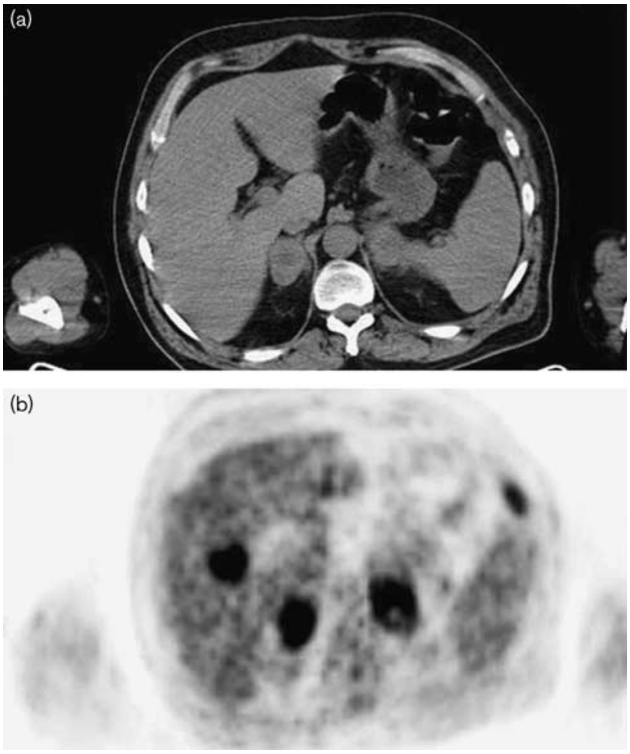
All 81 patients had histopathologically proven malignancies. The most common malignancy was lung cancer. All the 81 patients had 104 adrenal lesions (34 benign and 70 malignant adrenal lesions), which were shown by a portion of the CT of the PET/CT scan. Twenty-three of 81 (28%) patients had bilateral adrenal lesions whereas 58

Fig. 1



A 49-year-old man with lung carcinoma and 49 × 55 mm right adrenal malignant mass with grade III uptake. Maximum standardized uptake value and computed tomographic Hounsfield units measurement of the adrenal lesion were 10.09 and 26, respectively, whereas liver mean standardized uptake value was 1.98.

Fig. 2



A 50-year-old man with lung carcinoma and bilateral adrenal malignant metastasis. Transaxial computed tomography (CT) (a) obtained from PET/CT shows bilateral adrenal masses with a diameter of 36 × 26 mm right adrenal and 35 × 22 mm left adrenal masses. Transaxial PET image (b) shows bilateral adrenal masses with grade III uptake pattern (maximum standardized uptake value for right adrenal mass: 14.14 and left adrenal mass: 12.20).

Table 2 Grades of uptake for benign and malignant adrenal lesions

Grade	I (%)	II (%)	III (%)
Benign adrenal lesions	13/34 (38)	18/34 (53)	3/34 (8)
Malignant adrenal lesions	0/34 (0)	6/70 (9)	64/70 (91)

of the 81 patients (72%) had unilateral. Figures 1 and 2 illustrate two patients with adrenal metastasis. The diagnosis of 22 benign adrenal lesions was obtained by CT attenuation value of less than or equal to 10 HU, whereas 12 of the 34 adrenal benign lesions had a CT attenuation value more than 10 HU. One malignant adrenal lesion had an attenuation value of less than 10. For malignant adrenal lesions all of the patients had grade II or III uptake. There was no adrenal malignant lesion showing grade I uptake. For benign adrenal lesions, the majority of patients had grade I or II uptake. Grades of uptake for benign and malignant lesions on PET/CT imaging are shown in Table 2. Size, density, and SUV_{max} values for benign and malignant adrenal lesions are shown

Table 3 Size, density (HU), and SUV_{max} values for adrenal benign and malignant lesions

Lesion type	Parameter	Size (mm)	HU	SUV_{max}
Benign (n=34)	Mean	18.44	9.26	3.02
	SD	5.07	16.0	1.15
	Minimum	9.0	−19.0	1.26
	Maximum	35.0	42.0	6.54
Malignant (n=70)	Mean	33.26	33.23	8.82
	SD	22.61	10.01	4.47
	Minimum	10.0	4.0	3.6
	Maximum	123.0	58.0	26.72
Total (n=104)	Mean	28.42	25.39	6.93
	SD	19.99	16.63	4.62
	Minimum	9.0	−19.0	1.26
	Maximum	123.0	58.0	26.72

HU, Hounsfield units; SD, standard deviation; SUV_{max}, maximum standardized uptake value.

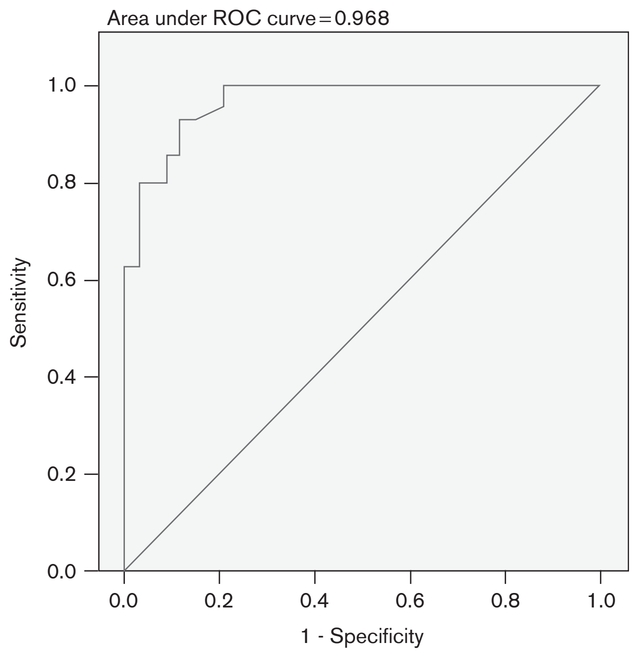
Table 4 Differentiation between adrenal benign and malignant lesions using maximum standardized uptake value, tumor/liver standardized uptake value ratios, and computed tomography attenuation values

	Sensitivity (%)	Specificity (%)	Accuracy (%)
SUV_{max} ≥ 2.5 or <2.5	100.0	38.2	80.0
T/L SUV_{max} ratio ≥ 1.8 or <1.8	87.0	91.0	88.5
SUV_{max} ≥ 4.2 or <4.2	88.2	88.6	88.5
T/L SUV ratio ≥ 1.68 or <1.68	90.0	91.1	90.4
CT attenuation value (HU ≤ 10 or >10)	64.7	98.6	87.5
CT attenuation value (HU ≥ 26.5 or <26.5)	79.4	76.0	76.9

CT, computed tomography; HU, Hounsfield units; SUV_{max}, maximum standardized uptake value; T/L, tumor/liver.

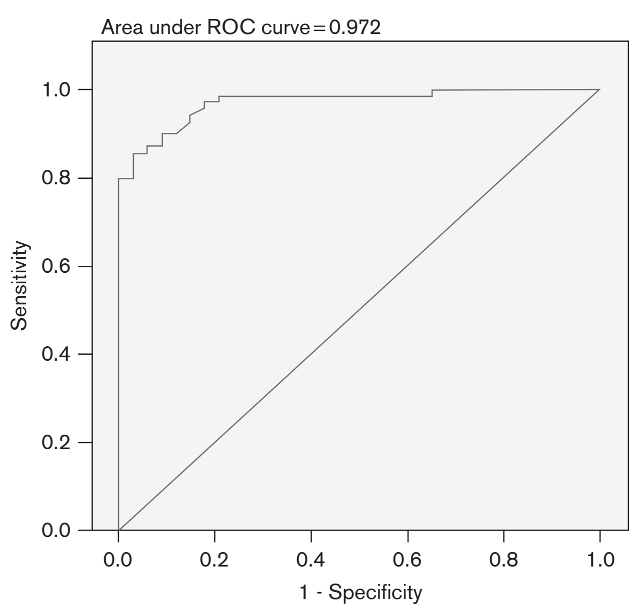
in Table 3. The mean size for adrenal malignant lesions was 33.26 ± 22.61 and 18.44 ± 5.07 for adrenal benign lesions ($P < 0.0001$). In adrenal malignant lesions SUV_{max} (8.82 ± 4.47) was higher than that of adrenal benign lesions (3.02 ± 1.15, $P < 0.0001$). In adrenal malignant lesions HU (33.2 ± 10.0) was higher than that of adrenal benign lesions (9.3 ± 16.0, $P < 0.0001$). In the differentiation of adrenal benign and malignant lesions, a CT threshold value of 10 HU corresponded to a sensitivity of 64.7%, specificity of 98.6%, and accuracy of 87.5%. A HU cut-off value of 26.5 provided a sensitivity of 76%, specificity of 79.4%, and accuracy of 76.9%. An SUV_{max} cut-off value of 2.5 corresponded to a sensitivity of 100%, specificity of 38.2%, and accuracy of 80%. An SUV_{max} cut-off value of 4.2 corresponded to a sensitivity of 88.6%, specificity of 88.2%, and accuracy of 88.5%. The T/L ratio was 3.61 ± 1.77 for adrenal malignant lesions and 1.20 ± 0.38 for adrenal benign lesions ($P < 0.0001$). The cut-off value of the T/L ratio of 1.8 corresponded to a sensitivity of 87%, specificity of 91%, and accuracy of 88.5%. The cut-off value of T/L ratio of 1.68 corresponded to a sensitivity of 90%, specificity of 91.1%, and accuracy of 90.4% (Table 4). ROC curves generated from SUV_{max}, T/L SUV ratio, CT HU data, and size are illustrated in Figs 3–6, respectively.

Fig. 3



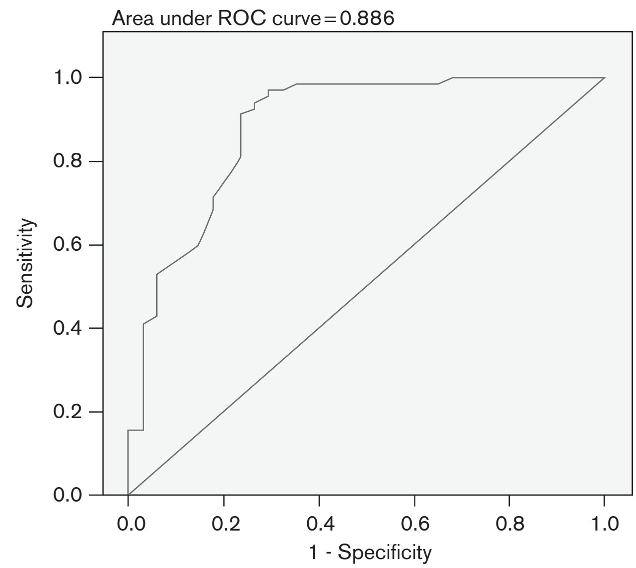
Receiver operating characteristics (ROC) generated from maximum standardized uptake value (SUV_{max}) information. An SUV_{max} cut-off of 2.5 provides a sensitivity of 100% and a specificity of only 38.2%. In contrast, an SUV_{max} of 4.2 provides a sensitivity of 88.6% and a specificity of 88.2.

Fig. 4



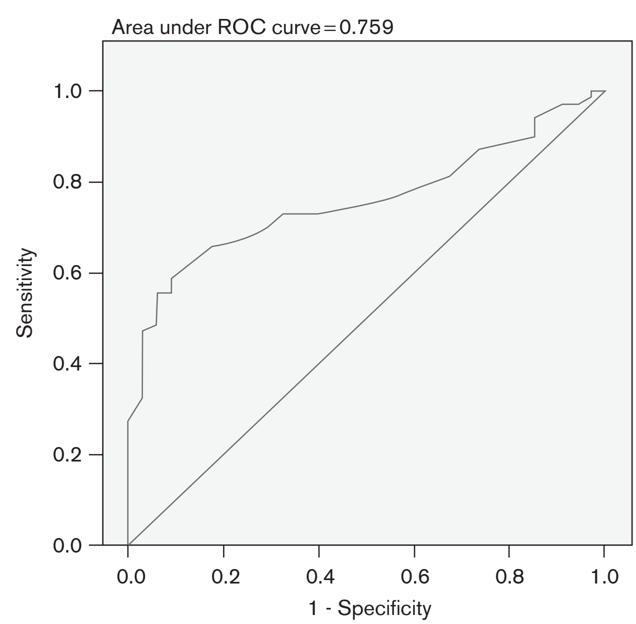
Receiver operating characteristics (ROC) generated from tumor SUV_{max}/liver SUV_{mean} ratio data. Tumor/liver (T/L) SUV ratio cut-off value of 1.8 corresponded to a sensitivity of 87%, specificity of 91%, and accuracy of 88.5%. T/L SUV ratio cut-off value of 1.68 corresponded to a sensitivity of 90%, specificity of 91.1%, and accuracy of 90.4%.

Fig. 5



Receiver operating characteristics (ROC) generated from computed tomography (CT) Hounsfield units (HU) information. A CT threshold of 10 HU corresponded to a sensitivity of 64.7%, specificity of 98.6%, and accuracy of 87.5%. A HU cut-off value of 26.5 provided a sensitivity of 76%, specificity of 79.4%, and accuracy of 76.9%.

Fig. 6



Receiver operating characteristics (ROC) generated from size information. Area under the curve was only 0.759.

Discussion

Discrimination of adrenal benign lesions versus malignant masses is essential, especially in cancer patients for choosing the appropriate treatment approach and assessing prognosis. In lung cancer and melanoma, a tumor with an adrenal metastasis is considered unresectable and is usually treated with chemotherapy [10]. Most of the incidentally discovered adrenal lesions are benign adenomas in patients without a primary malignancy and they are usually detected incidentally. However, in patients with a known malignancy, despite the fact that approximately 40–57% of adrenal lesions are benign [11–13], a noninvasive evaluation method in an adrenal lesion is essential. Adrenal biopsy is a relatively invasive procedure with various complications and high failure rate. A CT threshold of 10 HU or less suggests lipid-rich adenoma with high specificity (98%). The reported sensitivity of this criterion is 71% [14]. Moreover, approximately 30% of adenomas are lipid poor. In this study, CT attenuation values were greater than 10 HU in 12 of 34 patients (35%) with benign adrenal lesions. In this study, for a CT cut-off value 10 HU, although the specificity was higher (98.6%), the sensitivity resulted from this cut-off value was 64.7%. Therefore, a CT attenuation cut-off value of 10 HU on an unenhanced CT scan, when used alone, is not enough for the differentiation of adrenal lesions. Adrenal masses with attenuation values more than 10 HU on a nonenhanced CT scan require further evaluation with either CT contrast material washout or chemical shift MRI or biopsy.

In a recent study by Miller *et al.* [15] diffusion MRI was not found to be useful for distinguishing benign from malignant adrenal lesions. The purpose of the study was to evaluate the utility of the apparent diffusion coefficient values for characterizing adrenal lesions and determining whether diffusion-weighted imaging can distinguish lipid-rich from lipid-poor adenomas. Lipid-poor adenomas could not be distinguished from lipid-rich adenomas and all other nonfatty lesions of the adrenal gland with diffusion-weighted imaging. Chemical shift MRI imaging had a high failure rate, especially in lipid-poor adenomas.

Several studies using visual inspection and considering adrenal FDG uptake higher than liver uptake to be suggestive of malignancy showed sensitivity ranging between 92 and 100% and specificity between 80 and 100% [16–20]. In an earlier report by Okada *et al.* [5], a SUV_{max} cut-off value of 2.5 corresponded to a sensitivity of 89%, specificity of 94%, and accuracy of 91%. However, the number of patients in this study was limited. In contrast to that report, in this study population, an SUV_{max} cut-off value of 2.5 corresponded to high sensitivity (100%), but lesser specificity (38.2%).

In this study, for malignant adrenal lesions all of the patients had grade II or III uptake. For benign adrenal lesions the majority of the patients had grade I or II uptake. There was no malignant adrenal lesion with grade I uptake. Although 18 of 34 (53%) benign lesions and six of 70 (9%) malignant adrenal lesions showed grade II uptake, three of the 34 (8%) benign lesions showed grade III uptake. An earlier study by Caoili *et al.* [21] stated that adrenal mass activity visibly less than that of the liver is more specific for adenoma, whereas adrenal mass activity, visibly greater than that of the liver is more specific for malignancy. This view is mostly consistent with this study. Although, according to the findings in this study, when visual analysis and grading are used alone, there would be undetermined lesions showing grade II uptake and high false-positive results (a benign lesion that was a PET-positive and grade III benign lesion). When adrenal lesion uptake exceeding liver uptake (grade III lesions) is thought to be a malignant criterion for adrenal lesions, the sensitivity of PET/CT were found to be 91.4%, and the specificity was 66.6%. If grade II and III lesions are thought to be malignant lesions, the sensitivity of PET/CT will be 100%, whereas the specificity will be only 38.2%.

One of the three benign lesions showing grade III uptake (false-positive visual analysis) had SUV_{max} more than 4.2 but the same lesion had a T/L SUV ratio of less than 1.68. In the remaining two of the three benign adenomas the cut-off value of SUV_{max} was less than 4.2. When we add SUV_{max} and T/L SUV ratio indexes to visual analysis, there will be no false-positive adrenal lesion.

A combined factor of SUV_{max} more than or equal to 4.2, T/L ratio more than or equal to 1.68, and CT HU more than or equal to 26.5, the overall sensitivity of PET/CT is 98.6%, specificity of 100%, positive predictive value of 100%, negative predictive value of 97%, and accuracy of 99%. There was one adrenal malignant mass with a diameter of 21 mm, which supported none of these criteria (false-negative grade II). However, the same patient had a contralateral malignant adrenal mass.

In an earlier report by Vikram *et al.* [9], the overall sensitivity of PET/CT in determination of malignancy was 83.3% and the specificity was 85.4%. Only adrenal nodules at least 1 cm in diameter were included in this study. Therefore, they could not apply these results to nodules smaller than 1 cm in diameter.

The mean size of the benign lesions was 18.44 ± 5.07 mm, and the mean size of the malignant lesions was 33.26 ± 22.61 mm. The difference was statistically significant. Despite the fact that this finding was in concordance with published findings that benign nodules are significantly smaller than malignant nodules, the standard deviations were high. SUV_{max} was found to be more useful when compared with size and HU measurement. A HU cut-off value of 26.5 provided a sensitivity of 79.4%, specificity of 76%, and accuracy of 76.9%. In this study population, a SUV_{max} cut-off value of

4.2 corresponded to a sensitivity of 88.6%, specificity of 88.2%. This study shows that the T/L SUV ratio 1.68 threshold is the best index for discrimination of adrenal benign versus malignant lesions.

Our study had some limitations. First, it was retrospective. Second, we used clinical and imaging follow-up in the majority of cases; we could obtain pathological confirmation only in two cases. Although in an earlier report by Paulsen *et al.* [22] biopsy is reserved for a few indeterminate lesions. Most adrenal nodules are characterized with either clinical or imaging follow-up. The third study population was of heterogenous cancer patients and the prevelance of malignant nodules was high.

Conclusion

FDG-PET/CT imaging improves the diagnostic accuracy in the differentiation of benign from malignant adrenal lesions in various cancer patients. Combined information obtained from PET/CT (SUV_{max}, T/L SUV ratio, visual analysis) and unenhanced CT scanning (size, HU measurement) is recommended for better differentiation.

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