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## FULL PAPER

# Utilisation of combined $^{18}\text{F}$ -FDG PET/CT scan for differential diagnosis between benign and malignant adrenal enlargement

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**Objective:** To assess the properties of adrenal lesions with and without known primary cancer and investigate predictors for differential diagnosis between benign and malignant adrenal enlargement.

**Methods:** This retrospective study used fluorine-18 fludeoxyglucose positron emission tomography (PET)/CT in 325 patients with adrenal lesions (229 with known primary cancer and 96 without primary cancer). Age, sex, the presence of right and left masses, nodules or hyperplasia, unenhanced attenuation, maximum standardised uptake value ( $\text{SUV}_{\text{max}}$ ) ratio, and the presence of metastasis in other body parts and locations of the primary cancer were assessed. Univariate and multivariate analyses were used to assess variables associated with risk of adrenal metastasis.

**Results:** Patients with adrenal metastasis vs those without had a higher frequency of primary lung cancer (52.3% vs 30.7%) but a lower frequency of gastrointestinal cancer (7.9% vs 16.6%). The frequency of other

abnormalities, including adenoma and hyperplasia, was similar between patients with and without known primary cancer. A higher proportion of patients with adrenal metastasis regardless of primary cancer site were younger, had a nodule or a mass, had an unenhanced attenuation of  $>10$  HU, had an  $\text{SUV}_{\text{max}}$  ratio of  $>2.5$ , and had metastasis in other body parts. Analysis found independent associations of age, unenhanced attenuation of  $>10$  HU,  $\text{SUV}_{\text{max}}$  ratio of  $>2.5$  and the presence of metastasis in other body parts with adrenal metastasis. The combination of the four variables was strongly associated with adrenal metastasis.

**Conclusion:** PET/CT was useful in characterising adrenal lesions as benign or malignant and helpful in identifying adrenal metastasis and cancer severity.

**Advances in knowledge:** PET/CT can help in the differential diagnosis between benign and malignant adrenal enlargement.

The adrenal gland is a common site of metastasis in patients with cancer. Up to 50% of adrenal lesions in patients with known primary non-adrenal cancers are malignant disease [1–4]. The most common malignant lesions that metastasise to the adrenal gland include lung, liver, colon, lymphoma, melanoma, breast, kidney, oesophagus, pancreas and stomach cancer [4–6]. However, diagnosis of an adrenal lesion as malignant or benign can be problematic. Characterisation of these adrenal lesions is therefore critical to stage the primary disease, direct therapy and predict prognosis. Although CT and MRI are typically used to characterise a lesion, a small but important number of adrenal lesions are found to be indeterminate on cross-sectional images [7–9].

Several reports have documented the effectiveness of stand-alone fluorine-18 fludeoxyglucose ( $^{18}\text{F}$ -FDG) positron

emission tomography (PET) to differentiate benign from malignant adrenal lesions [8–10]. Interest has focused on the ability of integrated in-line PET/CT to definitively characterise these lesions given that this technique combines the anatomical and densitometrical applications of CT and the functional and metabolic advantages of PET. Several studies have reported PET/CT's high sensitivity, specificity and accuracy for detecting adrenal metastatic lesions [7–10].

PET/CT can also be used as a non-invasive method to help assess the lesion, facilitating diagnosis and treatment decisions. The purpose of our study was to investigate whether PET/CT can reliably detect differences between malignant and benign lesions, tumour characteristics associated with the location of the primary cancer and predictors for adrenal metastasis.

## METHODS AND MATERIALS

Our study was approved by Institutional Review Board of local general hospitals, and the requirement of informed consent was waived owing to the retrospective nature of our study.

### Patient population

From January 2006 to July 2012, 325 consecutive patients had adrenal lesions as identified by an initial integrated in-line PET/CT that were diagnosed as adrenal metastasis (for those with known primary cancers) or adenoma and hyperplasia by examination 6–30 months after the initial PET/CT. The mean follow-up period was 18 months. During the follow-up period, we characterised the lesions as either benign or malignant.

Patients whose lesions were diagnosed as myelolipomas by the presence of macroscopic fat were excluded from our study, as were patients who had been treated for malignant or benign lesions in the adrenal gland, had diabetes or any other disorder affecting glucose metabolism.

### PET/CT techniques

Patients fasted for at least 6 h before PET/CT. Blood glucose was measured 1 h before injection of  $^{18}\text{F}$ -FDG and was ideally less than  $150\text{ mg dL}^{-1}$ . The used  $^{18}\text{F}$ -FDG dose was 10–12 mCi (370–444 MBq), with 1 h uptake. Imaging was acquired with an integrated in-line PET/CT system (Discovery<sup>TM</sup> ST; GE Healthcare, Waukesha, WI). Unenhanced CT from the base of the skull to the upper thigh was performed for attenuation correction and diagnosis (300 mA; tube rotation time 0.5 s; 120 kVp; table speed 13.5 mm per rotation; beam collimation  $8 \times 1.25\text{ mm}$ ). Axial CT images were reconstructed with a soft reconstruction kernel with a slice thickness of 3.75 mm and an interval of 3.27 mm to match the PET images.

The PET images were obtained in the two-dimensional mode for 3 min per bed position, and the images were reconstructed with standard vendor-provided reconstruction algorithms incorporating ordered subset expectation maximisation. Attenuation correction of PET images was performed with attenuation data from the CT component of the examination. The manufacturer's software was used to correct emission data for scatter, random events and dead-time losses.

### PET/CT analysis

The PET/CT components were reviewed on a high-resolution workstation (Marosis; Infinity, Seoul, Republic of Korea). The PET and fused CT images were analysed in both axial and coronal planes. Two radiologists and one nuclear medicine physician reviewed the images, and decisions were reached by consensus.

The CT component measured the size of the adrenal lesion. The adrenal lesion unenhanced attenuations were measured from the unenhanced attenuation correction CT by taking the mean of two measurements from a region of interest (ROI). The ROI covered from one-half to two-thirds of the surface area of the lesion, avoiding adjacent retroperitoneal fat and inhomogeneous areas.

The PET and fused CT images were used to measure the average standardised uptake value (SUV) over an ROI placed on the liver

and the adrenal lesion. The PET/CT images reconstructed in the coronal and axial planes were used to confirm accurate placement of the ROI on the adrenal gland. The ROI included at least two-thirds of the adrenal lesion. A similar-sized ROI was placed within the right hepatic lobe free from the detectable metastatic lesion. Care was taken to avoid the periphery of the lesion, thereby minimising the partial volume effect. Maximum SUV ( $\text{SUV}_{\text{max}}$ ) and average SUV ( $\text{SUV}_{\text{avg}}$ ) were generated by the software with the equation  $\text{SUV} = C_{\text{tis}}/D_{\text{inj}}/\text{body weight}$ , in which SUV is normalised for body weight in kilograms,  $C_{\text{tis}}$  is tissue concentration in megabecquerels per milliliter and  $D_{\text{inj}}$  is the injected dose in megabecquerels. The adrenal  $\text{SUV}_{\text{max}}$  ratio was divided by the liver  $\text{SUV}_{\text{avg}}$  to calculate a ratio ( $\text{SUV}_{\text{ratio}}$ ) for each lesion.

### Standard reference

The results of follow-up images were all used as reference standards for final characterisation of the adrenal lesion in our study. Lesions that remained stable in size for more than 6 months at follow up were considered benign. Criteria for malignancy included an interval increase in size or more than 20% decrease in size after appropriate therapy. The mean follow-up period for lesions was 18 months. As this study is a retrospective examination and analysis of the clinical data, there were a variety of follow-up methods, such as contrast-enhanced CT, MRI and PET/CT.

### Statistical analysis

Age was shown as mean  $\pm$  standard deviation and compared between groups by independent Student's *t*-test. Other categorical variables were shown as proportions, and the association between categorical variables was compared with Fisher's exact test. The variables associated with adrenal metastasis were shown by their odds ratios with the 95% confidence interval (CI) in the univariate and multivariate logistic regression models.

The cut-off point of unenhanced attenuation (10 HU) in the prediction of adrenal metastasis was determined by the commonly accepted value for distinguishing between benignancy and malignancy, and the cut-off point of  $\text{SUV}_{\text{max}}$  ratio (2.5) was determined by the Youden's index (the maximum of sensitivity and specificity-1) in the receiver operating characteristic curves analysis. The variables with *p*-values  $<0.05$  were included in a multivariate logistic regression model, selected by a forward conditional method. Statistical analysis was performed using appropriate software (SPSS<sup>®</sup> v. 18.0 for Windows; SPSS, Chicago, IL). Null hypotheses of no difference were rejected if the *p*-value was  $<0.05$  or, equivalently, if the 95% CI of odds ratio estimates excluded 1.

## RESULTS

### Patient demography analysis

PET/CT was performed on 10750 patients, including 3562 patients with primary cancer and 7188 patients without primary cancer. Of these, 325 patients had adrenal lesions, 229 of whom had known primary cancer and 96 of whom did not have known primary cancer. Among the 325 patients with adrenal lesions, 28 were histologically diagnosed; of these, 21 were diagnosed as having malignant lesions and the remaining 7 were diagnosed as having benign lesions.

Patients' demographics and PET/CT characteristics are summarised in Table 1. The presence of lesions in both groups of patients was not associated with age or sex, and the majority of patients in both groups were males. Over half of the patients with primary cancer had a metastatic lesion. The types of primary cancers included lung (44.9%), gastrointestinal (13.5%), liver (10.9%) and others (30.7%).

The proportion of patients with a mass in both adrenal glands was small in both groups but was significantly higher for the patients with known primary cancer. The proportion of lesions that were nodule, hyperplasia or normal was similar in both groups. Unenhanced attenuation >10 HU and SUV<sub>max</sub> ratios >2.5 were significantly higher in patients with known primary cancer than in those without. More patients without known primary cancer had evidence of no <sup>18</sup>F-FDG uptake.

#### Analysis of characteristics in patients with known primary cancer

The characteristics of patients with known primary cancer and categorisation by primary cancer types are summarised in Table 2.

Patients with adrenal metastasis were younger, more often had nodules or masses and more often both unenhanced attenuation >10 HU and an SUV<sub>max</sub> ratio >2.5. As would be expected, more patients with adrenal metastasis had metastasised tumours in other parts of their body. Patients with adrenal metastasis most often had primary lung cancer and less often had primary tumours in the gastrointestinal tract and the liver. Patients without adrenal metastasis had a higher rate of gastrointestinal cancer. Those with adrenal metastasis and a gastrointestinal cancer primary were significantly younger than those without adrenal metastasis.

Univariate analysis of predictors of adrenal metastasis  
The results of univariate analysis for predicting adrenal metastasis in patients with known primary cancer and categorisation by primary cancer are summarised in Table 3. Age, presence of left and right nodules or masses, unenhanced attenuation, SUV<sub>max</sub> ratio, and metastasis in other parts and locations of the primary cancer are significantly associated with adrenal metastasis. However, only age, unenhanced CT attenuation, SUV<sub>max</sub> ratio and the presence of metastasis in other parts were associated with adrenal metastasis after stepwise forward selection.

Table 1. Patients' demographics and PET/CT characteristics

Parameters	Findings	With known primary cancer (n=229)	Without known primary cancer (n=96)	p-value
Age (years)		59.5±14.2	54.3±16.5	0.250
Sex (male/female)		146/67	88/34	0.380
Adrenal lesions	Metastasis	163 (71.2%)	0 (0.0%)	<0.001
	Benign	66 (28.8%)	96 (100.0%)	
Primary cancer	Lung cancer	103 (44.9%)	—	
	Gastrointestinal cancer	31 (13.5%)	—	
	Liver cancer	25 (10.9%)	—	
	Others	70 (30.7%)	—	
PET/CT				
Left adrenal gland	Mass	22 (9.6%)	2 (2.0%)	0.026
	Nodule	78 (34.0%)	44 (45.8%)	
	Hyperplasia	62 (27.2%)	32 (33.3%)	
	Normal	67 (29.2%)	18 (18.9%)	
Right adrenal gland	Mass	17 (7.45%)	1 (1.0%)	0.024
	Nodule	43 (18.7%)	17 (17.8%)	
	Hyperplasia	27 (11.8%)	15 (15.6%)	
	Normal	142 (62.0%)	63 (65.6%)	
Unenhanced attenuation	>10 HU	148 (64.6%)	12 (8.4%)	<0.001
	≤10 HU	81 (36.4%)	88 (91.6%)	
SUV <sub>max</sub> ratio	>2.5	52 (22.7%)	3 (3.1%)	<0.001
	≤2.5	109 (47.5%)	25 (26.0%)	
	Absence of uptake	68 (29.8%)	68 (70.9%)	
	Unknown	—	96% (100.0%)	

PET, positron emission tomography; SUV<sub>max</sub>, maximum standardised uptake value.

Table 2. Characteristics in patients with known primary cancer and categorisation by primary cancer type

Parameters	Findings	Adrenal metastasis											
		All patients with known primary cancer (n=229)			Patients with lung cancer (n=103)			Patients with gastrointestinal cancer (n=31)			Patients with liver cancer (n=25)		
		Yes (n=151)	No (n=78)	p-value	Yes (n=79)	No (n=24)	p-value	Yes (n=13)	No (n=18)	p-value	Yes (n=12)	No (n=13)	p-value
Age (years)		54.8±12.5	65.5±11.7	0.028	59.2±13.0	62.4±11.7	0.090	56.1±12.7	64.8±10.4	0.010	60.4±9.9	57.3±11.2	0.160
Left adrenal	Nodule or mass	76 (50.3%)	24 (30.7%)	0.003	36 (45.5%)	8 (33.3%)	0.125	6 (46.1%)	7 (38.8%)	0.381	5 (41.6%)	7 (53.8%)	0.580
Right adrenal	Nodule or mass	49 (32.4%)	11 (14.1%)	0.009	19 (24.0%)	5 (20.8%)	0.430	4 (30.7%)	5 (27.7%)	0.600	5 (41.6%)	9 (69.2%)	0.057
Unenhanced	≤10HU	11 (8.8%)	31 (89.9%)	0.001	5 (9.0%)	10 (76.9%)	0.009	2 (20.0%)	11 (91.6%)		0	5	
Attenuation	>10HU	114 (91.2%)	4 (11.1%)	0.001	50 (91.0%)	3 (23.1%)	0.010	8 (80.0%)	1 (8.4%)		6	0	
SUV <sub>max</sub> ratio	≤2.5	68 (45.0%)	41 (52.5%)		29 (36.7%)	5 (20.8%)		8 (61.5%)	6 (33.3%)		0 (0.0%)	0 (0.0%)	
	>2.5	50 (33.1%)	2 (2.1%)		32 (40.5%)	1 (4.1%)		5 (38.4%)	0 (0.0%)		6 (50.0%)	5 (38.4%)	
	No <sup>18</sup> F-FDG uptake	9 (5.9%)	59 (75.6%)	<0.001	3 (3.7%)	15 (62.5%)	<0.001	1 (7.6%)	11 (61.8%)	<0.001	1 (8.3%)	7 (53.8%)	<0.001
Metastasis in other parts	Yes	121 (73.5%)	24 (29.4%)	<0.001	62 (74.6%)	9 (29.1%)	<0.001	11 (84.6%)	9 (50.0%)	0.008	8 (58.3%)	4 (23.0%)	0.214
	No	30 (13.2%)	54 (66.6%)		17 (18.9%)	15 (54.1%)		2 (15.3%)	9 (50.0%)		4 (0.25%)	9 (61.5%)	
	Lung cancer	77 (49.0%)	26 (37.1%)	0.002									
Primary	Gastrointestinal cancer	15 (7.9%)	16 (24.3%)	0.014									
	Liver cancer	13 (7.2%)	12 (17.9%)	0.174									
	Other	46 (28.4%)	24 (34.6%)	0.156									

<sup>18</sup>F-FDG, fluorine-18 fludeoxyglucose; SUV<sub>max</sub>, maximum standardised uptake value.

Table 3. Univariate analysis for predicting adrenal metastasis in patients with known primary cancer and categorisation by primary cancer type

Parameters	Findings	All patients with known primary tumour (n=229)		Patients with gastrointestinal cancer (n=103)		Patients with lung cancer (n=31)		Patients with liver cancer (n=25)	
		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (years)		0.96 (0.94, 0.98)	0.024	0.95 (0.94, 1.00)	0.142	0.91 (0.86, 0.99)	0.028	1.05 (0.97, 1.18)	0.176
Left adrenal	Nodule or mass	2.31 (1.34, 3.95)	0.042	2.15 (0.88, 5.30)	0.093	2.04 (0.51, 8.24)	0.317	1.68 (0.31, 9.01)	0.553
Right adrenal	Nodule or mass	2.38 (1.29, 4.21)	0.038	1.35 (0.46, 3.58)	0.631	1.45 (0.35, 7.29)	0.638	9.07 (0.86, 97.53)	0.068
Unenhanced	≤10 HU	3.25 (1.54, 9.26)	<0.001	2.99 (1.34, 9.06)	<0.001	12.57 (1.42, 86.51)	0.031	NA	NA
Attenuation	>10 HU	414.5 (34.1, 3712.1)	<0.001	321.5 (12.1, 2095.1)	<0.001	6.54 (1.01, 78.42)	0.044	NA	NA
SUV <sub>max</sub> ratio	≤2.5	15.4 (6.3, 38.2)	<0.001	39.4 (7.3, 210.8)	<0.001	17.5 (1.4, 171.5)	0.015	8.30 (0.76, 93.22)	0.085
	>2.5	509.8 (58.2, 4215.4)	<0.001	321.0 (27.2, 3712.8)	<0.001	NA	NA	NA	NA
Metastasis in other parts	Yes	5.35 (2.05, 8.99)	<0.001	5.05 (2.09, 12.51)	<0.001	14.2 (1.6, 129.2)	0.019	3.68 (0.88, 23.23)	0.141
	Lung cancer	2.52 (1.32, 4.93)	0.004						
Primary	Gastrointestinal cancer	0.68 (0.32, 1.43)	0.180						
	Liver cancer	0.71 (0.32, 1.81)	0.006						
	Other	—	—						

NA, not applicable; OR, odds ratio; SUV<sub>max</sub>, maximum standardised uptake value; 95% CI, confidence interval. Reference groups indicate that the corresponding variable had a significant influence on adrenal metastasis. NA indicates that the odds ratio was not performed owing to small or zero count.

Table 4. Impact variables of adrenal metastasis by multivariate analysis

Parameters	Findings	All patients with known primary tumour <sup>a</sup> (n=229)		Patients with lung cancer <sup>b</sup> (n=103)		Patients with gastrointestinal cancer <sup>c</sup> (n=31)	
		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (years)		0.97 (0.94, 0.99)	0.021	NA		0.87 (0.78, 1.00)	0.070
Unenhanced	>10 HU	2.62 (1.23, 8.53)	<0.001	2.10 (1.24, 8.76)	<0.001	1.27 (0.29, 5.01)	0.638
Attenuation	≤10 HU	356.1 (29.8, 3213.2)	<0.001	278.3 (10.9, 1825.8)	<0.001	12.0 (1.3, 57.5)	0.035
SUV <sub>max</sub> ratio	≤2.5	13.9 (5.3, 36.8)	<0.001	35.8 (5.9, 194.6)	<0.001	21.7 (1.5, 280.5)	0.020
	>2.5	471.5 (53.9, 4240.2)	<0.001	310.7 (25.4, 3750.7)	<0.001	NA	NA
Metastasis in other parts	Yes	4.41 (1.74, 9.22)	< 0.001	4.07 (1.04, 14.23)	0.042	NA	NA

NA, not applicable; OR, odds ratio; SUV<sub>max</sub>, maximum standardised uptake value; 95% CI, confidence interval. Reference group indicates that the corresponding variable had a significant influence on adrenal metastasis. NA indicates that the odds ratio was not performed owing to small or zero count. <sup>a</sup>p=0.321 in Hosmer and Lemeshow test indicates that the multivariate model fit well. <sup>b</sup>p=0.686 in Hosmer and Lemeshow test indicates that the multivariate model fit well. <sup>c</sup>p=0.136 in Hosmer and Lemeshow test indicates that the multivariate model fit well.

The results of multivariate analysis for variables associated with adrenal metastasis are summarised in Table 4. After controlling for the unenhanced attenuation, SUV<sub>max</sub> ratio and metastasis to other parts, the risk for developing adrenal metastasis decreased slightly by each year of increasing age. Controlling for age, unenhanced attenuation and SUV<sub>max</sub> ratio, patients with metastasis to other parts had a significantly higher risk of adrenal metastasis than those with no adrenal metastasis. After controlling for the other two variables, unenhanced attenuation >10 HU and an SUV<sub>max</sub> ratio >2.5 raised the risk of adrenal metastasis significantly. This relationship held consistently across the major sites of lung and gastrointestinal cancer, although numbers were too small for significance with liver cancer.

### Multivariate analysis of predictors of adrenal metastasis

The results of multivariate analysis for predicting adrenal metastasis in patients with known primary cancer and in patients with lung and gastrointestinal cancers are summarised in Table 5. For patients with known primary cancer, age, unenhanced attenuation, SUV<sub>max</sub> ratio and metastasis to other parts were associated with adrenal metastasis. The highest accuracy for predicting adrenal metastasis was for the combination of “unenhanced attenuation >10 HU, SUV<sub>max</sub> ratio >2.5, metastasis to other parts or age”, with 92.0%, 88.4% and 90.8% sensitivity, specificity and accuracy, respectively (Figure 1). The pairing of “unenhanced attenuation >10 HU or SUV<sub>max</sub> ratio >2.5” had relative lower sensitivity, specificity and accuracy than the combination of the variables. These findings held for primary site-specific analysis as well as for both lung and gastrointestinal cancer.

### DISCUSSION

Our retrospective study used PET/CT to assess the characteristics of adrenal lesions in patients with known primary cancer and without primary cancer. Once an adrenal lesion has been detected in patients with cancer, its characterisation is critical to stage the primary disease. The most common clinical conundrum is to differentiate benign non-functioning lesions from metastatic lesions. Patients with known primary cancer were more likely to have an adrenal metastatic lesion than patients with no primary tumour. The risk of adrenal metastases is very low in patients with no history of primary cancer. Song et al [11] reported that a study of 1049 consecutive incidental adrenal masses in patients with no history of cancer did not find a single malignancy.

Imaging techniques to differentiate these lesions must be as close to 100% specific as possible so as not to risk making a diagnosis of benignancy in error [12]. The unenhanced CT and contrast-enhanced CT washout study and chemical shift MRI meet these principles [13–17]. The use of an integrated PET/CT enables confident localisation and characterisation of adrenal lesions [18]. Unenhanced attenuation data from an integrated PET/CT can characterise most benign adenomas given that the 10-HU threshold to differentiate benign from indeterminate lesions has been firmly established in clinical practice [19–23]. The use of a 10-HU threshold brings the sensitivity up to 79% and decreases the specificity to 96% [13,16,23]. The integrated PET/CT is useful in cases in which the adrenal lesion has metabolic activity equal to or less than the background activity. Bagheri

Table 5. The sensitivity, specificity, PPV and NPV of combining variables in the prediction for adrenal metastasis

Parameters	Adrenal metastasis (n)		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
	Yes	No					
For known primary tumour							
Unenhanced attenuation >10 HU	128	20	84.7	74.3	86.4	71.6	81.2
SUV <sub>max</sub> ratio >2.5	125	22	82.7	70.5	85.0	67.9	78.6
Unenhanced attenuation >10 HU and SUV <sub>max</sub> ratio >2.5	132	13	87.4	83.3	91.0	77.3	81.6
Unenhanced attenuation >10 HU and SUV <sub>max</sub> ratio >2.5 and metastasis in other parts	136	11	90.6	85.8	92.5	81.7	88.6
Unenhanced attenuation >10 HU and SUV <sub>max</sub> ratio >2.5 and metastasis in other parts and age <55	139	9	92.0	88.4	93.9	85.1	90.8
For lung cancer							
Unenhanced attenuation >10 HU	68	6	87.1	75.0	91.8	62.0	83.4
SUV <sub>max</sub> ratio >2.5	65	8	82.2	66.6	89.0	53.3	78.6
Unenhanced attenuation >10 HU and SUV <sub>max</sub> ratio >2.5	70	4	88.6	83.3	94.5	68.9	87.3
Unenhanced attenuation >10 HU and SUV <sub>max</sub> ratio >2.5 and metastasis in other parts	72	3	91.1	87.5	96.0	75.0	90.2
For gastrointestinal cancer							
Unenhanced attenuation >10 HU	10	5	76.9	72.2	66.6	81.2	74.1
SUV <sub>max</sub> ratio >2.5	9	6	69.2	66.6	60.0	75.0	67.7
Unenhanced attenuation >10 HU and SUV <sub>max</sub> ratio >2.5	11	3	84.6	83.3	84.6	88.2	83.8

NPV, negative predictive value; PPV, positive predictive value; SUV<sub>max</sub>, maximum standardised uptake value.

et al [24] found that 68% of normal adrenal glands had increased <sup>18</sup>F-FDG activity compared with the background and that identification of adrenal glands was difficult with PET alone. Metser et al [20] suggested using an SUV<sub>max</sub> of 3.1 for detecting malignant adrenal lesions.

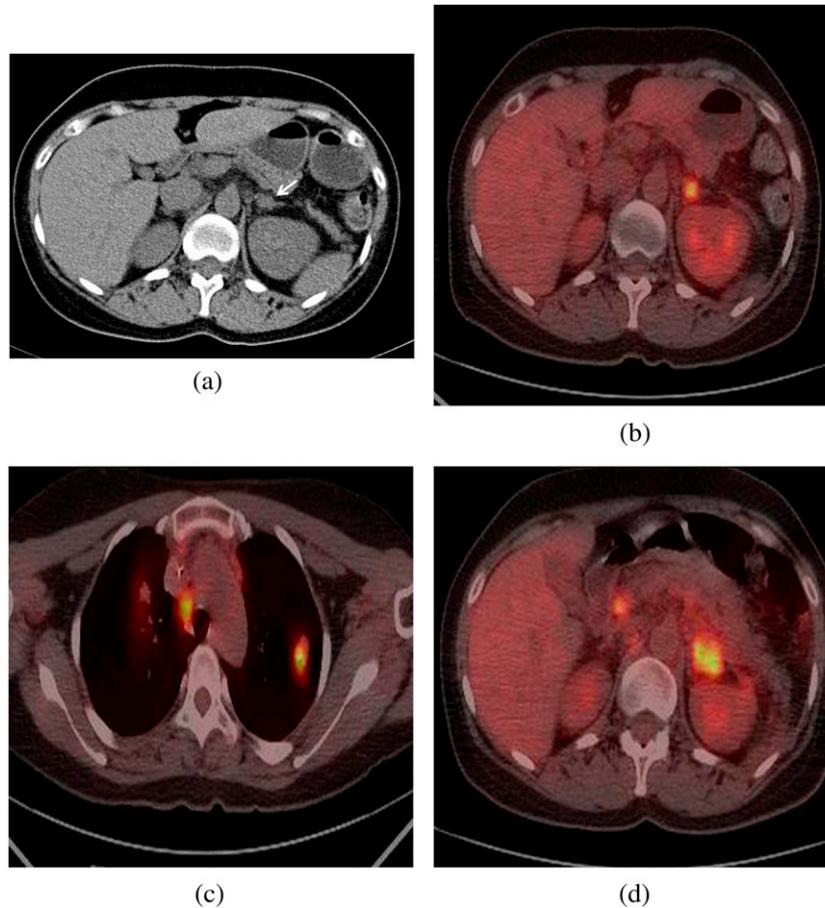
The combination of unenhanced CT and SUV<sub>max</sub> ratio is highly accurate in distinguishing between benign and malignant adrenal lesions [25]. In our study, applying the suggested unenhanced attenuation and SUV<sub>max</sub> ratio cut-off values of 10 HU and 2.5, respectively, substantially increased the accuracy of the test and would have decreased the number of false-positive results. Our study found that PET/CT was efficient in differentiating between benign and malignant adrenal lesions. Our study found that approximately 40% of patients with primary cancer did not have a malignant adrenal lesion, similar to previous reports [26]. Moreover, adrenal lesions in patients without primary cancer were all benign or owing to hyperplasia, consistent with the low frequency (approximately 10%) of primary adrenal tumours [26]. Of the patients without known primary cancer, 8.4% had an unenhanced attenuation of >10 HU and 3.1% had an SUV<sub>max</sub> ratio of >2.5. Of the patients with known primary

cancer but no adrenal metastasis, 11.1% had unenhanced attenuation of >10 HU and 2.1% had an SUV<sub>max</sub> ratio of >2.5.

Among patients with known primary cancer, metastatic tumours were predominantly found in the left adrenal gland (50.3% of patients). Generally, left adrenal lesions such as nodules or hyperplasia were overrepresented [27]. This may have been owing to developmental differences between the left and right adrenal glands, such as different anatomical positioning and formation of the asymmetrical mass. Also, liver SUV<sub>avg</sub> likely had no effect on our results, as the difference in the means of liver SUV<sub>avg</sub> was small and would have had minimal impact on a calculated SUV ratio.

Many malignant lesions are capable of adrenal gland metastasis [10]. In our study, the most common primary cancer was lung (44.9%). Our study was performed with a heterogeneous group of patients with all types of malignant diseases. It may be that groups of patients with lung, gastrointestinal and liver cancer are more likely to have adrenal metastasis than are group of patients with different cancers, potentially introducing interpreter bias. The majority of patients with adrenal metastasis also had metastatic

Figure 1. A 39-year-old female with uterine cervical cancer. (a) The unenhanced CT scan shows a lesion measuring approximately 15 mm in the left adrenal nodule (arrow) with homogeneous attenuation (22 HU). (b) On integrated PET/CT scan, the lesion shows a high  $^{18}\text{F}$ -FDG uptake ( $\text{SUV}_{\text{max}}$  ratio 4.8). (c) A high  $^{18}\text{F}$ -FDG uptake lesion ( $\text{SUV}_{\text{max}}$  ratio 5.0) is shown in the left upper lung. (d) At follow-up 8 months later after appropriate chemotherapy, integrated PET/CT scan shows interval increases in size and aggravated  $^{18}\text{F}$ -FDG uptake ( $\text{SUV}_{\text{max}}$  ratio 12.1). The left adrenal lesion did prove to be metastasis.  $^{18}\text{F}$ -FDG, flourine-18 fludeoxyglucose; PET, positron emission tomography;  $\text{SUV}_{\text{max}}$ , maximum standardised uptake value.



cancer in other body parts (73.5%), especially patients with primary gastrointestinal cancer (84.6%). These results were consistent with the fact that patients in our study who had adrenal metastasis had advanced cancer.

Univariate analysis revealed that age, unenhanced attenuation,  $\text{SUV}_{\text{max}}$  ratio and the presence of metastasis in other parts were independent predictors for adrenal metastasis in patients with known primary cancer. The risk of adrenal metastasis from known primary cancer decreased with every increasing year of age. The same variables, except age, were associated with adrenal metastasis in patients with lung and gastrointestinal cancer. Multivariate analysis revealed that in patients with primary cancer, unenhanced attenuation  $>10$  HU, an  $\text{SUV}_{\text{max}}$  ratio  $>2.5$  and the presence of metastasis in other parts yielded high sensitivity, specificity and accuracy for predicting adrenal metastasis. For patients with gastrointestinal cancer, unenhanced attenuation  $>10$  HU and an  $\text{SUV}_{\text{max}}$  ratio  $>2.5$  were the best combination of sensitivity, specificity and accuracy for predicting adrenal metastasis.

Our study had a few important limitations. First, like many similar studies, it was conducted retrospectively. Second, we

used follow-up data to determine the nature of the adrenal lesions because we had pathological proof for only a few patients. However, this situation is reflective of current practice. Most adrenal nodules are characterised with either follow-up data or imaging, and biopsy is reserved for a few selected indeterminate lesions. Third, our analysis was quantitative. It can be argued as to whether quantitative or qualitative methods are more effective in distinguishing between malignant and benign adrenal lesions. Finally, the population of the study was small ( $n=325$ ), and patients with lung cancer accounted for roughly 50% of our population. Therefore, the findings of the total population with known primary cancers may reflect the characteristics of a lung cancer population. Larger scaled studies including sizable populations representing multiple primary cancer types are needed to more fully assess the variables that predict adrenal metastasis.

In conclusion, on the basis of all our findings, we conclude that PET/CT is useful for characterising adrenal lesions present with or without known primary cancers. We identified variables that may be useful in assessing the risk of developing adrenal metastasis. PET/CT may help the clinician in diagnosis and in determining the optimal treatment strategies in patients with cancer.

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