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^{18}F-FDG PET/CT in the evaluation of adrenal masses in lung cancer patients

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The aim of this study was to assess the usefulness of integrated ^{18}F-FDG PET/CT in differentiating benign from metastatic malignant adrenal masses in patients with lung cancer.

One hundred and ten adrenal masses (size range, 0.5 - 6.3 cm, mean size, 1.9 cm) were evaluated retrospectively in 87 lung cancer patients. Integrated PET/CT images were assessed. PET findings were interpreted as positive if the ^{18}F-FDG uptake of the adrenal mass was greater than or equal to that of the liver. PET findings were interpreted as negative if the ^{18}F-FDG uptake of the adrenal mass was less than that of the liver. All studies were reviewed independently by 3 nuclear medicine physicians, and the results were then correlated with clinical follow-up or biopsy results when available.

PET/CT findings were positive in 77adrenal masses. Seventy-four of these were eventually considered to be metastatic adrenal disease. In the remaining 3, in the course of follow-up, two underwent percutaneous puncture, and one underwent surgery. In the end, histopathological examinations of the adrenal lesions demonstrated the presence of adenomas. PET/CT findings were negative in 33 adrenal masses, of which 31 eventually proved to be benign. The 2 adrenal masses that were false-negative, underwent PET/CT twice with a two-month interval. At the initial study, the size was 0.5cm, 0.9cm in diameter, respectively. However, at the follow-up study, PET/CT showed both positive result with the size of 1.6cm, and 2.3cm in diameter, respectively. Both adrenal masses were interpreted as metastasis. The sensitivity, specificity, and accuracy for detecting metastatic disease were 97 %(74 of 76), 94 %(31 of 34), and 95% (105 of 110), respectively. The positive predictive value was 95 %(74 of 77), and the negative predictive value was 94% (31 of 33).

Integrated ^{18}F-FDG PET–CT is an accurate, noninvasive technique for differentiating benign from metastatic adrenal lesions detected on CT or MRI in patients with lung cancer. It allows early detection and accurate localization of adrenal lesions and differentiation of metastatic nodules from benign lesions, thereby facilitating treatment planning.

Key words: ^{18}F-FDG; PET/CT; lung cancer; adrenal masses; adrenal metastasis

The adrenals are a common site of metastases in patients with lung cancer. Autopsy series have shown a high occurrence of adrenal metastases in patients with lung cancer, ranging from 35% to 59% [1, 2] .The incidence of adrenal masses in clinical studies of patients with non-small cell lung cancer may vary from 4.1% to 18% [3].However, not all adrenal masses can be assumed to represent metastasis, because 2%-9% of the general population has been shown to harbor benign adenomas [4]. Therefore, it is important to characterize adrenal masses accurately when they are discovered in patients with lung cancer. Percutaneous biopsy remains the gold standard for confirmation of the nature of the masses, but is invasive and difficult to perform, and thus frequently leads to complication or study failure [5].

Noninvasive imaging techniques, which include CT and MRI, have been used to differentiate metastases from benign adrenal adenoma. CT has shown usefulness because of its ability to measure attenuation, on both unenhanced images and on delayed contrast-enhanced images, to differentiate benign from malignant lesions [6]. But diagnosis based on attenuation measurement is often not feasible in unenhanced or delayed contrast-enhanced CT [7]. MRI has shown initial promise in T2-weighted and chemical shift imaging, but the signal intensity of benign and malignant lesions overlaps considerably [8, 9].

Recently, ^{18}F-FDG PET has shown encouraging results in differentiating benign from metastatic adrenal masses in patients with known or suspected malignancies [10, 11]. Several studies have documented the usefulness of ^{18}Fluorine-fluoro-

deoxyglucose (^{18}F-FDG) PET for evaluating adrenal masses specifically in patients with lung cancer [12, 13].The development of integrated PET/CT has allowed functional PET and anatomical CT imagines to be obtained in one session. The combination of PET and CT data sets using the integrated PET/CT approach is additive; in fact, it is highly synergistic [14]. Several recent studies on the accuracy of PET/CT versus PET have shown that PET/CT helps resolve this problem for ambiguous lesions, especially for anatomy-related lesions [15, 16].This study investigated the usefulness of integrated ^{18}F-FDG PET/CT in differentiating benign from metastatic malignant adrenal masses in patients with lung cancer.

Materials and mathods

Patients. We conducted a retrospective review of 87 lung cancer patients with uncharacterized adrenal masses detected by thoracic CT (covering from thoracic inlet to middle portion of both kidneys) or MRI. All patients were from Shandong Cancer Hospital and Institute PET/CT center from June 2003 to June 2008. To avoid any potential effects of the therapies as seen by adrenal ^{18}F-FDG uptake, patients that had undergone integrated PET/CT were enrolled before chemotherapy or radiation therapy. Patients were excluded if the clinical follow-up period was less than 6 months. Patients were also excluded if they had type I diabetes.

Eighty-seven patients, 49 men and 38 women with a mean age of 61 years old (age range, 32 to 76 years old). Histological analyses shown that the primary lung cancers were adenocarcinomas in 45 patients, squamous cell carcinomas in 22, adenosquamous carcinomas in 5, small cell carcinomas in 13 and large cell carcinomas in 2 patients. All patients who entered this study signed an informed consent agreement approved by our institutional review board.

The characteristics of adrenal masses. An adrenal gland mass was considered present when a round or oval mass (short-and long-axis diameters were within a factor of 1.5 of each other) with a discrete margin was identified in the adrenal gland. Of these 87 patients, 65 had unilateral adrenal masses (including one case with one mass on the left side on CT, but two masses discretely on PET and PET/CT, so two masses were confirmed)and 22 were bilateral. Thus 110 masses were studied of which 47 were present on the left side, and 63 were located on the right side. The size of the adrenal masses on CT or MRI ranged from 0.5 to 6.3 cm, with a mean of 1.9 cm.

The final diagnosis of the adrenal masses was based on clinical follow-up or percutaneous puncture biopsy, or surgery of biopsy specimens, when available. In the clinical follow-up studies, an adrenal lesion was considered benign if it had not changed for at least 6 months, and it was considered malignant if the size had increased or decreased after treatment or if a new adrenal lesion had developed [17].

^{18}F-FDG PET/CT Imaging. All patients fasted and rested for at least 6 h before undergoing PET/CT (Discovery LS PET/CT system; GE Healthcare). Serum glucose levels were measured to ensure that the results were <6.6 mmol/L. Patients received no urinary bladder catheterization, no oral muscle relaxants, and no CT contrast agents. Sixty minutes after intravenous injection of 370 MBq (10 mCi) of ^{18}F-FDG, PET emission images were acquired from the level of the middle skull to that of the proximal thigh for 5 min per field of view, each covering 14.5 cm, at an axial sampling thickness of 4.25 mm per slice. The spiral CT component was performed with an x-ray tube voltage peak of 120 kV, 90 mA, a 6:1 pitch, a slice thickness of 4.25 mm, and a rotation speed of 0.8 s per rotation. A full-ring dedicated PET scan of the same axial range followed. Both the PET and the CT scans were obtained during normal tidal breathing. The total acquisition time varied between 25 and 35 min per patient. PET images were reconstructed with CT-derived attenuation correction using the ordered-subset expectation maximization (OSEM) algorithm. The attenuation-corrected PET images, CT images, and fused PET/CT images displayed as coronal, sagittal, and transaxial slices were viewed on a Xeleris workstation (GE Healthcare).

^{18}F-FDG PET/CT Image Interpretation. Three experienced nuclear medicine physicians, who were unaware of the patient's clinical history and pathologic findings, interpreted the PET/CT images independently. In cases of disagreement, a final decision was made by consensus. When interpreting the dedicated PET images, Special attention was given to ^{18}F-FDG uptake in the region of the adrenal glands. PET findings were interpreted as positive if the ^{18}F-FDG uptake of the adrenal mass was greater than or equal to that of the liver. PET findings were interpreted as negative if the ^{18}F-FDG uptake of the adrenal mass was less than that of the liver. According to past experience, visual assessment of suspected lesions was just as effective at differentiating active from inactive disease as is quantitative analysis using the standardized uptake value (SUV). Therefore, the maximum SUV was not used to differentiate benign and malignant adrenal lesions [13].

PET/CT-positive results were defined as true positive (TP) when confirmed by the final diagnosis as malignant, and were defined as false positive (FP) when confirmed by the final diagnosis as benign; PET/CT- negative results were defined as true negative (TN) when confirmed by the final diagnosis as benign, and were defined as false negative (FN) when confirmed by the final diagnosis as malignant. The sensitivity, specificity and accuracy of PET/CT for the diagnosis of adrenal metastases were assessed using a generalized estimating equation.

Results

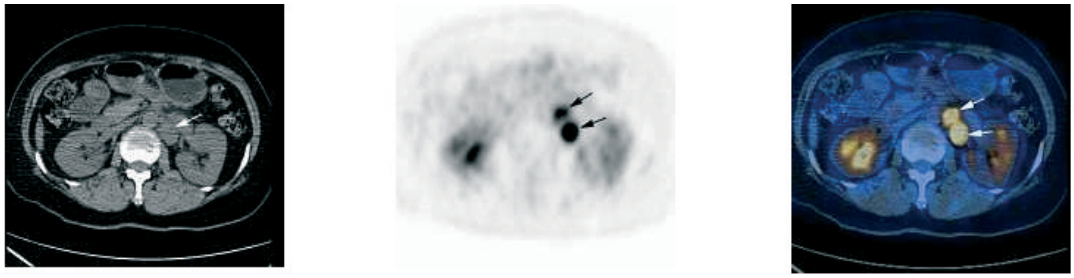
A total of 87 patients qualified for the study including 49 men and 38 women (age range 32 to 76 years old, median 61y), 65 had unilateral adrenal masses and 22 were bilateral. Of 110 masses, the size of the adrenal masses on CT or MRI ranged from 0.5 to 6.3 cm; with a mean of 1.9 cm. Patient detailed characteristics are shown in Table 1.

Of 110 adrenal masses, 77 were positive for ^{18}F-FDG uptake, the ^{18}F-FDG uptake of the adrenal mass greater than or equal to that of the liver (Fig 1). Seventy-four of these masses eventually

Table 1 The characteristics of patients

Parameter	Value
Total number of patients	87
Sex	
Male	49
Female	38
Age(y)	
Median	61
Range	32-76
Histology of primary lung cancer	
Adenocarcinoma	45
Squamous cell carcinoma	22
Adenosquamous carcinoma	5
Small cell carcinomas	13
Large cell carcinoma	2
Number of adrenal masses on CT or MRI	
Total	110
Unilateral	65
Bilateral	22
Location of adrenal masses	
Right	63
Left	47
Size of adrenal masses on CT(cm)	
Mean	1.9
Range	0.5-6.3
The final diagnosis of the adrenal masses(n)	110
Clinical follow-up	78
Percutaneous puncture	22
Surgery	10

were proved to be metastatic adrenal disease, by surgery (n=7), by percutaneous puncture biopsy (n=12), and by clinical follow-up (n=55). Thus these seventy-four masses were confirmed as TP. The remaining 3(3 patients with a single unilateral adrenal gland masse) shown no change in size on follow-up CT or MRI for at least 6 Mons. In the course of follow-up, two of these 3 patients underwent percutaneous puncture, and one underwent surgery. In the end, histopathological examinations of the adrenal lesions demonstrated the presence of adenomas. Therefore the three masses were considered to be benign, so confirmed as FP. 33 adrenal masses were negative for[18]F-FDG uptake (Fig 2). Thirty-one of these were eventually proved to be benign, either by surgery (n=2), percutaneous puncture biopsy (n=8), or by clinical follow-up (n=21), confirmed as TN. For the 2 adrenal masses that gave FN findings, one patient had two masses with one each in each gland. The patient underwent PET/CT twice with a two-month interval. At the initial study, the size was 0.5 cm, 0.9 cm in diameter, respectively. However, at the follow-up study, PET/CT showed both positive result with the size of 1.6 cm, and 2.3 cm in diameter, respectively. Both adrenal masses were interpreted as metastasis. Among 110 adrenal masses, seventy-six (69%) adrenal masses were classified as metastases, whereas thirty- four (31%) classified as benign. The mean diameter of the malignant masses was 2.1 cm (range, 0.5–4.5 cm). The mean diameter of the benign masses was 1.7 cm (range, 0.6–6.3 cm).



A B C

Fig .1. 40-year-old man with lung adenocarcinoma was a true-positive case confirmed by surgical excision.
A. An unenhanced CT scan shows a mass (white arrow) on the left adrenal gland. B. PET shows two discrete masses with increased uptake (black arrows) on the left adrenal gland. C. Integrated PET/CT shows two discrete masses with high uptake (white arrows) on the left adrenal gland.

A B C

Fig.2. 57-year-old man with lung squamous cell carcinoma was a true- negative case confirmed by clinical follow-up.
A. An unenhanced CT scan shows a soft-tissue mass with low-attenuation area (white arrow) on the right adrenal gland. B. PET shows no abnormal uptake (black arrow) in the region of the right adrenal gland. C. Integrated PET/CT shows the soft-tissue mass has no abnormal uptake (white arrow) on the right adrenal gland.

Table 2 PET/CT findings and final diagnosis for 110 adrenal masses

Final Diagnosis	PET/CT Findings		Total
	Positive	Negative	
Malignant	74	2	76
Benign	3	31	34
Total	77	33	110

Table 2 illustrates the ^{18}F-FDG PET/CT results and final outcome for 110 adrenal masses. The sensitivity, specificity, and accuracy for detecting metastatic disease were 97 %(74 of76), 94 %(31 of 34), and 95% (105 of 110), respectively. The positive predictive value was 95 % (74 of 77), and the negative predictive value was 94% (31 of 33).

Discussion

Adrenal metastases originating from NSCLC and small cell lung carcinoma are not uncommon. It is estimated that up to 4% of patients with otherwise operable NSCLC will have a unilateral adrenal mass; up to 40% of these may be malignant and present as a solitary site of metastasis [18]. The detection of an adrenal lesion in patients with lung cancer poses a diagnostic problem in terms of whether the lesion is a metastatic growth or a benign "incidentaloma." In addition, the accurate diagnosis of malignant adrenal involvement in lung cancer patients is required for evaluation of treatment approaches and prognostic assessments.

CT is the primary diagnostic imaging method for adrenal gland lesion evaluation. Lipid within adenomas causes low attenuation in unenhanced CT images. In addition, adenomas demonstrate rapid washout after intravenous contrast administration [6, 19]. The sensitivity and specificity of unenhanced CT (at a threshold attenuation of 10 HU) for distinguishing an adenoma from other diseases has been determined as 79% and 96%, respectively [20]. The sensitivity, specificity, and diagnostic accuracy as reported by a dynamic study were 98%, 92%, and 96%, respectively [6].

Signal intensity on T2-weighted and chemical shift imaging using signal intensity reductions between in-phase and opposed-phase MR images were initially investigated in an effort to differentiate benign from malignant lesions. However, benign and malignant lesions were found to overlap considerably in terms of signal intensity [9, 21, 22]. Burt et al [18] reported a false-positive level for unilateral adrenal masses of 67% in patients with operable non-small cell lung cancer, i.e., 14 of 21 histological benign masses were interpreted as malignant masses based on the relative signal strengths of T1- and T2-weighted images.

Unlike CT and MRI, FDG PET intensities are dependent on the glucose metabolism in the malignant lesions. FDG PET in patients with lung cancer and adrenal masses has reported ranges for sensitivities of 93 -100%, specificities of 80-100%, and diagnostic accuracies of 92-100% (11–13). However, the limited accuracy of lesion localization using PET alone, due to the lack of precise anatomical landmarks, has been demonstrated by several previous studies [15, 23, 24, 25].

Recently, integrated ^{18}F-FDG PET/CT was introduced. This technique can produce directly functional PET and anatomical CT images in one session. Integrated 18F-FDG PET/CT findings are not simply the summation of PET and CT findings; in fact they are the result of a high level of synergism between the two modalities [14, 26].

FDG PET–CT is better able to help differentiate benign from malignant adrenal lesions than is ^{18}F-FDG PET alone. In one study of 175 adrenal masses in 150 patients [27], PET data alone (maximum SUV, 3.1) yielded a sensitivity, specificity, and accuracy of 99% (67 of 68 nodules), 92% (98 of 107), and 94% (165 of 175), respectively, and combined PET/CT data yielded corresponding values of 100% (68 of 68 nodules), 98% (105 of 107), and 99% (173 of 175). Moreover, specificity was significantly higher for PET/CT ($P<0.01$). Y M Sung, et al [28] evaluated Sixty-one adrenal lesions in 42 lung cancer patients. For the depiction of adrenal gland metastasis, the sensitivity, specificity, and accuracy of PET were 74%, 73%, and 74%, respectively, whereas those of integrated PET/CT were 80%, 89%, and 84%,respectively (p values; 0.5, 0.125, and 0.031, respectively). The use of integrated PET/CT is more accurate than the use of PET alone for differentiating benign and metastatic adrenal gland lesions in lung cancer patients.

In this study, the FDG uptake of an adrenal lesion was compared with that of liver, thus an adrenal lesion was interpreted as positive for metastasis if the FDG uptake was greater or equal to that of the liver. In the present study, ^{18}F-FDG PET/CT showed a high sensitivity of 97%, a specificity of 94%, a positive predictive value of 95%, a negative predictive value of 94%, and an accuracy of 95% to differentiate between benign and malignant adrenal masses in patients with lung cancer. The results of our study were similar to the results of previously published studies using 18F-FDG PET to assess adrenal masses in cancer patients. The common causes of false-positive 18F-FDG PET results are pheochromocytomas and benign adenomas [11, 29]. There were three cases of false-positive findings shown by integrated PET/CT in the present study. Three cases all were due to benign adenomas. It is not fully understood why some adenomas show increased 18F-FDG uptake and some do not. A previous article has suggested that the functional state of an adenoma is a factor determining the intensity of uptake, with 18F-FDG uptake being increased in functioning adrenal masses [30].

Commonly reported causes of false-negative results are a small lesion size, necrotic metastases, and metastases from neuroendocrine tumors [11, 31]. In the present study, two adrenal masses were false-negative findings at the initial PET/CT study, and all were due to small lesion size (0.5cm, 0.9cm in diameter, respectively). However, at the follow-up study after two months, PET/CT showed both positive results with the size of 1.6cm, and 2.3cm in diameter, respectively.

One potential limitation of this study is that not all adrenal lesions can be proven histopathologically. In addition, cortisol, dehydroepiandrosterone, and sex hormone levels were not determined to examine the possibility of stress induced adrenal activation.

In conclusion, integrated [18]F-FDG PET–CT is an accurate, noninvasive technique for differentiating benign from metastatic adrenal lesions detected on CT or MRI in patients with lung cancer. It allows early detection and accurate localization of adrenal lesions and differentiation of metastatic nodules from benign lesions, thereby facilitating treatment planning.

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