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Use of [^{18}F]Fluorodeoxyglucose Positron Emission Tomography in Evaluating Locally Recurrent and Metastatic Adrenocortical Carcinoma

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Context: Adrenocortical carcinomas are uncommon, and their evaluation by [^{18}F]fluorodeoxyglucose positron emission tomography (FDG PET) has not been well evaluated.

Objective: The purpose of this study was to examine the potential utility of FDG PET in the detection of recurrent or metastatic adrenocortical carcinoma.

Design: In patients with known adrenocortical carcinoma who underwent FDG-PET imaging for suspected recurrence or metastasis, FDG activity was compared with other imaging findings, clinical features, and the presence or absence of disease as confirmed by resection, biopsy, or clinical follow-up.

Setting: The study took place at four tertiary referral centers.

Patients or Other Participants: Twelve patients (10 females and two males, 5–71 yr of age) were evaluated.

Main Outcome Measures: The main outcome measures were FDG activity, other imaging findings, and clinical features.

Results: Abnormal FDG uptake correctly indicated tumor recurrence in 10 patients. One patient with no abnormal FDG activity had a morphological abnormality subsequently proven to be a postoperative scar. Two patients, one with very small pulmonary lesions and one with a hepatic metastasis, had false-negative findings.

Conclusions: Most adrenocortical carcinomas accumulate and retain FDG and thus can be visualized by PET. However, false-negative findings are possible, especially with very small lesions. (***J Clin Endocrinol Metab* 91: 2665–2671, 2006**)

ADRENOCORTICAL CARCINOMA (ACC) is an uncommon malignant neoplasm. Its estimated annual incidence in the United States is approximately 1–2 per million. Its age distribution is bimodal, with peak frequency at ages younger than 5 yr and ages 30–50 yr. The mean age at diagnosis is approximately 45 yr (1). Adrenocortical cancer is slightly more common in females than in males (59:41) (2). The etiology of ACC is not known, but smoking and oral contraceptives may be risk factors (3, 4). Additionally, there is an association with the Li-Fraumeni and Beckwith-Wiedemann syndromes (5, 6). ACC may be biochemically active in more than 50% of patients (7).

Computed tomography (CT) or magnetic resonance (MR) imaging is used most often in the initial imaging investigation of ACC. Although both modalities are useful for distinguishing benign from malignant adrenal disease and for detecting local tumor extension, their accuracy in the detection of metastatic ACC and in disease restaging during follow-up is less well established. Recent evidence suggests that positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose (FDG) or [^{11}C]metomidate may be useful for detection of ACC. FDG PET is widely used for imaging of solid tumors, but because of the rarity of ACC, few studies have addressed the role of FDG PET in its assessment. There have been two studies that have specifically addressed this. A study of 10 patients with ACC consistently demonstrated abnormal metabolic activity (8). Leboulleux *et al.* (9) recently evaluated individual metastatic lesions in 22 patients with ACC, finding the sensitivity of PET/CT for the detection of individual lesions to be 90%. The study did have a selection bias because only patients with abnormal CT findings were included (22 of 28 patients presenting). Other adrenal FDG PET studies that included small numbers (1–3) of patients with ACC as part of an assessment of adrenal lesions in general invariably found abnormal FDG activity within ACC (10–13). We therefore investigated the utility of FDG PET in detecting recurrent and metastatic ACC.

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Abbreviations: ACC, Adrenocortical carcinoma; CT, computed tomography; FDG, [^{18}F]fluorodeoxyglucose; MR, magnetic resonance; PET, positron emission tomography; ROI, region of interest; SUV_{max}, standardized uptake value; TAP-CT, thoraco-abdominopelvic CT.

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Patients and Methods

Patients

This study was initiated at the University of Michigan Medical Center and was subsequently expanded to include three additional institutions. The study was approved by the Institutional Review Board for the Use of Human Subjects in Research and the Subcommittee for the Human Use of Radioisotopes at the University of Michigan and by the Institutional Review Boards of St. Jude Children's Research Hospital. Eligible participants received FDG PET imaging to assess suspected recurrent or metastatic ACC at the four institutions between January 2000 and September 2005. Written informed consent was obtained from patients, parents, or guardians, as appropriate.

Imaging technique

Six patients were imaged on a Siemens Biograph PET CT scanner, three patients were imaged on a Siemens ECAT HR+ scanner, one on a Siemens ECAT HR, one on a GE Discovery PET CT scanner, and one on a GE Discovery PET scanner. After an overnight or 4-h fast, patients were injected with 296–370 MBq (8–10 mCi) FDG per 1.7 m^2 of body surface area. Approximately 45 min later, the patients were positioned within the PET scanner, and emission and transmission imaging were begun. Patients 1–9 and 11–12 were scanned from neck to thigh, and patient 10 was scanned from the top of the head to the bottom of the feet in two separate acquisitions. Patient 10 has undergone multiple PET scans in conjunction with clinical care for planning and evaluating the effects of radiofrequency ablation of pulmonary metastases. Images were acquired over a period of 40–60 min. Attenuation correction was performed in all patients. Attenuation correction maps were acquired either by use of a retractable germanium-68 source or by transmission imaging with CT. Images were reconstructed using an ordered subset expectation maximization (OSEM) algorithm and reviewed in multiple planes.

Image analysis

Reviewers of the images (G.C.M. and B.L.S.) were blinded to the results of other studies. Tumor uptake of FDG was assessed both qualitatively and semiquantitatively. Organs that normally accumulate FDG were identified by visual inspection of the images. FDG activity in regions that did not normally accumulate FDG was considered abnormal. Uptake of tracer by the abnormal regions was analyzed qualitatively by rating it on a scale of 0–3 in comparison with uptake by a normal region of the patient's liver: 0, no uptake; 1, uptake less than that of the liver; 2, uptake equal to that of the liver; 3, uptake greater than that of the liver.

Semiquantitative analysis was also performed. The standardized uptake value (SUV_{max}) was calculated in all patients (Table 1) as follows. When an area of abnormal FDG uptake was evident on PET imaging, an elliptical region of interest (ROI) was defined over that site(s) and over a region of the liver, which served as reference organ. The elliptical ROI was defined to encompass the majority of the lesion, and the same ROI was defined in an area of normal-appearing liver, usually in the same transverse plane. The SUV_{max} was derived from the area of greatest FDG accumulation in the ROI using software that identifies the area of maximal FDG uptake on a pixel by pixel basis. The tumor-to-liver activity ratio was calculated as SUV_{max} (lesion)/SUV_{max} (liver). In the one patient who underwent PET/CT and whose study did not show abnormal FDG uptake, the ROI was determined on the basis of the CT image.

The results of the FDG PET imaging were correlated with the findings of histology from biopsy/resection in four patients. In the remaining eight patients, the disease status was established by follow-up demonstrating disease progression (in seven patients) and stable disease for 36 months (in one patient).

Results

Patients

Twelve patients, 10 female and two male (ages 5–71 yr), with a history of ACC underwent FDG PET imaging during the study period to assess suspected recurrent or metastatic disease. Patient demographics, FDG PET results, and clinical findings are summarized in Table 1.

Image analysis

Ten of the 12 patients showed abnormally high FDG activity, and recurrent or metastatic ACC was subsequently demonstrated (Figs. 1 and 2). SUVs ranged from 1.9–14.2 in lesions showing abnormal FDG uptake. The tumor-to-liver activity ratio was greater than 2.0 in 10 of the 12 patients. Four of these patients had recurrent tumor in the adrenal bed, and seven had hepatic or pulmonary metastases (Table 1). All tumors were confirmed either by biopsy or follow-up CT examination. Tumor uptake was greater than liver uptake (grade 3) in each case of abnormal uptake due to ACC.

Two patients (patients 1 and 2) had abnormal findings on CT that were initially suspected to be ACC but that showed no corresponding abnormal FDG activity. Patient 1 presented with a low-density lesion in the liver on CT considered suspicious for recurrent disease. The SUV of 1.9 on the PET scan corresponding to this region and the tumor-to-liver activity ratio of 0.9 suggested that this was benign disease, and this was supported by a subsequent biopsy demonstrating postoperative scar tissue and stable findings on subsequent CT studies over the next 36 months. Patient 2 had both a true-positive finding (hepatic metastasis) and a true-negative finding (postoperative scar tissue in the adrenal bed); both were confirmed by needle biopsy, with the patient dying of progressive metastatic disease after 15 months.

Patient 5 had widely disseminated disease involving the adrenal bed, liver, and lungs. Although the bulky recurrent tumor in the adrenal bed showed substantial FDG activity (SUV 3.5), abnormal uptake was evident only in the largest of the numerous pulmonary nodules (~30%), which ranged in size from barely detectable on CT imaging to 2 cm in diameter (Fig. 3). Although there was not histological confirmation of each of these nodules, they were classified as metastatic disease on the basis of their CT appearance and subsequent disease progression.

There was one additional false-negative finding. Patient 3 had a hepatic metastasis that showed no abnormal FDG uptake (Fig. 4). The measured SUV in the metastatic lesion was 2.9, but this was lower than the SUV of the surrounding liver and the tumor-to-liver activity ratio was only 0.7. This patient had undergone adrenalectomy at the time of initial diagnosis, 5 yr previously. The pathology report at that time described a 7-cm ACC that had invaded the adrenal capsule. At the time of follow-up 5 yr later, a 3-cm mass was evident in the inferior aspect of the right lobe of the liver on CT imaging (Fig. 4). Despite the absence of significant metabolic activity, the lesion was resected and found to be recurrent ACC.

Discussion

Our findings indicate that most ACC accumulate and retain FDG. However, an occasional or very small tumor may not accumulate sufficient FDG to allow detection. Other PET imaging tracers, such as [^{11}C]metomidate, that probe characteristics specific to adrenal cortical lesions may prove to be more useful (14).

TABLE 1. Patient characteristics

No.	Age (yr)	Sex	Study	Relative FDG uptake	Size (cm)	SUV	Tumor-to-liver SUV ratio	Diagnosis	History	Confirmation
1	37	F	PET/CT	2	1	1.9	0.9	Postoperative changes	Cushing's syndrome; right adrenalectomy 6 yr earlier; recurrence in liver 1 yr later; routine follow-up imaging	Follow-up at 36 months: stable
2	50	F	PET	3	2.5	9.2	2.7	Metastatic ACC	Resection of ACC 2 yr earlier; routine follow-up imaging	Follow-up: progressive disease (deceased, 15 months)
3	71	M	PET/CT	1	3	2.9	0.7	Metastatic ACC	Presented 5 yr earlier with refractory hypertension, elevated aldosterone; routine follow-up imaging	Resection
4	51	F	PET	3	2.5	8.5	2.1	Recurrent ACC	Hirsutism, acne, weight gain, elevated testosterone; routine follow-up imaging	Resection
5	39	F	PET/CT	3	6	3.5	2.2	Recurrent ACC	Presented with nonfunctioning abdominal mass; routine follow-up imaging	Follow-up at 12 months: progressive disease
6	66	F	PET/CT	3	4	14.2	4.8	Metastatic ACC	Presented 2 yr earlier with hirsutism and elevated testosterone; routine follow-up imaging	Follow-up at 12 months: progressive disease
7	24	F	PET/CT	3	5	9.5	4.3	Metastatic ACC	Cushing's syndrome at presentation 1 yr earlier; routine follow-up imaging	Needle biopsy
8	51	F	PET/CT	3	2	6.9	2.3	Recurrent ACC	Cushing's syndrome at presentation 1 yr earlier; routine follow-up imaging	Needle biopsy
9	8	M	PET	3	3	4.5	2.2	Metastatic ACC	Precocious puberty at presentation, elevated plasma testosterone	Follow-up
10	5	F	PET/CT	3	4	7.0	2.1	Metastatic ACC	Virilization, hypertension, seizures at presentation at age 2 yr; pulmonary metastases developed, complete remission after chemotherapy; routine follow-up imaging;	Progressive disease
11	8	F	PET	3	3	10.8	6.4	Metastatic ACC	Precocious puberty at presentation; resection; pulmonary metastases after 6 months; complete response chemotherapy; relapse 1 yr later	Follow-up
12	6	F	PET	3	1.5	3.9	4.3	Recurrent ACC	Precocious puberty at presentation; resection; rising DHEAS 1 yr after resection	Follow-up

Reference scale for relative uptake is as follows: 0 = no uptake; 1 = less than liver uptake; 2 = equal to liver uptake; 3 = greater than liver uptake. DHEAS, Dehydroepiandrosterone sulfate; F, female; M, male.

CT or MR imaging is most often used for the initial evaluation of ACC. These anatomically based methods generally show a heterogeneous adrenal mass with variable enhancement of the solid components. Both techniques are useful in assessing local tumor extension, and MR imaging is particularly useful for detecting vascular invasion. Considerable efforts have been made to assess the ability of CT and MR imaging to distinguish adrenal adenoma from metastatic carcinoma. This distinction is generally based on the high lipid content of adrenal adenomas. Chemical-shift MR imaging and low Hounsfield unit measurements on CT may demonstrate the presence of lipid, suggesting benign lesions

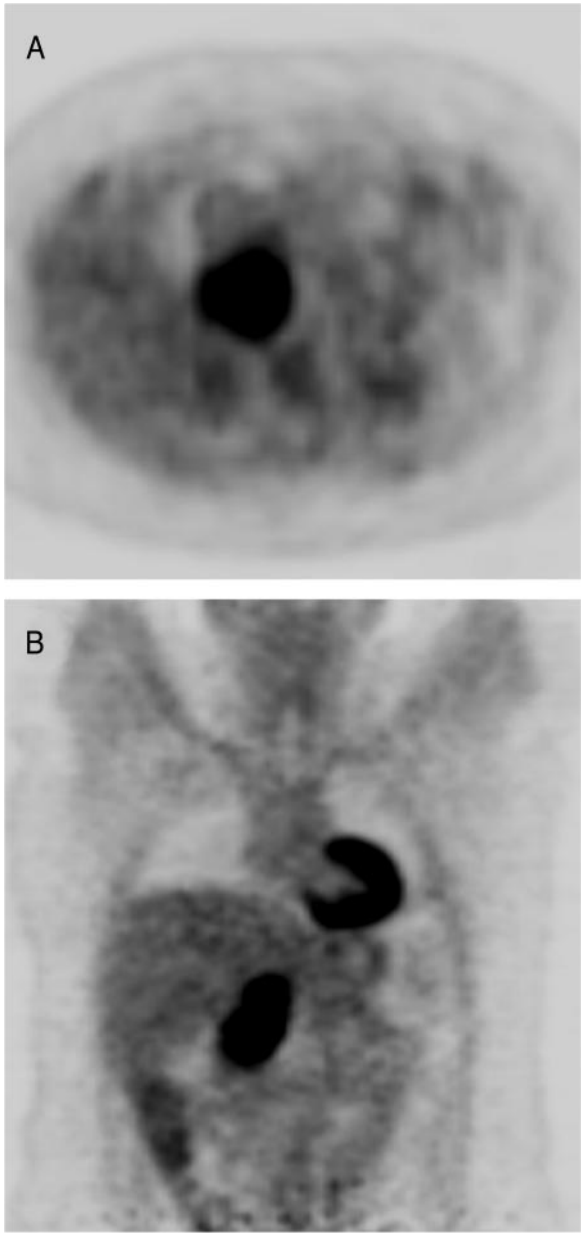

FIG. 1. Patient 7, true-positive FDG PET. Axial (A) and coronal (B) FDG PET images demonstrate intense metabolic activity in the right adrenal bed caused by recurrent adrenocortical carcinoma.

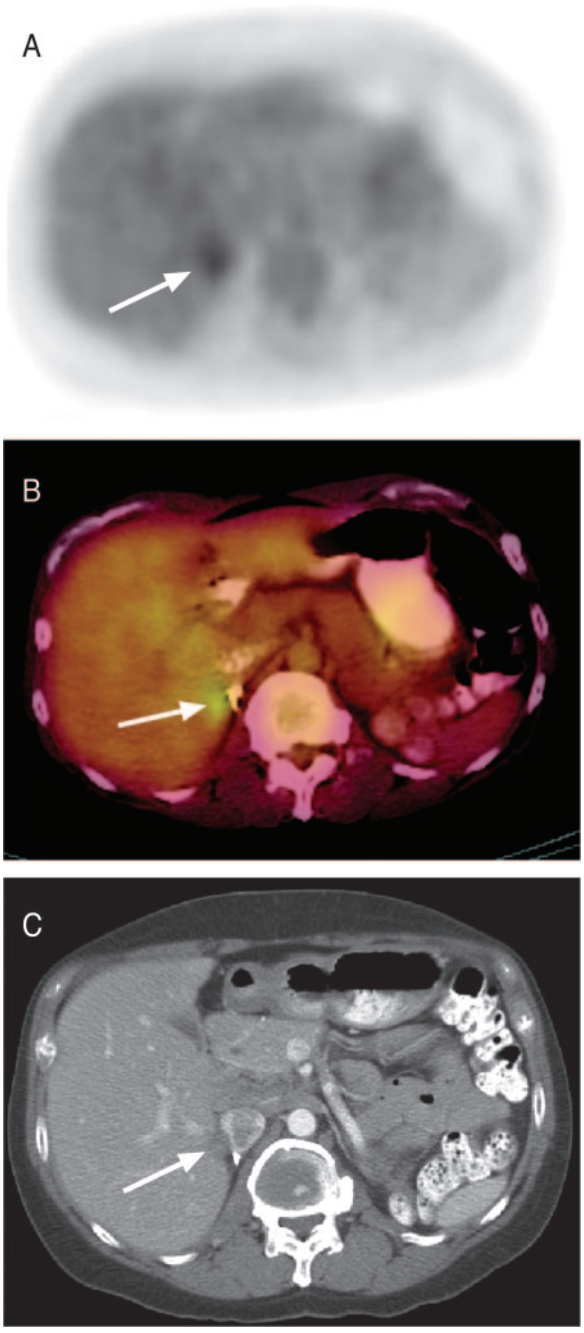

FIG. 2. Patient 8, true-positive FDG PET. A and B, Transverse FDG PET images (A) and fusion image (B) from concurrent CT demonstrating mild activity in the right adrenal bed. C, This lesion is barely visible just adjacent to the inferior vena cava on contrast-enhanced CT. Surgery was performed to remove a small retroperitoneal focus of well-differentiated ACC invading the liver adjacent to the inferior vena cava.

(15, 16). A more recent technique distinguishes benign from malignant adrenal disease by assessing the washout characteristics of iv contrast agent (17, 18). FDG PET, on the other hand, relies on differences in metabolic activity to distinguish benign from malignant disease. FDG PET cannot yet distinguish ACC from metastatic disease in the adrenal glands. Neither can it distinguish among pheochromocytoma, metastatic disease, and lymphoma, which generally exhibit high glycolytic activity (19).

FDG PET can help to distinguish between benign and malignant adrenocortical disease. Recently, Bagheri *et al.* (20) showed that FDG uptake could be identified in normal adrenal glands in 68% of patients when coregistered PET/CT images were examined. However, in the vast majority of normal adrenal glands that showed FDG uptake in that study, the intensity of uptake was equal to or less than that of the liver. Adrenal adenomas generally do not show abnormal metabolic activity, and hence, in the case of an enlarged adrenal gland, PET imaging may help to distinguish adenoma from carcinoma. In the rare cases in which an adrenal adenoma does show elevated metabolic activity on

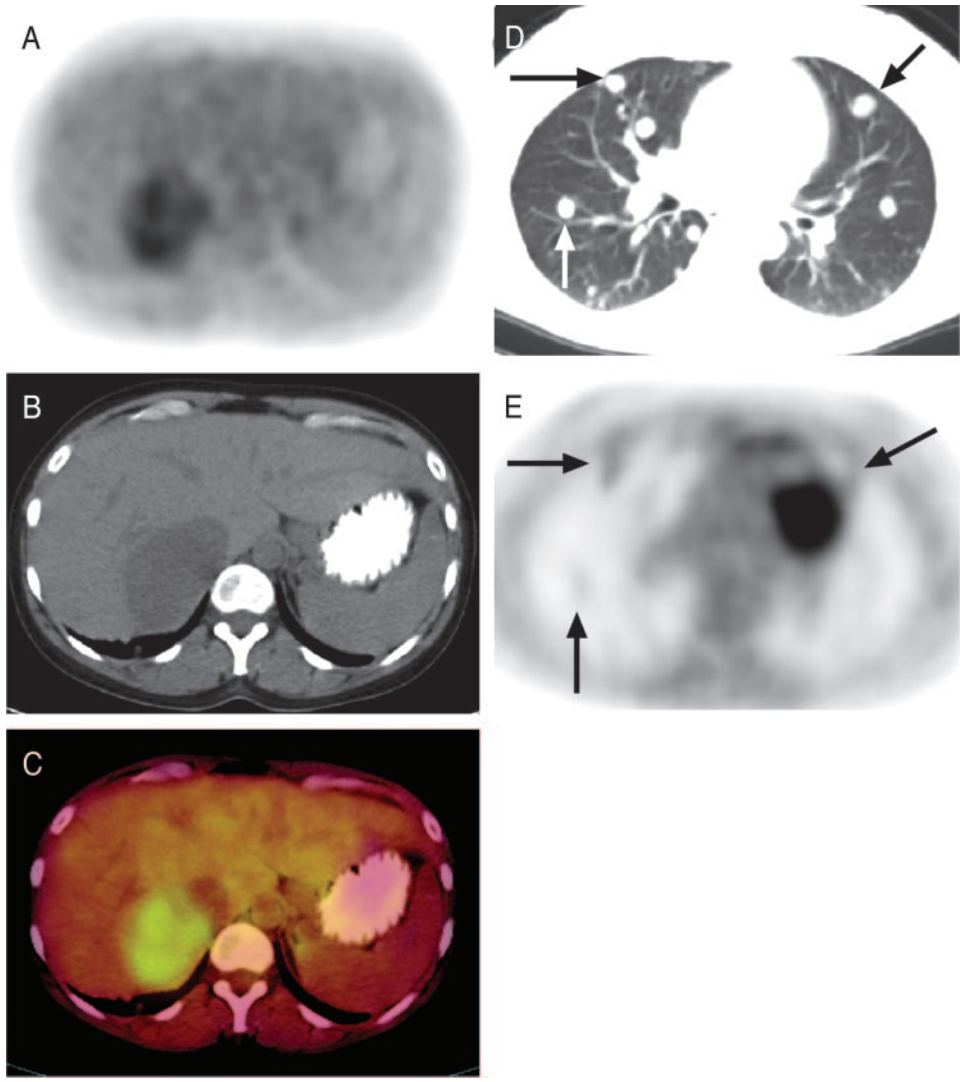

FIG. 3. Patient 5, true-positive FDG PET. A–C, Transverse FDG PET (A), concurrent CT (B), and fused PET and CT images (C) demonstrate moderately increased activity in the right adrenal bed (recurrent tumor). D and E, Innumerable pulmonary nodules were apparent on CT (D) (lung windows), but only the larger of these (E) demonstrated activity on FDG PET (the large area of markedly increased uptake is myocardium).

FDG PET, the activity may reflect inflammation within the lesion (21).

In the future, FDG PET imaging will likely be used to restage disease and to evaluate patients for local recurrence and distant metastasis. The most common sites of distant metastasis of ACC are the liver, lung, lymph nodes, and peritoneum (22, 23). In our small, multi-institutional series, we found FDG PET to detect local recurrent disease reliably (within the adrenal bed), even when anatomic imaging was inconclusive, and to be somewhat less reliable for detection of metastatic disease in the liver and lungs. The sensitivity of the scan will depend on several factors, including the inherent metabolic activity of the individual tumor studied, receiver-operator characteristics, and scanner and protocol details. For patient 5, despite the largest tumor in the series, the adrenal bed lesion SUV was only 3.5, indicating that this tumor did not display as high uptake as tumors of the other patients. This may be the reason why many of the relatively large pulmonary lesions in this patient showed only faint uptake of FDG. In other patients with more metabolically active tumors, smaller lesions may be identified.

FDG PET is useful in distinguishing malignant from benign adrenocortical lesions other than ACC (24–27). Most of the malignant lesions in these studies have been metastatic adrenal lesions. Two previous studies have specifically assessed the use of FDG PET in ACC. Becherer *et al.* (8) prospectively studied 10 patients with ACC and found FDG PET imaging to be 100% sensitive and 95% specific for malignancy. The authors observed that FDG-PET could detect multiple lesions that were not evident by other imaging modalities. More recently, Leboulleux *et al.* (9) compared the use of PET/CT to conventional thoraco-abdominopelvic CT (TAP-CT) in the diagnosis. They found that although PET/CT was more sensitive than TAP-CT, the techniques were complementary, because lesions not seen on one modality were often seen on the other. One patient in their study had a liver lesion detected on TAP-CT that was not evident on PET/CT, but it is not clear whether this was a false-negative PET/CT finding or whether it was because the liver lesion was benign (*e.g.* a hemangioma or cyst) or too small to reasonably be expected to be detected on CT. The patient with a 3-cm liver lesion that was proven metastatic ACC is the only false-negative ACC that we have been able to document.

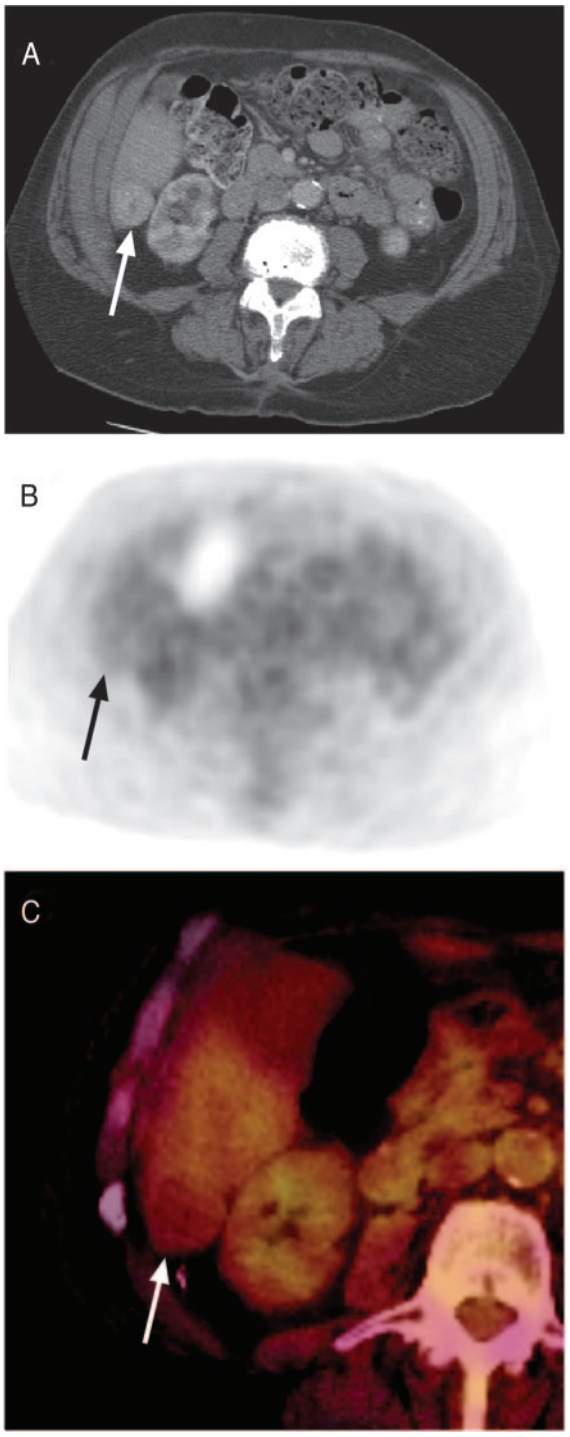

FIG. 4. Patient 4, false-negative FDG PET. A, Transverse contrast-enhanced CT image demonstrating a round, enhancing mass in the posterior aspect of the right lobe of the liver; B and C, transverse FDG PET image (B) at same level with a fused PET/CT image (C) of the lesion (concurrent CT without contrast) demonstrating no activity within the lesion. Biopsy and subsequent resection confirmed this mass to be metastatic ACC.

Conclusion

FDG PET is useful for the detection of recurrent and metastatic ACC. However, an occasional tumor and small pulmonary lesions may not accumulate sufficient FDG to allow detection, resulting in false-negative findings. Additional evaluation is required to determine the utility of FDG PET for monitoring the response to chemotherapy and/or radiotherapy.

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