Original Article

Fluoro-2-Deoxyglucose-Positron Emission Tomography/Computed Tomography in the Diagnosis and Management of Adrenocortical Carcinoma: A 10-Year Experience from a Tertiary Care Institute

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Abstract

Purpose: Adrenocortical carcinoma (ACC) is a rare primary malignancy of the adrenal gland. The present study was aimed to compare the performance of fluoro-2-deoxyglucose-positron emission tomography–computed tomography (FDG-PET-CT) compared to contrast-enhanced computed tomography (CECT) in diagnosis and management of ACC. **Materials and Methods:** A retrospective analysis of the PET-CT studies from January 2010 to October 2020 was performed. Patients with adrenal lesions suspicious of ACC and diagnosed cases of ACC who underwent PET-CT for staging, restaging, and surveillance were reanalyzed. The PET-CT parameters were compared with the clinical, biochemical, histopathological, and CECT parameters. **Results:** The study included 96 scans performed in 77 patients (36 males, aged 40.4 ± 17.9 years). Of these, 55 scans were performed to diagnose and stage suspected ACC (30 of them diagnosed as ACC), 31 for restaging, and 10 scans for surveillance of ACC. PET/CT revealed metastases from an extra-adrenal primary in 5/55 patients. FDG-PET-CT had a sensitivity and specificity of 100% and 70% to diagnose ACC. Standardized uptake value-peak more than 5.4 had a sensitivity of 90.9% and specificity of 91.7% for differentiating ACC from non-ACC lesions, while tumor-to-liver ratio peak (TLRpeak) of 3.3 was most specific. PET-CT changed the staging in 23.3% of the patients with an accuracy of 100%. PET-CT changed the management plan in 25.8% of the patients during restaging with a sensitivity and specificity of 95.6% and 100%, respectively. For surveillance, CECT was as sensitive as PET-CT; however, PET-CT was more specific (100% vs. 97.9%). **Conclusion:** FDG-PET-CT performs better than CECT in the diagnosis, staging, restaging, and surveillance of ACC.

Keywords: *Adrenocortical carcinoma, fluorodeoxyglucose F18, positron-emission tomography*

Introduction

Benign adrenal lesions such as adrenal cysts and lipid-rich adenomas have pathognomonic image findings with a relatively straightforward diagnosis. However, adrenal adenomas without lipid content may be difficult to distinguish from the malignant entities.[1] The malignant adrenal tumors are adrenocortical carcinomas (ACCs), pheochromocytoma, and secondary metastatic disease. Adrenocortical tumors are quite common in older people, with a prevalence of 3% in the population with age more than 50 years.[2] Among these, ACC is a rare primary malignant tumor with a yearly incidence of 0.5–2 per million. It has a bimodal age distribution with a relatively higher incidence in children <10 years and a second peak in late adulthood.[3-5]

Adrenocortical tumors have characteristic computed tomography (CT) features such as CT attenuation (Hounsfield units [HU]), enhancement, and contrast washout. Chemical-shift magnetic resonance imaging (MRI) is also used in inconclusive cases.[6] These patients require repeated imaging for staging, restaging, and response evaluation of the disease.[6]

2-fluoro-2-deoxyglucose-positron emission tomography–computed tomography (FDG-PET-CT) has been seen to provide beneficial information during staging and response evaluation.[7-10] However, literature regarding the use of FDG-PET-CT in the various stages of management in cases of ACC is relatively sparse. In the present study, we aimed to evaluate the incremental value of FDG-PET-CT in the diagnosis of ACC in patients with adrenal

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masses suspicious for ACC and in the management of ACC as compared to a contrast-enhanced computed tomography (CECT) acquired during the PET-CT study.

Materials and Methods

Study population

We retrospectively analyzed our database of FDG-PET-CT scans pertaining to ACC from January 2010 to March 2020. We identified all the patients who underwent PET-CT imaging for diagnosis of adrenal masses at our institute, which included patients with clinical/biochemical suspicion of ACC and a prior CECT showing adrenal mass suspicious for ACC and those for the staging, restaging, and surveillance after successful therapy in diagnosed cases of ACC. The ethics committee approved the study and waived the written informed consent given retrospective data analysis. The patients with adrenal lesions with biochemical or clinical suspicion of pheochromocytoma were excluded. The clinical information was also retrieved from the PET registry.

Fluoro-2-deoxyglucose-positron emission tomography–computed tomography acquisition parameters

All the PET-CT studies were acquired according to our departmental protocol where the patients fasted for 4–6 h and blood glucose levels were ensured to be 150 mg/dL before the injection of FDG. The whole-body PET-CT image acquisition was performed 45–60 min after intravenous injection of ~ 5 MBq/Kg of F-18 FDG on a dedicated PET-CT system (Discovery STE 16 and Discovery 710, GE Healthcare Systems). Portal venous phase of CECT was acquired 60 s after the injection of 1 ml/kg body weight of iodinated contrast (300 mgI/ml iohexol) at the rate of 3 ml/sec during the PET-CT imaging.

Image analysis

The PET-CT studies that met the inclusion criteria were re-read by two experienced nuclear medicine physicians blinded to the final diagnosis. Images were read qualitatively by visual assessment and semi-quantitatively. Focal FDG uptake in the adrenal gland distinctly more than the liver in the same transaxial section was considered PET positive. FDG uptake that was comparable or lesser than the liver was considered PET negative. Any disagreement was resolved by mutual consensus. The semi-quantitative analysis was done by measuring the FDG uptake in the lesion, i.e., SUVmax, SUVmean, and standardized uptake value-peak (SUVpeak) of the adrenal lesion by placing a region of interest (ROI) encompassing the entire adrenal lesion. The SUVmax and SUVpeak of the contralateral adrenal gland were also measured. If both the adrenal glands were involved, the larger lesion was considered the primary target lesion. An ROI was drawn in the segment VIII or uninvolved liver segment (in case of metastases in segment VIII) for FDG activity in the liver. The SUVmax (SUVmax liver) and SUVmean (SUVmeanLiver) were recorded. The tumor-to-liver ratios (TLRs) and tumor-to-contralateral adrenal ratios (TCRs) ratios were calculated, as shown in Table 1. The CECT parameters such as lesion size, outline (smooth or lobulated), enhancement pattern (nonenhancing, homogeneous, or heterogeneous), average attenuation (HU) in the portal venous phase, presence or absence of necrosis, and calcifications were also recorded from the PET-CT study. The size of the lesion more than 4 cm or the presence of heterogeneous contrast enhancement on CECT was considered suspicious for malignancy.[11]

Apart from the primary site, PET-CT images were also assessed by a five-site scoring system (postoperative adrenal bed/contralateral adrenal, regional lymph nodes, liver, lung, and skeletal lesions/other distant sites) during the disease staging, restaging, and surveillance. Criteria for positivity are defined in Table 1. The SUVmax at these sites was also recorded.

The gold standard for evaluating primary disease was histopathological examination (HPE) reports from the lesion. However, a reference standard was set in case of staging, restaging, and surveillance, which included histopathology and clinical or imaging follow-up over a minimum period of 6 months as it was unethical to sample all metastatic sites.

Data collection

The data pertaining to the clinical details of the patients, age and sex, the duration and nature of the symptoms, history of previously diagnosed extra-adrenal malignancies, and biochemical parameters (serum cortisol, serum adrenocorticotropic hormone, estradiol, and testosterone levels) were retrieved from the records. Additional data on the indication of the scan, histopathology, and imaging follow-up or pathological diagnosis of identified lesions in case of staging and restaging, nature of the treatment given, and the duration since the treatment in case of restaging and time since last negative PET scan in case of patients presenting for surveillance PET were also recorded. The scans were categorized based on these indications and analyzed separately to identify the incremental role of FDG-PET-CT in each indication. Comparisons were done with the CECT parameters acquired as a part of the PET-CT acquisition.

Statistical analysis

The statistical analysis was performed using SPSS version 22.0 (IBM systems, Armonk, NY, USA). Shapiro–Wilk test was used as the test of normality. Continuous normal data were expressed in terms of mean and standard deviations, while continuous nonnormal data were expressed as median and interquartile ranges. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were

Table 1: Calculation of semi-quantitative parameters analyzed in the study pertaining to the diagnosis of adrenal lesions and criteria for positivity of a lesion at various regions on computed tomography and positron emission tomography/computed tomography

Parameter	Calculated as	
TLRmax (target-to-liver ratio SUVmax)	SUVmaxLesion/SUVmeanLiver	
TLRpeak (target-to-liver ratio SUVpeak)	SUVpeakLesion/SUVmeanLiver	
TCRpeak (target-to-contralateral adrenal SUVpeak)	SUVpeakLesion/SUVpeakCL	
Site of lesion	**Criteria for positivity**	
	CT	**FDG-PET/CT**
Contralateral adrenal	Any lesion on CT irrespective of size	SUVmax of lesion more than SUVmean of liver (of any size on CT)
Postoperative bed (for restaging only)	Any abnormal soft-tissue density lesion irrespective of size	
Lymph node	Short-axis diameter>1.0 cm	
Lung	Any lung nodule suspicious for metastases irrespective of size	
Bone	Any lesion suspicious of metastases (lytic or sclerotic)	
Liver	Hypodense lesion in the liver of any size	Any focal FDG avidity greater than the surrounding liver parenchyma

TLR: Tumor-to-liver ratio, SUVmax: Maximum standardized uptake value, TCR: Tumor-to-contralateral adrenal, FDG: 2-Fluoro-2-deoxy-glucose, PET/CT: Positron emission tomography/computed tomography

calculated for CT and FDG-PET-CT in the various scenarios. These parameters were compared between CT and PET-CT using McNemar's test for matched proportions. In the case of initial diagnosis, patients were subgrouped based on the final histopathological diagnosis. The CT and PET parameters in the form of continuous and categorical variables were analyzed and compared between the ACC and non-ACC patients using the unpaired *t*-test/Mann–Whitney U-test and Fisher's exact test, respectively. Receiver operating characteristic (ROC) curves were drawn to obtain cutoff values for these semi-quantitative PET variables. Correlation between the semi-quantitative PET parameters, CT parameters, and histopathological parameters was analyzed using Spearman's rank correlation (rho). $P < 0.05$ was considered statistically significant. For staging and restaging PET-CT scans, the number of metastatic sites picked up on CT and FDG-PET-CT was analyzed based on the five-site scoring system. The sensitivity, specificity, and accuracy of the two investigations were compared.

Results

A total of 96 scans were evaluated in 77 patients (36 males) aged 40.4 ± 17.9 (range: 1–84) years, including six children aged <5 years. Of these 96 scans, 55 scans were for initial diagnosis and staging of adrenal lesions, 31 for restaging of ACC patients following different treatment forms, and 10 for surveillance purposes.

Fluoro-2-deoxyglucose-positron emission tomography–computed tomography in patients with clinical/imaging or biochemical suspicion of adrenocortical carcinoma

A total of 55 patients underwent FDG-PET-CT with clinical and/or biochemical and conventional imaging suspicion of ACC. None of these had an extra-adrenal malignancy before the PET-CT. The symptomatology, demographic profile, and final histopathological diagnoses are given in Table 2.

Of these 55 patients, the diagnosis of ACC was established in 30 patients (54.5%) on HPE. The remaining 25 patients had non-ACC lesions on histopathology (adrenal adenoma [n = 6], adrenal tuberculosis [n = 2], adrenal hemorrhage [n = 1], ganglioneuroma [n = 2], spindle cell tumor [n = 2], leiomyosarcoma [n = 3], lymphoma [n = 4] and metastases from lung [n = 3], and renal cell carcinoma [n = 2]). PET was positive in 45/55 (81.8%) patients. Five patients with metastases to the adrenal gland on HPE (where the primary sites were also detected during the PET/CT study) were excluded from further analysis. Of the remaining 50 patients, 42 (84%) had PET-positive primary adrenal lesions. FDG-PET findings lead to 30 TP, 12 FP, and 8 TN giving a sensitivity, specificity, PPV, NPV, and accuracy of 100% (95% confidence interval –88.4%–100%), 40% (19.1%–64.0%), 71.4% (63.6%–78.1%), 100%, and 76% (61.8%–86.9%), respectively, to diagnose ACC. The sensitivity and specificity of CECT were 100% (88.43%–100%) and 55% (31.5%–76.9%) based on the CT criteria of size >4 cm and heterogeneous contrast enhancement. Combining both the PET and CT criteria (FDG-positive lesion with positive CT criteria) increased the specificity to 70.0% (45.7%–88.1%) while retaining the sensitivity of 100% (30 TP, 6 FP, and 14 TN). Figure 1 demonstrates the FDG PET/CT findings in two patients with suspicion of ACC.

A semi-quantitative analysis was performed by SUV parameters in patients with ACC (Group A; n = 30) and non-ACC (Group B; n = 20). The CT and PET findings

Table 2: Demographic profile of patients for diagnosis positron emission tomography/computed tomography

Parameter	Value
Age of the patients (years), mean±SD	40.9±19.8
Children <5	5 (9.1)
Adults >12	50 (90.9)
Sex distribution	
Male:female	27:28
Clinical symptoms and biochemical values (%)	
Incidental imaging diagnosis	4 (7.2)
Cortisol excess	11 (20)
Sex steroid excess	10 (18.1)
Abdominal pain	26 (47.3)
Adrenal insufficiency	2 (3.6)
Nonspecific symptoms (fatigue, weight loss)	11 (20)
Side of involvement (%)	
Left only	19 (34.5)
Right only	27 (49.1)
Bilateral	9 (16.3)
Final histopathological/cytological diagnosis (%)	
Adrenocortical carcinoma	30 (54.5)
Benign	
Adrenal adenoma	6 (10.9)
Adrenal tuberculosis	2 (3.6)
Adrenal hemorrhage	1 (1.8)
Ganglioneuroma	2 (3.6)
Benign spindle cell tumor	2 (3.6)
Malignant	
Leiomyosarcoma	3 (5.4)
Lymphoma	4 (7.2)
Metastases from renal cell carcinoma	2 (3.6)
Metastases from primary lung malignancy	3 (5.4)

SD: Standard deviation

are given in Table 3. The background SUVmean of the liver was comparable between the two groups ($P = 0.714$). The SUVmaxLesion, SUVpeakLesion, SUVmeanLesion, TLRmax, TLRpeak, and TCRpeak were significantly higher in ACC ($P \leq 0.005$). Among the CT parameters, the lesion's size was significantly larger in ACC patients ($P = 0.004$). The presence of necrosis and a heterogeneous contrast enhancement pattern favored a diagnosis of ACC ($P < 0.001$ and $= 0.001$, respectively). The average attenuation and presence of calcifications were comparable in both the groups ($P > 0.05$).

ROC curve analyses demonstrated that SUVpeakLesion was the most reliable parameter (AUC = 0.958) for differentiating ACC from the other observed benign lesions including adrenal adenoma with a sensitivity of 90.9% and specificity of 91.7% at a cutoff of 5.4. Similarly, SUVmaxLesion more than 6.7 had a sensitivity of 90% and specificity of 84.6% with an AUC of 0.926. The parameters SUVmeanLesion (cutoff – 3.1), TLRmax (cutoff – 4.6), and TLR peak (cutoff – 3.3) demonstrated a specificity of 100% of which TLRpeak had the highest sensitivity (81.8%). In ACC, none of the CT or PET parameters showed significant correlation with the histopathological parameters ($n = 16$), i.e., Weiss score (in adults) or Wieneke (in children) score, number of mitosis, or Ki-67 values.

Fluoro-2-deoxyglucose-positron emission tomography–computed tomography in staging of adrenocortical carcinoma

A total of 30 PET-CT scans in 30 patients (males 14) diagnosed with ACC were evaluated for disease staging. Bilateral adrenal involvement was noted in three patients. The staging was done based on the European Network for the Study of Adrenal Tumors (ENSAT) staging system. On PET and CT imaging, ENSAT stage was noted to be I or II ($n = 18$; 60%), III ($n = 3$; 10%), and IV ($n = 9$; 30%), respectively. CT and PET-CT findings were not concordant in all the patients. PET-CT upstaged the disease in four (13.3%) patients while downstaged in three (10%). PET-CT identified in the metastases to contralateral adrenal gland ($n = 3$), regional lymph nodes ($n = 6$), liver ($n = 5$), lungs ($n = 5$), and supraclavicular lymph nodes ($n = 4$). The sensitivity, specificity, and accuracy for whole-body CT were 65.2%, 97.6%, and 92.7%, respectively, while for FDG-PET-CT, they were all 100%. CT demonstrated three false-positive lesions (lung: 2, regional lymph node: 1) which were PET negative. CT revealed eight false-negative findings (supraclavicular lymph nodes: 4, regional lymph nodes: 4), but all these were PET positive and confirmed on clinical or imaging follow-up. The parameters of both CT and PET-CT regarding staging are given in Table 4.

Fluoro-2-deoxyglucose-positron emission tomography–computed tomography in the restaging of adrenocortical carcinoma patients

For restaging of ACC, FDG-PET-CT was performed in 31 patients. Of these, 11 patients (35.5%) also underwent FDG-PET-CT imaging for initial workup. The treatment received before undergoing PET-CT was predominantly surgical excision of the primary tumor only ($n = 21$, 67.7%). The patient characteristics are shown in Table 5.

FDG-PET-CT helped to change the management plan in eight (8/31, 25.8%) patients. The disease was upstaged in one (1/31, 3.2%) by identifying the additional retroperitoneal lymph node and downstaged in seven (7/31, 22.6%) patients. CECT localized the disease at the postoperative bed in five patients (5/31, 16.1%) and lung nodules (2/31, 6.5%), and none of them had FDG avidity. PET-CT was false negative in one of these patients with local disease in which follow-up imaging demonstrated progression. The sensitivity (95.6% vs. 91.3%) and specificity (100% vs. 94.7%) of FDG-PET-CT were significantly better than CECT ($P = 0.025$) for disease localization. Figure 2 demonstrates the FDG PET/CT findings during staging workup [Figure 2 a-d] and during re-staging [Figure 2 e-h] in two different patients with ACC.

Table 3: Computed tomography and positron emission tomography/computed tomography parameters of patients for diagnosis of adrenal lesions (*n*=55)

Parameters	Adrenocortical Carcinoma (ACC) (*n*=30)	Non-ACC lesions (*n*=20) (excluding secondary metastases *n*=5)	*P*
CT parameters (percentages/mean±SD)			
Bilateral involvement	3 (10)	4 (20)	0.416
Largest dimension (cm)	11.0±3.6	7.6±5.5	0.004
Enhancement pattern			
Homogeneous	0	10 (50)	<0.001
Heterogeneous	30 (100)	10 (50)	
Nonenhancing	0	0	
Average attenuation (HU)	48.9±12.4	45.2±11.9	0.334
Presence of necrosis	27 (90)	9 (45)	0.001
Calcifications present	8 (26.7)	5 (25)	0.895
PET parameters (percentages/median [IQR])			
FDG-PET positive	30 (100)	12 (60)	<0.001
SUVmax of lesion	10.1 (8.3-14.5)	6.6 (3.5-8.7)	0.001
SUVpeak of lesion	9.8 (6.7-12.5)	4.9 (2.8-6.5)	0.001
SUVmean of lesion	3.5 (2.3-5.0)	1.9 (1.5-3.1)	0.005
SUVmean of liver	1.8 (1.4-2.2)	1.8 (1.4-2.3)	0.714
TLRpeak	5.8 (3.6-9.0)	2.7 (1.3-4.5)	0.003
TLRmax	7.5 (4.5-10.2)	3.8 (2.0-5.8)	0.005
TCRpeak*	7.0 (4.0-10.4)	2.4 (1.4-4.5)	0.001

*In unilateral involvement only (*n*=43). ACC: Adrenocortical carcinoma, CT: Computed tomography, SD: Standard deviation, PET: Positron emission tomography, IQR: Interquartile range, FDG: 2-Fluoro-2-deoxy-glucose, SUVmax: Maximum standardized uptake value, TLR: Tumor-to-liver ratio, TCR: Tumor-to-contralateral adrenal, HU: Hounsfield units

Table 4: Role of computed tomography and positron emission tomography/computed tomography in staging of adrenocortical carcinoma

Characteristics	Value (%)
Total number of sites positive for disease	23/150 sites (15.3)
Contralateral adrenal	3/23 (13.0)
Lymph nodal metastases	6/23 (26.1)
Liver metastases	5/23 (21.7)
Lung metastases	5/23 (21.7)
Distant lymph node - left supraclavicular	4/23 (17.4)
Change in staging after PET/CT (from CT)	7/30 patients (23.3)
Upstaging of disease	4/30 (13.3)
ENSAT stage I-II to stage III	2/30 (6.7)
ENSAT stage I-II to stage IV	1/30 (3.3)
ENSAT stage III to stage IV	1/30 (3.3)
Downstaging of disease	3/30 (10)
ENSAT stage IV to stage I-II	2/30 (6.7)
ENSAT stage III to stage I-II	1/30 (3.3)
ENSAT stage IV to stage I-II	0/30 (0)

PET/CT: Positron emission tomography/computed tomography, ENSAT: European Network for the Study of Adrenal Tumors

Fluoro-2-deoxyglucose-positron emission tomography–computed tomography in surveillance of adrenocortical carcinoma

A total of ten PET-CT scans were performed in eight patients (males: 5) for surveillance following remission of metastatic ACC with at least one normal previous FDG-PET-CT scan. The median duration from the preceding normal PET scan was 13.5 months. Of the 50 sites of disease analyzed (5 per patient), CT imaging was suspicious for local recurrence (n = 2) and liver metastases (n = 2). Of these, PET and CT were concordant in three patients, while the remaining one was PET negative (adrenal bed lesion). A clinical and imaging follow-up was done in these four patients for a minimum period of 6 months, during which all three patients except the PET-negative patient showed the presence of disease. Thus, CECT had a sensitivity and specificity of 100% and 97.9%, respectively, while FDG-PET-CT had both sensitivity and specificity of 100% for recurrence evaluation.

Discussion

ACC is an uncommon malignancy, but adrenal incidentalomas are seen in up to 7% of the adult population.[12] Among the adrenal incidentalomas, only less than 5% are ACCs.[5,13] Primary imaging for evaluation of incidental adrenal lesions is noncontrast computed tomography (NCCT) of the abdomen. The attenuation of <10 HU on NCCT has a sensitivity and specificity of 98% and 92%, respectively, to diagnose a benign adenoma.[14] Adrenal myelolipomas have fatty attenuation on NCCT and that can help in ruling out malignancy. Adenomas with attenuation >10 HU are challenging and require follow-up with contrast washout studies, MRI with special sequences such as chemical shift, or FDG-PET-CT

Table 5: Patient characteristics and role of positron emission tomography/computed tomography in restaging of adrenocortical carcinoma

Characteristics	Value, *n* (%)
Treatment received before restaging PET	Number of patients (***n***=31)
Surgery only	21/31 (67.7)
Chemotherapy only	1/31 (3.2)
Radiotherapy only	1/31 (3.2)
Surgery+radiotherapy	4/31 (12.9)
Surgery+chemotherapy	1/31 (3.2)
Surgery+radiotherapy+chemotherapy	3/31 (9.7)
Time to PET since last treatment received (months), median (IQR)	
Following surgery	5 (3-7)
Following chemotherapy	4 (1.5-6)
Following radiotherapy	2 (2-5)
Total number of sites positive for disease	23/155 sites (14.8)
Primary site/postoperative bed/ contralateral adrenal	11/23 (47.8)
Lymph nodal metastases	4/23 (17.4)
Liver metastases	4/23 (17.4)
Lung metastases	3/23 (13.0)
Bone metastases	1/23 (4.4)
Change in management after PET/CT (from CT)	8/31 patients (25.8)
No change in management	23/31 (74.2)
Observation to local therapy (RT/surgery)	0/31 (0)
Local treatment to systemic chemotherapy	1/31 (3.2)
Systemic chemotherapy to local therapy	2/31 (6.5)
Local therapy to observation	5/31 (16.1)*

*Includes 1 patient with false-negative PET. PET/CT: Positron emission tomography/computed tomography, IQR: Interquartile range, RT: Radiotherapy

to rule out malignancy.[6] In the present study, patients having indeterminate lesions with attenuation >10 HU and either size more than 4 cm or heterogeneous contrast enhancement underwent FDG-PET-CT imaging. No adrenal contrast washout CECT or MRI study was performed in our study population.

FDG-PET-CT could help to detect extra-adrenal sites of malignancy, even in clinically unsuspected cases, as seen in the five patients in our study. The sensitivity and specificity of CECT versus PET for diagnosing any primary malignant adrenal lesion were 91.9% versus 100% and 61.5% versus 61.5%, respectively, in our study. Further, FDG-PET had a sensitivity of 100% with a specificity of 40%, while CECT had a sensitivity of 100% and specificity of 55% for diagnosing ACC specifically. The lower specificity of both these modalities is due to the presence of few malignant but non-ACC lesions (lymphoma [n = 4] and leiomyosarcoma [n = 3]), which may share some similar imaging characteristics to ACC. Higher FDG avidity in few benign lesions (tuberculosis [n = 2], adenoma [n = 1], hemorrhage [n = 1], and benign spindle cell tumor [n = 1]) also contributed to the lower specificity. The decreased specificity of CECT was due to the presence of benign lesions (n = 5) and other malignancies (n = 4), which had lesions with a size more than 4 cm and heterogeneous contrast enhancement. When lesions that were positive on both PET and CECT were taken into account, the specificity improved to 70% while the sensitivity remained at 100%, which shows the incremental benefit of a combined PET/CT imaging to characterize adrenal lesions of indeterminate malignant potential on conventional imaging.

Previous literature has also reported FDG avidity in these benign findings, as seen in our study.[15-17] The role of PET-CT imaging is established in differentiating benign and malignant adrenal lesions (mainly metastases).[18] FDG-PET-CT revealed a sensitivity and specificity of 95% for diagnosing adrenal metastases.[19-21] However, literature on the diagnostic accuracy of FDG-PET-CT in ACC is sparse, with a sensitivity of FDG-PET-CT 100% and specificity of 70% to distinguish ACC from adenoma reported in one study.[22]

The present study demonstrated that SUVpeakLesion had the highest diagnostic accuracy (AUC = 0.958 on the ROC curve, sensitivity of 90.9%, and specificity of 91.7%) for differentiating benign lesions from ACC at a cutoff of 5.4. Similarly, The TLRpeak proved to be the most specific with a specificity of 100% (sensitivity of 81.8%) at a cutoff value of >3.3. Previous literature revealed that an SUV cutoff of 3.1 had a sensitivity of 98.5% and specificity of 93% for differentiating malignant lesions vs. benign adrenal adenomas. However, in this study, only two of the 68 malignant lesions were ACC.[8] Groussin *et al*.,[22] in their study (n = 22 patients) to differentiate ACC from benign adenomas with FDG-PET-CT, found that SUVmax cutoff of 3.4 had a sensitivity of 100% and a specificity of 70%. The adrenal-to-liver SUVmax ratio of 1.45 had a sensitivity of 100% and a specificity of 88%. Similar findings were seen in our study. However, SUVpeak and TLRpeak were seen to be more robust parameters than SUVmax and TLRmax. Higher specificity is seen at a TLRpeak of 3.3 without significant compromise on sensitivity.

In the present study, the CT parameters, i.e., size, heterogeneous enhancement, and necrosis within the lesion, were seen to be different in ACC as compared to other non-ACC lesions. Calcifications were seen in 26.7% of ACCs, which was concordant with previous literature.[23] However, calcifications and attenuation on CECT were similar in ACC and non-ACC subgroups. Similar to the study by Tessonnier *et al*.,[24] the present study also documents that SUV parameters had no significant correlation with histopathological parameters, i.e., Weiss score (in adults) or Weineke score (in children), the mitotic index, or Ki-67 values.

In the present study, patients were staged based on the ENSAT system[25] and FDG-PET-CT changed the

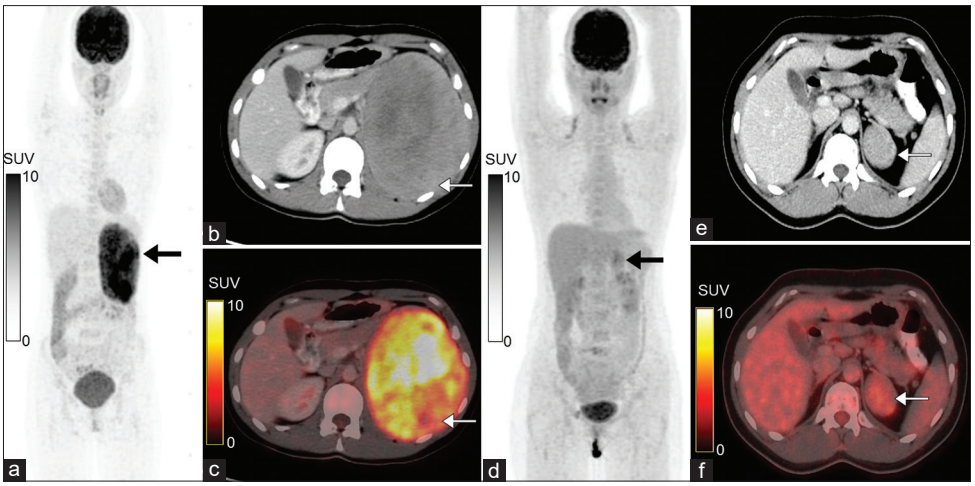

Figure 1: Maximum intensity projection image (a) of the fluoro-2-deoxyglucose-positron emission tomography–computed tomography of a patient with adrenal lesion suspicious of adrenocortical carcinoma shows an area of abnormal tracer activity in the left hypochondrium (black arrow) which on the transaxial contrast-enhanced computed tomography (b) and fused positron emission tomography–computed tomography (c) images localized to a heterogeneously enhancing lesion in the left adrenal gland with fluoro-2-deoxyglucose avidity significantly higher than the liver suggesting a malignant lesion (white arrow). The standardized uptake value-peak and TLRpeak of the lesion were 12.2 and 11.1, respectively. The final histopathological diagnosis was adrenocortical carcinoma. Another patient with a similar left adrenal lesion underwent fluoro-2-deoxyglucose-positron emission tomography–computed tomography which showed a low-grade tracer avid lesion in the left adrenal which is seen on the maximum intensity projection (d, black arrow), transaxial contrast-enhanced computed tomography (e), and fused positron emission tomography–computed tomography images (f). The lesion was diagnosed on positron emission tomography–computed tomography as benign as the fluoro-2-deoxyglucose avidity was comparable to the liver fluoro-2-deoxyglucose activity on the transaxial fused positron emission tomography–computed tomography (f, white arrow). The standardized uptake value-peak and TLRpeak of the lesion were 4.8 and 1.5, respectively, which were suggestive of a benign lesion. The final histopathological diagnosis was adrenal adenoma

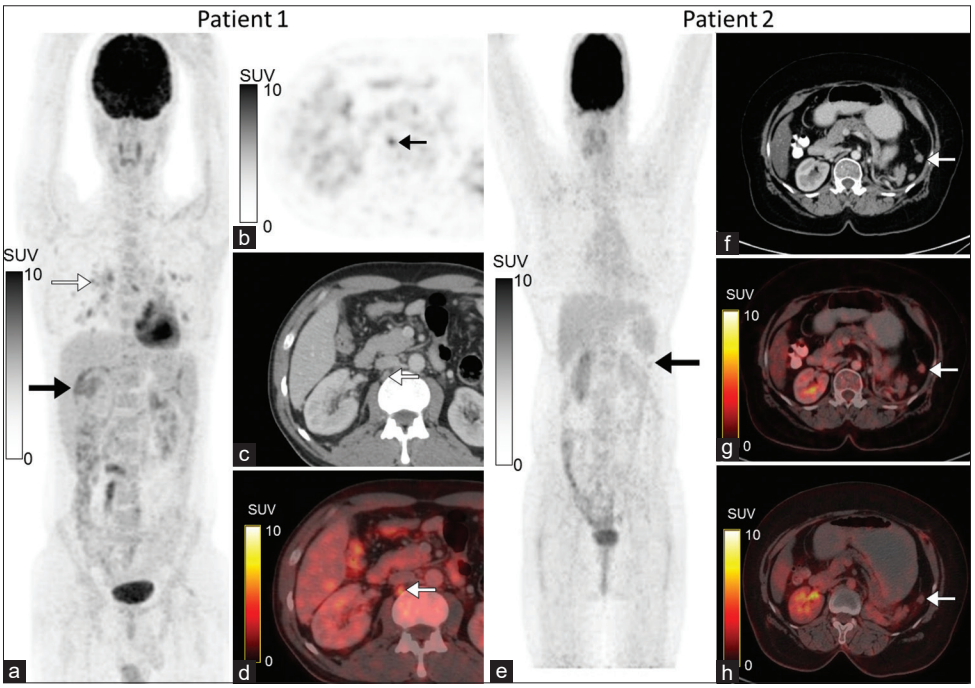

Figure 2: Patient 1 (a-d): A 37-year-old male, a diagnosed case of adrenocortical carcinoma, underwent fluoro-2-deoxyglucose-positron emission tomography–computed tomography for staging. Maximum intensity projection image (a) showed fluoro-2-deoxyglucose avidity in the primary lesion in the right adrenal gland (black arrow) and multiple foci of fluoro-2-deoxyglucose avidity in the lung region (white arrow) which was secondary to infective infiltrates in the lung. Transaxial positron emission tomography (b) was showing a focus of increased fluoro-2-deoxyglucose avidity (black arrow) which localized to a subcentimetric retrocaval lymph node which was negative for metastasis in the computed tomography component (c) but the fused positron emission tomography–computed tomography (d) images showed focal fluoro-2-deoxyglucose avidity in the lymph node which altered the management to include adjuvant radiotherapy. Patient 2 (e-h): A 50-year-old female underwent fluoro-2-deoxyglucose-positron emission tomography–computed tomography for restaging (e) following surgical resection of left adrenal adrenocortical carcinoma, which showed a faintly fluoro-2-deoxyglucose avid lesion (black arrow) in the left infrasplenic region which was suspicious for metastatic deposit on computed tomography (f) but negative according to fluoro-2-deoxyglucose-positron emission tomography–computed tomography (g). The fluoro-2-deoxyglucose-positron emission tomography–computed tomography done for surveillance after 2 years (h) showed no change in the lesion confirming its benign nature. Fluoro-2-deoxyglucose-positron emission tomography–computed tomography helped in changing the management from local radiotherapy to observation alone

management plan in 7/30 (23.3%) patients (upstaging in 4, downstaging in 3) during staging workup which was higher than the 5% reported by Takeuchi *et al*.[26] Higher false-negative lesions were noted on CECT in our study compared to PET due to subcentimetric metastatic lesions showing FDG avidity, which helped in altering management. FDG-PET-CT revealed more sensitivity (100% vs. 65.2%) and specificity (100% vs. 97.6%) as compared to CECT (P = 0.004). Leboulleux *et al*. revealed that PET changed the management plan in 14% of the patients with a sensitivity of 93% compared to 82% with CT.[7] Contrary to their study, FDG avidity was seen in metastatic lung nodules in our study, explaining the higher sensitivity. In the present study, FDG-PET-CT revealed a better sensitivity and specificity than CECT in restaging ACC patients. Low-grade FDG avidity can be seen in postsurgical inflammation.[7] Hence, FDG avidity with SUVmax of the lesion greater than the SUVmean of the liver was considered PET positive to eliminate any false-positive findings in postsurgical patients.[9] We used SUVmean of the liver instead of SUVmax to eliminate aberrantly high liver activity in a particular pixel due to technical factors.

The study also demonstrated that CECT revealed a lesion in the postoperative bed during the restaging workup in three PET-negative patients and follow-up revealed no disease. The management plan was changed in 8/31 (25.8%) patients with only one false negative on PET imaging. Similar results with FDG-PET-CT were also documented by Mackie *et al*.[9]

Although the literature is limited, FDG-PET-CT has been used to evaluate recurrence and surveillance in ACC.[10] In our study, both CT and PET-CT had a sensitivity of 100% for recurrence evaluation. CT showed one false-positive lesion in the postoperative bed, which was true negative on PET. However, further studies are needed to evaluate the role of FDG-PET-CT imaging in surveillance due to the limited number of patients and apparent similar sensitivities of CT and PET in this limited number of patients.

The main limitation of this study was the retrospective nature of the study. However, performing a prospective study in a condition such as ACC is challenging because of its rarity. Secondly, some non-ACC lesions malignant lesions were present in the study population, which affected the specificity of the imaging results. Thirdly, the patients with suspicious adrenal lesions were directly subjected to a PET-CT without performing CT contrast washout studies or MRI. Hence, the performance parameters of those modalities could not be compared here.

Conclusion

FDG-PET-CT can serve as a valuable tool for diagnosing ACC and differentiating it from benign adrenal lesions. The SUVpeak of the lesion and SUVpeak of the lesion to liver SUVmean ratios can serve as valuable diagnostic tools to improve accuracy. PET is also seen to be superior to CECT in staging the disease. During restaging, using the positivity criteria of SUVmax greater than the liver SUVmean can help in truly identifying disease involvement. The role in surveillance has to be better established in further multicenter studies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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