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Role of ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography in restaging of adrenocortical carcinoma

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ABSTRACT

Background: The objective was to retrospectively evaluate the contribution of fluorodeoxyglucose [^{18}F] positron emission tomography/computed tomography (^{18}FDG-PET/CT) to the re-staging of adrenocortical carcinoma (ACC).

Materials and methods: A total of 16 patients (10 males and 6 females), who underwent adrenalectomy due to adrenocortical carcinoma and ^{18}FDG-PET/CT scan to re-stage the tumor between July 2007 and April 2013, were included in the present study. The mean age was 53.37 ± 13.91 years (min: 30, max: 74) The patients were required to fast for six hours prior to scanning, and whole-body PET scanning from the skull base to the upper thighs was performed approximately 1 h after the intravenous injection of 555 MBq of F-18 FDG. Whole body CT scanning was performed in the cranio-caudal direction. FDG-PET images were reconstructed using CT data for attenuation correction. Suspicious recurrent or metastatic lesions were confirmed by histopathology or clinical follow-up.

Results: Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of ^{18}FDG-PET/CT were 100%, 83.3%, 90.9%, 83.3%, and 93.7%, respectively.

Conclusion: ^{18}FDG-PET/CT detects local recurrence and/or distant metastases with high accuracy in the re-staging of operated adrenocortical carcinoma. It is considered that the procedure could play an important role in treatment decision after the operation and post-operative follow-up and could influence the entire decision-making process.

Key words: adrenocortical carcinoma; restaging; PET; FDG-PET/CT

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Introduction

Primary adrenal cortical carcinoma (ACC) is a rare tumor with highly malignant potential and is often associated with poor prognosis. The incidence of this tumor is approximately 1–2 patients per one million. The majority of the cases occur in patients aged between 30–50 years; however, there is bimodal occurrence by age, with a peak incidence before the age of 5 and the second peak in the fourth and fifth decades. Life expectancy is determined by early diagnosis and treatment. The tumor generally exhibits a more aggressive course in adults than in children. ACC accounts for 0.2% of all cancer-related deaths. Although the etiology of ACC is unknown, the mutations in tumor suppressing genes as an important factor for adrenal carcinogenesis have been implicated and co-occurrence with hereditary cancer syndromes has been detected such as with Li-Fraumeni syndrome,

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Beckwith-Wiedemann syndrome, and multiple endocrine neoplasia (MEN type 1) [1]. Around 60% of adrenocortical carcinomas are functional and produce steroid hormones. Cushing's syndrome is the most common presentation in adult patients (45%). Bilateral ACCs are rarely reported in clinical series, with an incidence of 1.1% among the national American cohort of 3982 ACC patients reported by Bilimoria et al. [2]. Apart from computed tomography (CT) and magnetic resonance imaging (MRI), iodomethyl-norcholesterol scintigraphy is another method used in the differential diagnosis of malignant adrenal masses. However, most adrenocortical carcinomas do not uptake this radionuclide agent, which results in a high rate of false negative results. Fluorodeoxyglucose [^{18}F] positron emission tomography/CT (^{18}FDG-PET/CT) is a more valuable method in this respect. Complete surgical resection is the most effective therapy for ACC. Adjuvant chemotherapy is often used after incomplete surgical resection of primary ACC and in patients with metastatic disease [1]. Adrenocortical carcinomas are resistant to radiotherapy. Mitotane, a chemotherapeutic agent with specific efficiency on the adrenal cortex, is currently used in the treatment of adrenal cortical carcinomas. In stage I–III tumors, metastases develop in around 40% of the cases over two years, despite complete resection of the tumor [3]. It was found that partial or complete response has been achieved using mitotane in patients with adrenal cancer. The use of adjuvant mitotane was shown to prolong survival when compared to primary tumor excision or the presence of local spread or metastasis. Surgical treatment offers a 50% 70-month survival, and this rate is only 10% with medical therapy alone. According to the literature, 5% of the patients had stage I tumor, 41% had stage II tumor, 22% had stage III tumor, and 32% had stage IV tumor at diagnosis [4]. The 5-year survival is 79% in stage I, 62% in stage II, 50% in stage III, and 17% in stage IV. The overall 5-year survival is 16–44% [5, 6]. FDG-PET is widely used to detect areas of increased glucose uptake, which are associated with malignancy; FDG-PET also provides functional information about glycolytic activity in tumors, including ACC. PET-CT identifies local or metastatic disease forms of ACC with high sensitivity and specificity. It offers a useful anatomical and functional imaging method for follow-up after adjuvant chemotherapy (CTx) for metastatic disease [7, 8].

The main objective of the present study was to determine the role of ^{18}FDG-PET/CT in the re-staging of patients with ACC after surgery. The histological findings (where available) or the entire clinical and radiological workup (hormonal activity, CT, MRI) were used as a standard reference.

Materials and methods

A total of 7,938 patients were evaluated and 10,553 ^{18}FDG-PET/CT scans were performed between July 2007 and April 2013. In this patient group, 16 were diagnosed with operated adrenocortical carcinoma and underwent ^{18}FDG-PET/CT to re-stage the tumor. The patients were diagnosed with primary adrenal tumor based on pathological and immunohistochemical examination. Of these patients, ten were males (62.5%) and six were females (37.5%), and the mean age was 53.37 ± 13.91 years (range min: 30, max: 74). The data on histological subtypes were available in all patients, and 11 patients (68.7%) had adrenocortical carcinoma, three patients (18.7%) had pheochromocytoma, one patient (6.2%) had undifferentiated carcinoma, and one patient (6.2%) had paraganglioma.

The patients were re-assessed with ^{18}FDG-PET/CT for the purpose of re-staging due to suspicion of disease recurrence and to perform routine follow-up. These patients were retrospectively evaluated, and pathological findings and ^{18}FDG-PET/CT data were recorded. This study was approved by the local ethics committee and written consents were obtained from all patients.

^{18}F FDG was synthesized using an in-house cyclotron (Siemens) and an automated synthesis system according the authorized procedure. After five hours of fasting, the blood glucose level of each patient was measured, and the patient was then intravenously injected with 370 MBq of ^{18}F FDG. One hour after ^{18}F FDG injection, a CT scan without contrast agent was performed, covering the area from the vertex to the proximal thigh, and the images were used for attenuation correction and image fusion. This was followed by whole-body 3D PET acquisition with 8 bed positions of 3 minutes of emission scan time each using a dedicated PET/CT scanner (HI-REZ Biograph 6, SIEMENS) which provides an in-plane spatial resolution of 4.8 mm,

an axial field view of 16.2 cm. The PET data were reconstructed using a Gaussian filter with an ordered-subset expectation maximization algorithm (3 iterations, 8 subsets), re-oriented in transverse, coronal and sagittal planes, and assessed by comparing them with corresponding CT images.

PET scans were visually analyzed and semi-quantitatively using SUV_{max} measurement. SUV was expressed in terms of body weight (SUVbw — g/mL). The parameters such as patient's weight (kg), height (cm), radioactivity during injection (MBq), residual radioactivity (MBq) after the injection, starting time of injection, and half-life of the radioisotope (taken as standard 109.8 minutes for ^{18}**18-FDG**) were calculated automatically by the software.

Two experienced nuclear medicine physicians blindly and independently reviewed the hybrid ^{18}FDG-PET/CT scans as positive or negative for a primary tumor site. Every focal tracer uptake that deviated from the physiological distribution was considered to the favor of disease spread. The background deviation and activity difference between the suspected lesion and the surrounding tissues were used to differentiate benign from malignant lesions. Therefore, no specific threshold for SUV was employed.

Results

^{18}FDG-PET/CT scans showed negative findings in five patients (31.2%) and positive findings in 11 patients (68.8%). Five patients (31.2%) had disseminated metastases with high standardized uptake values (SUV) involving at least two organs (lungs, liver, and lymph nodes), six patients (37.5%) had lymph node metastasis, three patients (18.7%) had local recurrence, two patients (12.5%) had bone metastasis, one patient (6.2%) had lung metastasis, one patient (6.2%) had liver metastasis, one patient (6.2%) had contralateral adrenal metastasis, and one patient (6.2%) had intraperitoneal metastasis. ^{18}FDG-PET/CT scans showed negative findings in three patients (27.2%) and positive findings in eight patients (72.8%) with adrenocortical carcinoma, negative findings in two patients (66.6%) and positive findings in one patient (33.4%) with pheochromocytoma, and positive findings in all patients with undifferentiated carcinoma and paraganglioma (Tab. 1). ^{18}FDG-PET/CT results according to histological subtypes are presented in Table 1.

Table 1. Positron emission tomography/computed tomography (PET/CT) results according to histological findings of the tumor

Histological type	PET/CT	
	Positive (%)	Negative (%)
Carcinoma	8 (72.8%)	3 (27.2%)
Pheochromocytoma	1 (33.4%)	2 (66.6%)
Undifferentiated carcinoma	1 (100%)	0
Paraganglioma	1 (100%)	0

^{18}FDG-PET/CT results did not correlate with histological subtype in the probability charts ($p > 0.05$). Suspicious recurrent or metastatic lesions were confirmed by histopathology or clinical follow-up. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of ^{18}FDG-PET/CT were 100%, 83.3%, 90.9%, 83.3%, and 93.7%, respectively.

Discussion

The accurate re-staging of the tumor and, particularly, the detection of metastatic regions in adrenocortical carcinoma are substantially important in patient management. These data can result in a change in treatment strategies and be used as a basis for the selection of surgical or systemic therapy options. PET/CT offers an important diagnostic tool in the re-staging of the operated ACC before microscopic disease becomes manifest. This imaging method provides valuable information on response to therapy. US, contrast enhanced computed tomography (CECT), MRI and ^{131}I–6β-iodomethyl-norcholesterol scintigraphy, ^{11}C-metomidate (^{11}C-MTO) PET, and ^{18}FDG-PET/CT can be used to re-stage ACC after surgery, to detect metastatic disease, and to monitor the response to therapy. However, there is limited data on the use of ^{18}FDG-PET/CT that enables functional and anatomical processing of the images in monitoring the response to therapy after surgery for ACC and re-staging of the tumor.

The widely used Response Evaluation Criteria in Solid Tumors (RECIST) to detect a response to systemic therapy depends mainly on cross-sectional body imaging to demonstrate changes in tumor measurements compared to baseline studies [9]. However, these criteria do not include a functional component in the evaluation, which led to

the proposal of new criteria [PET Response Criteria in Solid Tumors (PERCIST)] that combine functional FDG-PET imaging with cross-sectional body imaging [10]. FDG-PET imaging can provide early indications of a response to anticancer treatments for ACC [11]. In the re-staging of most tumors, metabolic activity of metastases and local recurrences becomes visible before the development of manifest anatomical lesions [12]. Normal adrenal gland can exhibit FDG uptake, but the level of this uptake is usually low. Meier et al. reported a mean SUVmax of 1.7 ± 0.49 for normal adrenal glands [13]. Another study reported a SUVmax ranging from 0.95 to 2.46. PET/CT permits more reliable visualization of normal adrenal glands than does PET alone [14]. FDG uptake increases with tumor cell replication, increased mitotic activity, Ki-67 proliferation index, and increased glucose transporter 1 (GLUT-1) expression.

In the study by Hubert et al. that evaluated the role of PET/CT in the evaluation of response to therapy in metastatic disease, the evaluation of metastatic disease using PERCIST provided a complete metabolic response and PET/CT provided a 51% response rate. Their study found that PET/CT was a sensitive diagnostic tool in monitoring response to therapy in ACC [15]. In the literature, the sensitivity of PET/CT in diagnosing ACC was 100%, specificity was 98%, and positive predictive value (PPV), negative predictive value (NPV), and accuracy were 97%, 100%, and 86–96%, respectively [16, 17].

In diagnosing primary tumors in the adrenal gland, commonly used PET tracer ^{18}FDG is able to differentiate benign from malignant adrenal tumors in most patients. ^{11}C-MTO is a more specialized PET tracer that binds to the 11-beta-hydroxylase enzyme in the adrenal cortex and thus makes it possible to differ adrenal tumors (benign adrenocortical adenoma and adrenocortical cancer) from those of non-adrenocortical origin [18]. In the image reading, the evaluation of the ^{18}FDG uptake in various organs and tissues is generally assessed visually. To facilitate the PET image evaluation, measurements of the 18FDG uptake in tumors and normal organs are regularly performed and often the liver is used as a normal tissue reference. The rationale for calculating the tumor-to-liver ratio is that malignant lesions generally exhibit a higher ^{18}FDG uptake than that of the liver [18] (Fig. 1, 2).

Tessonnier et al. reported 100% sensitivity, 86% specificity, and 100% NPV for ^{18}FDG-PET/CT in the verification of adrenal masses. If the tumor/liver SUV_{max} ratio was taken as 1.8, sensitivity would be 100% and specificity would be 100%. These

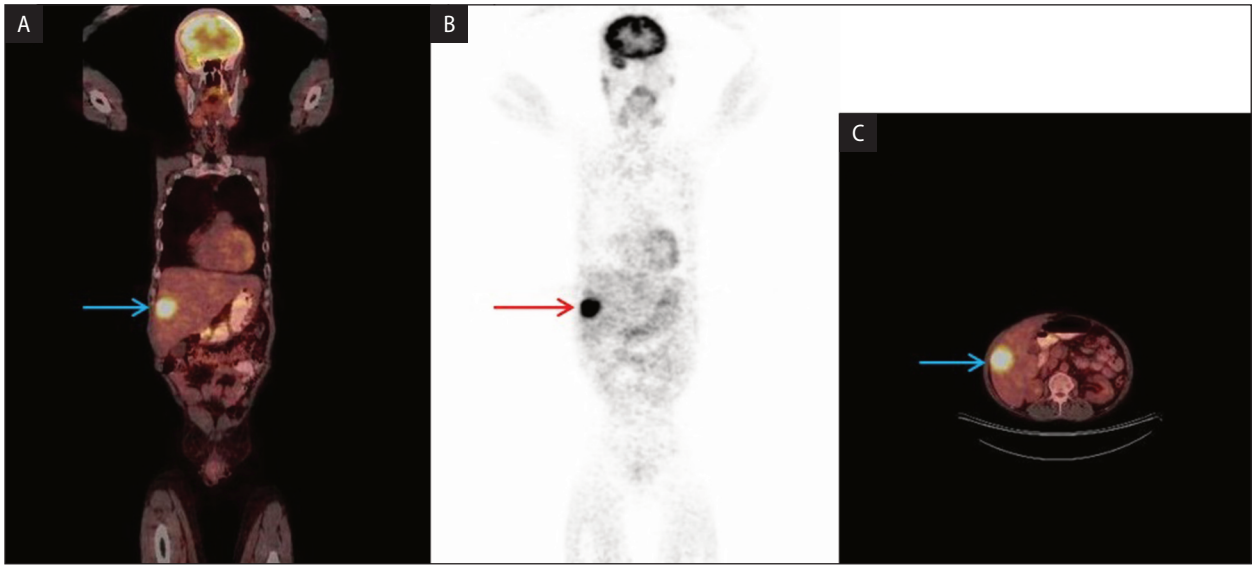

Figure 1. Liver metastasis of adrenocortical carcinoma in a 45-year-old patient. **A.** The coronal fluorodeoxyglucose [^{18}F] positron emission tomography/computed tomography (^{18}FDG-PET/CT) scans show liver metastasis (arrow), SUV_{max}: 16.5; **B.** Maximum intensity projection (MIP) images, (arrow: liver metastasis); **C.** The axial ^{18}FDG-PET/CT scans show liver metastasis (arrow), SUV_{max}: 16.5

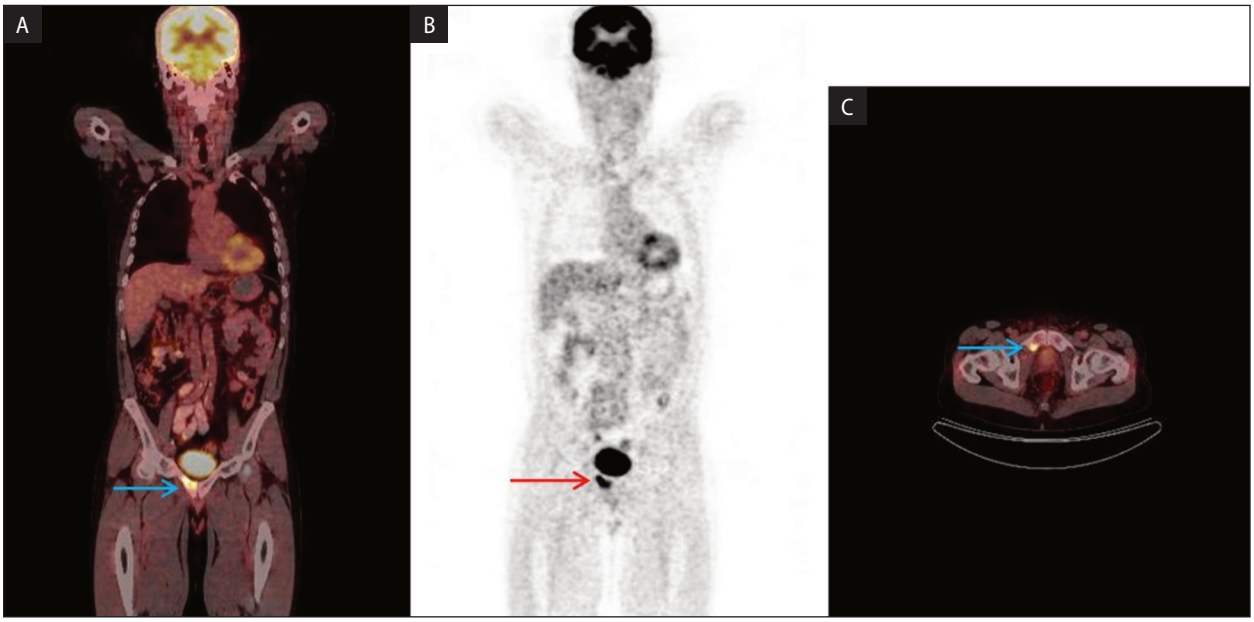

Figure 2. Bone metastasis of adrenocortical carcinoma in a 70-year-old patient. **A.** The coronal fluorodeoxyglucose [^{18}F] positron emission tomography/computed tomography (^{18}FDG-PET/CT) scans show bone metastasis (arrow); SUV_{max}: 17.7; **B.** Maximum intensity projection (MIP) images (arrow: bone metastasis); **C.** The axial ^{18}FDG-PET/CT scans show bone metastasis (arrow), SUV_{max}: 17.7

findings facilitate the differentiation of malignant lesions and change treatment preferences [19]. According to the data of 567 malignant adrenal lesions included in a meta-analysis, PET/CT provided 95% sensitivity and 91% specificity in diagnosing malignant adrenal lesions [20]. Ozcan et al. studied 81 patients with ACC using adrenal tumor-to-liver ratio. A cut-off value of 1.8 for the adrenal tumor-to-liver ratio corresponded to 87% sensitivity and 91% specificity, whereas a cut-off value of 1.68 corresponded to 90% sensitivity and 91% specificity [21]. In a study by Groussin et al. on 22 patients with ACC, a wide range of SUVmax in FDG-PET was identified between 3.6 and 26.2. This study reported 95% sensitivity and specificity [22]. Ansquer et al. reported more aggressive FDG uptake in patients with ACC. This was considered to be a poor prognostic factor [23]. In another series of adrenocortical carcinomas in relapse, tumor size and mitotic rate were found to be significantly associated with FDG uptake. The intensity (SUV_{max} > 10) and the volume of FDG uptake (> 150 mL) were significant prognostic factors for survival in these patients with disease recurrence [24].

In addition to these findings, some studies in the literature reported differing results. There are some limitations regarding the SUVmax value ın FDG-PET/CT scan. According to Cegla et al., the biggest limitation of using the SUVmax value is that it represents a single maximum pixel within the tumor without the possibility of reflecting metabolic activity within the entire tumor [25]. Tessonnier et al. evaluated 23 patients without metastasis and 14 patients with a metastatic disease in order to determine the prognostic values of preoperative SUV in patients with ACC. Tumor/liver SUV (max) ratio was 4.2 (range: 1.3–15), median SUV_{max} was 11. Although classic risk factors (tumor stage, Weiss score) were associated with poor outcome, there was no correlation between primary tumor FDG uptake with overall survival and disease free survival in M0 patients and with overall survival in M1 patients. ^{18}FDG uptake correlated inconsistently with sinister histological features, such as atypical mitoses or necrosis. In conclusion, patient prognosis and treatment strategy should not be based on uptake values [26]. In the current study, SUV_{max} values for metastases or local recurrences ranged from 2.7 to 21.1. This is parallel to the values reported in the literature. A French study included 28 patients with AAC that underwent ^{18}FDG-PET/CT imaging and reported 90% lesion-based sensitivity and 93% specificity for ^{18}FDG-PET/CT [24]. In a study by Mackie et al. that evaluated 12 patients

with AAC, the sensitivity for FDG-PET was reported to be 83% in diagnosing local recurrence or metastatic disease. In two of the patients, small lung metastases and a liver metastasis, respectively, remained undetected [27]. It has not been fully understood how low volume of metastatic disease in the liver and lungs remains undiagnosed. The studies have found that PET/CT imaging can provide information in the presence of an increased number of tumor cells with abnormal glucose metabolism (10^4–10^7). The diagnostic failures are mostly encountered in lung and liver metastases of ACC. Metastatic lung lesions measuring less than 5 mm cannot be evaluated accurately. It is not known why the lung lesions below this threshold do not produce high SUV values. This can be caused by motion artifacts and low metabolic activity of the metastatic lesion. The reduction of motion artifacts using certain techniques, achieving a better spatial resolution, and finding a higher cut-off SUV values for such lesions can increase diagnostic accuracy [28]. In the study of 13 patients with ACC by Hennings et al., ^{11}C-MTO-PET provided 89% sensitivity and 96% specificity in diagnosing AAC confirmed by histopathological examination [29]. Becherer et al. reported 97% sensitivity and 95% specificity in patients (n = 10) diagnosed with AAC. According to the results of this study, FDG-PET was highly useful in diagnosing ACC and should be included in the work-up for initial staging as well as for follow-up. In this study, PET findings changed treatment strategies in 20% of the patients and changed the tumor stage in 30% of the patients [30]. In monitoring response to therapy and re-staging of ACC, ^{18}FDG-PET/CT can be used to diagnose increased FDG uptake in cardiac thrombus related to the tumor [31]. By virtue of the well-recognized propensity of malignancies to preferentially use glycolysis as an important energy source and the stimulation of mechanisms designed to absorb substrate glucose, the glucose analog, ^{18}FDG, has become a successful radiopharmaceutical in the scintigraphic evaluation of adrenal tumors and metastatic adrenal tumors. The 11b-hydroxylase inhibitor, metomidate labeled with ^{11}C has been used to scintigraphically identify tissues of adrenocortical origin, to accurately identify recurrent and metastatic adrenocortical carcinoma, and may be useful in assessing the malignant potential of these tumors and predicting survival in afflicted patients [32]. FDG-PET is therefore widely used in the follow-up of patients with ACC and malignant pheochromocytoma (PH) [24]. Leboulleux evaluated 62 patients with ACC and eight patients with PH using PET/CT (62 patients with ACC; 35 females, 27 males; mean age at ACC diagnosis: 51 years, range: 23-75) (eight patients with malignant PH; three females, five males; median age at PH diagnosis: 46 years, range: 23–73). This study reported FDG-PET activity in 14 to 29% of the patients with ACC after adrenalectomy. This is an important finding determining the treatment strategy before the initiation of therapy with 1,ortho-1,para'-dichlorodiphenyl-dichloro-ethane (o,p'DDD) [24].

The mean survival for metastatic ACC was found to be 20 months in a cohort of 124 patients diagnosed with ACC. The patients with high mitotic activity (> 20 per 50 high-power field) and liver and bone metastases were found to have the worst prognosis [33].

In the current study and in some studies in the literature, increased mitotic count and associated FDG uptake were defined as poor prognostic factors. Therefore, increased SUV can be related to poor prognosis. In the current study, the patients with high SUV value were those with bone or soft tissue metastases and exhibited poorer response to the treatment after chemotherapy. In the current study, increased SUV values observed during re-staging of ACC after surgery were taken as an indicator of poor prognosis. Timmers et al. studied the response to therapy in 30 patients with paraganglioma (PGL). With a sensitivity approaching 100%, ^{18}FDG-PET is the preferred functional imaging modality for the staging and treatment monitoring of *SDHB*-related metastatic PGL [34]. One patient with PGL and a SUV value of 5.9 included in the current study had lymph node metastasis and this patient was diagnosed with metastatic disease with 100% accuracy.

he studies that used PET and PET/CT methods exhibited that the highest diagnostic performances, which are summarized in Table 2. The data obtained in the present study are in conformity with the literature data, particularly with the studies that utilized PET/CT as the standard technological method. In the opinion of the researchers of the current study, PET/CT is superior to PET due to the highest specificity and lower rates of false positive results. The current study achieved a sen-

Table 2. The most important studies and diagnostic performances of positron emission tomography (PET) and PET/ computed tomography (CT)

Author	Modality	n	Sensibility (%)	Specificity (%)	Accuracy (%)	Positive predictive value (%)	Negative predictive value (%)
Leboulleux et al. [18]	PET/CT	28	90	93	–	–	–
Mackie et al. [20]	PET	12	83	–	–	–	–
Becherer et al. [23]	PET	10	97	95	–	–	–
Hennings et al. [22]	^{11}C-MTO-PET	13	89	96	–	–	–
Present study	PET/CT	16	100	83.3	90.9	83.3	93.7

^{11}C-MTO — ^{11}C-metomidate

sitivity of 100%, a value higher than reported in the literature. The specificity was 83%, which was lower than the reported in the literature.

Despite the small number of patients included in the current study, the results suggest that PET/CT was a feasible and useful method in evaluating the response to therapy and clinical management of the patients. Consecutive PET/CT scans showed new metastases in patients who received chemotherapy and some lesions showed regression. SU-V_{max} values of the residual metastases were lower after the treatment. However, there were only six patients who were followed for their response to therapy. Therefore, further studies are required with a larger number of patients in order to predict the response to therapy and change treatment strategies.

The findings of PET/CT scans must be verified by histopathological work-up in order to confirm disease recurrence. Theoretically, this remains the gold standard. Unfortunately, in daily practice, this is seldom possible due to clinical reasons, feasibility of the procedure, and effective advantages of this approach in the absence of a radical surgical intent. In the current study, histological confirmation was available in six patients, and all other patients were compared with clinical and radiological findings. In conclusion, the current study retrospectively evaluated the contribution of PET/CT scans in the re-staging of ACC and found results similar to those reported in the literature. The most important parameters that limited the current study and the other studies in the literature were low rate of correlation with histopathological findings and the difficulty encountered in detecting small lung and liver metastases. Therefore, the diagnosis of microscopic disease could not be established with high accuracy. Despite the small number of patients in the current study, it is considered that ^{18}FDG-PET/CT could prove useful in monitoring response to therapy, which could be clarified with further studies. ^{18}FDG-PET/CT can prove useful in the re-staging of patients with ACC owing to its high sensitivity and accuracy rates.

Conflicts of interest

There are no conflicts of interest as the letter has been written by only one author.

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Peer-review

Externally peer-reviewed.

Informed consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study. Additional information consent was obtained from all patients for which identifying information is included in this article.

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