¹⁸F-FDG PET/CT in the post-operative monitoring of patients with adrenocortical carcinoma

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Abstract

Context: The role of ¹⁸F-labeled 2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)/computed tomography (CT) in the post-operative monitoring of patients with adrenocortical carcinoma (ACC) is still unclear.

Objective: To assess the accuracy of FDG PET/CT to diagnose ACC recurrence in a real world setting.

Design and methods: Retrospective evaluation of data of 57 patients with presumed ACC recurrence at CT scan who underwent FDG PET/CT within a median time of 20 days. We compared the results of either FDG PET/CT or CT with a gold standard confirmation of recurrence (positive histopathology report of removed/biopsied lesions or radiological progression of target lesions at follow-up) to assess their diagnostic performance at different body sites to correctly categorize target lesions. We also assessed whether FDG PET/CT findings may be useful to inform the management strategy.

Results: In 48 patients with confirmed ACC recurrence, we found that FDG PET/CT had lower sensitivity than CT in diagnosing liver and lung recurrences of ACC. FDG PET/CT had higher specificity than CT in categorizing liver lesions. FDG PET/CT had a greater positive likelihood ratio than CT to identify liver and abdominal ACC recurrences. The management strategy was changed based on FDG PET/CT findings in 12 patients (21.1%).

Conclusions: The greater sensitivity of CT may be partly expected due the specific inclusion criteria of the study; however, the greater specificity of FDG PET/CT was particularly useful in ruling out suspected ACC recurrences found by CT. Thus, use of FDG PET/CT as a second-line test in the post-operative surveillance of ACC patients following CT finding of a potential recurrence may have a significant impact on patient management.

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Introduction

Positron emission tomography (PET) with ¹⁸F-labeled 2-fluoro-2-deoxy-D-glucose (FDG) has an established role in the diagnostic approach of different types of tumors (1). More recently, PET/computed tomography (CT), a technique combining the anatomic and densitometric applications of CT and the functional and metabolic advantages of PET, has been increasingly used in oncology (2, 3).

Several studies have reported the effectiveness of FDG PET or PET/CT to differentiate benign from malignant adrenal tumors (4, 5, 6, 7, 8, 9, 10, 11) but only a few

studies reported on the use of functional imaging techniques in the follow-up of adrenocortical carcinoma (ACC) (9, 10, 11). Thus, there is limited evidence that PET/CT may refine staging of ACC patients at initial diagnosis or during follow-up. This is not surprising due to the rarity of ACC that hampers progress in the development of management strategies (12, 13).

It could be expected that PET/CT may provide useful and complementary information to CT in the detection of post-operative recurrences. In this clinical scenario,

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prompt detection of ACC re-growth and a precise definition of disease extension are of the utmost importance because surgery is a mainstay for treatment of ACC recurrence whenever it is done with radical intent (12, 14). However, repeating surgery is often technically demanding and not without risk for the patient while debulking does not offer much benefit (14); thus, an accurate pre-operative estimate of tumor burden is mandatory for the appropriate selection of patients for surgery. However, no recommendation on the use of FDG PET or PET/CT in the follow-up of patients following ACC removal or patients with advanced ACC has been provided in recent reviews (15, 16).

The objective of this work was to assess the accuracy of FDG PET/CT to diagnose ACC recurrence in a real world setting. Owing to the limited availability of the technique and cost issues, we have employed FDG PET/CT as a second-line test in patients with a potential ACC recurrence found by CT during post-surgical follow-up. We have retrospectively correlated FDG PET/CT and CT findings with histopathologic results for patients who underwent surgery or biopsy or radiological progression of target lesions (RECIST criteria) for patients who were not operated on.

Subjects and methods

Patients

Patient data were retrieved from the ACC database of the San Luigi Hospital, a tertiary referral center for patients with adrenal tumors. The database was established in 2001 with the development of a structured data form to collect comprehensive information of all patients with ACC treated at our center. Data of patients before 2011 were collected retrospectively, while in the following years data were input prospectively. Data were retrieved by trained medical personnel using specifically tailored data forms. For the purpose of this study, patients diagnosed between January 1998 and July 2012 were considered and follow-up for this study was closed on December 2013. The Institutional Ethics Committee of our hospital approved the study, and all patients provided written informed consent. Selected patients underwent surgery either at the San Luigi Hospital or at other institutions.

Inclusion criteria for the study were age ≥ 18 , pathologically confirmed diagnosis of ACC (in 50 of 57 cases, diagnosis was made or confirmed by the pathologists of San Luigi Hospital), availability of pre-operative and post-operative CT scans, ACC stages I–III at diagnosis,

radical resection of primary tumor, confirmed diagnosis of ACC recurrence during follow-up of a previously tumor-free patient, availability of concomitant FDG PET/CT and complete follow-up information until death or end of the study period. Exclusion criteria were incomplete tumor staging, European Network for the Study of Adrenal Tumors (ENSAT) stage IV ACC, history of other previous/concomitant malignancies, incomplete resection, follow-up of <12 months or incomplete follow-up information, time elapsed between the index CT showing potential ACC recurrence and FDG PET/CT > 60 days.

We collected data on patients' demographic and clinical characteristics, their tumor stage at diagnosis, hormonal workup, surgical approach, pathology report, adjuvant mitotane treatment, date and modality of recurrence, and either the date and cause of death or the date of the last follow-up. Staging at diagnosis was based on imaging studies and corroborated by pathological findings at surgery. Staging was reported according to the ENSAT staging system (17). Radical resection was defined as no evidence of microscopic residual disease at pathological analysis. Follow-up visits, which included physical examination, routine laboratory and hormone evaluation, and cross-sectional imaging of the chest and abdomen, were performed every 3–6 months until either disease progression or end of study occurred. For this study, suspected disease recurrence was defined as CT evidence of a possible new tumor site during follow-up (target lesion). The study included only patients with a presumed recurrence (target lesion) found on CT during follow-up.

Imaging techniques

FDG PET images were acquired using the PET Discovery ST (General Electric Medical Systems, Waukesha, WI, USA). Patients were asked to fast for at least 6 h before the exam and a serum glucose level below 160 mg/dl was ensured. Image acquisition was performed after 60 min from i.v. administration of 222–370 MBq of FDG. First an imaging field (CT scout view, with thickness of slices of 3.75 mm) was determined performing a CT scan (140 kV, tube current 80 mA/S) for both anatomical localization and calculation of attenuation correction. Then, PET data were acquired in a three-dimensional mode from the pelvic floor to the skull basis in six to seven bed positions. The acquisition time for PET was 2.5 min/bed position. Coronal, sagittal, and transverse data sets were reconstructed. Co-registered scans were displayed by using dedicated software (Advantage 4.2; GE Healthcare, Buckinghamshire, UK) and integrated FDG PET/CT data sets

Table 1 Baseline characteristics of the 57 patients.

Characteristics	Values
Age – median, range	42, 18–68
Sex – <i>n</i> , %	
Males	25, 43.8%
Females	32, 56.2%
Tumor stage – <i>n</i> , %	
I	4, 7.0%
II	33, 57.9%
III	20, 35.1%
Diameter (cm) – median, range	10.5, 3.3–30
Weiss score – median, range	7, 3–9
Ki-67% – median, range	20, 1–70
Secreting tumors – <i>n</i> , %	
Glucocorticoids	18, 31.6%
Mineralocorticoids	3, 5.2%
Androgens	9, 15.8%
Estradiol	1, 1.8%
Non-secreting/hormonal investigations not available	26, 45.6%
Incidentalomas	18, 31.6%
Type of surgery – <i>n</i> , %	
Open	47, 82.5%
Laparoscopy	10, 17.5%
Adjuvant mitotane – <i>n</i> , %	38, 66.6%
Confirmed recurrence – <i>n</i> , %	48, 85.9%
RFS (months) – median, range	41, 6–105
Treatment of recurrence – <i>n</i> , %	
Surgery	21, 36.8%
Chemotherapy	12, 21.1%
Radiofrequency ablation	5, 8.8%
Radiotherapy	1, 1.8%
Combination therapies	8, 14.0%
Not treated	10, 17.6%

RFS, recurrence-free survival.

were prospectively evaluated in consensus by three nuclear medicine physicians. To qualify a PET imaging as positive, we used qualitative visual criteria following the guidelines of the European Association of Nuclear Medicine (18). The rationale is that there is no single lower limit of the intensity of FDG uptake for the detection of abnormal uptake within lesions as it depends on the degree of contrast between the tumor and its immediate surroundings. Thoraco-abdomino-pelvic CT scans were performed after i.v. iodinated contrast with multislice CT whose thickness of slices varied from 0.5 to 1 mm. Images were captured every 3–6 months and were compared to the previous ones with a storage system (Picture Archiving and Communication System (PACS)). Lesions observed with CT and FDG PET/CT were analyzed by location and number, categorizing the findings according to the district (local, abdominal and peritoneal, liver, lung, bone, peritoneal lymph nodes, thoracic lymph nodes, and other districts). Results of CT scans were also evaluated in consensus and compared to the results of FDG PET/CT

scans. All evaluations were blinded to the subsequent patient management.

Confirmation of recurrence

The gold standard test for categorizing any target lesion found in a given patient by imaging as ACC recurrence was one of the following: positive histopathology report of removed, or biopsied, lesions and radiological progression according to RECIST criteria of target lesions at follow-up when they were not removed or biopsied.

Statistical analysis

All statistical analyses were performed with Statistica (StatSoft, Tulsa, USA) Statistical Software. Rates and proportions were calculated for categorical data and medians and ranges for continuous data. CT and FDG PET results were compared with the gold standard test by means of 2×2 tables. For FDG PET/CT, we calculated sensitivity ($SST = \text{true positive} / (\text{true positive} + \text{false negative})$), specificity ($SPC = \text{true negative} / (\text{true negative} + \text{false positive})$), positive predictive value ($PPV = \text{TP} / (\text{TP} + \text{FP})$), negative predictive value ($NPV = \text{TN} / (\text{TN} + \text{FN})$), positive likelihood ratio ($LR+ = SST / (1 - SPC)$), and negative LR ($LR- = 1 - SST / SPC$). The diagnostic accuracy of CT and FDG PET was analyzed by means of the χ^2 test and Fisher's exact test. Because the inclusion criteria of the study required positivity of the CT scan (detection of new lesion(s) during follow-up), we did not make a formal comparison of FDG PET/CT vs CT to categorize patients as with or without ACC recurrence. However, we compared the results of either FDG PET/CT or CT with the gold standard confirmation of recurrence to assess their diagnostic performance at different body sites to correctly categorize target lesions as ACC recurrences. We also assessed whether FDG PET/CT findings may be

Table 2 Analysis of pathological lesions detected by CT and FDG PET/CT compared to the gold standard confirmation (histopathology report or radiological evidence of progression). Data are presented per patient.

	CT				FDG PET/CT			
	TP	FP	TN	FN	TP	FP	TN	FN
Liver	16	4	33	4	10	0	37	10
Peri-renal space	21	2	31	3	19	2	31	5
Abdomen	16	2	34	5	15	0	36	6
Thorax	13	4	38	2	8	2	40	7
Bone/other	6	1	49	1	6	1	49	1

TP, true positive; FP, false positive; TN, true negative; FN, false negative.

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Table 3 Diagnostic accuracy of CT and FDG PET/CT at different sites.

	Liver		Peri-renal space		Abdomen		Thorax		Bone and other sites	
	CT	PET	CT	PET	CT	PET	CT	PET	CT	PET
Sensitivity (SST)	0.80	0.50	0.87	0.79	0.76	0.70	0.86	0.53	0.86	0.86
CI	0.58/0.92	0.30/0.70	0.69/0.96	0.60/0.91	0.55/0.89	0.50/0.85	0.62/0.96	0.30/0.75	0.49/0.97	0.49/0.97
Specificity (SPC)	0.89	0.99	0.94	0.94	0.94	0.99	0.90	0.95	0.98	0.98
CI	0.75/0.96	0.89/1.0	0.80/0.98	0.80/0.98	0.82/0.99	0.88/1.0	0.78/0.96	0.84/0.99	0.90/1.0	0.90/1.0
PPV	0.80	0.95	0.91	0.91	0.89	0.97	0.76	0.80	0.86	0.86
CI	0.58/0.92	0.68/1.0	0.73/0.98	0.71/0.97	0.67/0.97	0.76/1.0	0.53/0.90	0.49/0.94	0.49/0.97	0.49/0.97
NPV	0.89	0.78	0.91	0.86	0.87	0.85	0.95	0.85	0.98	0.98
CI	0.75/0.96	0.65/0.88	0.77/0.97	0.71/0.94	0.73/0.94	0.71/0.93	0.84/0.99	0.72/0.93	0.90/1.0	0.90/1.0
LR+	7.40	38.0	14.44	13.06	13.71	52.14	9.10	11.2	42.86	42.86
CI	2.9/19.2	2.3/616.5	3.7/55.8	3.4/50.8	3.5/53.9	3.3/828.9	3.5/23.6	2.7/46.9	6.0/0.9	6.0/0.9
LR–	0.22	0.51	0.13	0.22	0.25	0.30	0.15	0.49	0.15	0.15
CI	0.09/0.54	0.33/0.78	0.05/0.39	0.10/0.49	0.12/0.54	0.16/0.57	0.04/0.54	0.28/0.85	0.03/0.90	0.03/0.90
Sensitivity, <i>P</i> value	<i>P</i> =0.0467		<i>P</i> =0.3504		<i>P</i> =0.5000		<i>P</i> =0.0543		<i>P</i> =0.7692	
Specificity, <i>P</i> value	<i>P</i> =0.0574		<i>P</i> =0.6934		<i>P</i> =0.2465		<i>P</i> =0.3379		<i>P</i> =0.7525	

useful to inform the management strategy. *P* values of <0.05 were considered to indicate statistical significance.

Results

From the overall series of 214 ACC patients who underwent radical resection between 1998 and 2012, four patients were excluded for concomitant malignancies, three were minors at the time of diagnosis, 62 patients did not recur during follow-up, and 33 patients were lost to follow-up. In 57 of 112 patients with presumed ACC recurrence, FDG PET/CT scan was done within a median time of 20 days (range, 3–60 days) from the index CT suggesting disease recurrence and these patients formed the study cohort. Baseline characteristics of the patients are provided in Table 1.

In 40 out of 57 patients (70.2%) with one or more new target lesions at CT as a marker of potential ACC

recurrence, FDG PET/CT showed at least one significant focal uptake. Assessment of the uptake was performed in a qualitative or quantitative way via the standardized uptake value (SUV). SUV of the target lesions ranged between 1.2 and 15.5, median 6.8. In 48 patients a definitive diagnosis of ACC recurrence was demonstrated by histological analysis of surgically removed lesions (23 cases), fine-needle biopsy (five cases), or detection of radiological progression (RECIST criteria) at imaging follow-up of target lesions (20 cases). In the remaining nine patients, ACC recurrence was not confirmed.

When assessing concordance of CT and FDG PET/CT target lesions with confirmed ACC recurrences, we found that FDG PET/CT had a lower sensitivity than CT in diagnosing liver and lung lesions as ACC recurrences (Tables 2 and 3); however, FDG PET/CT had higher specificity than CT in categorizing liver lesions. FDG PET/CT had a greater LR+ than CT to identify liver and

Table 4 False positive findings of FDG PET/CT scan.

<i>n</i>	CT findings	PET/CT findings	Confirmation of status with gold standard	Gold standard method
1	Peri-renal lesion	Peri-renal uptake	Disease free	Histology Imaging F-UP
2	Peri-renal lesion	Peri-renal uptake	Disease free	Histology Imaging F-UP
3	Peri-renal lesion	Peri-renal and thymic uptake	Local recurrence	Histology Imaging F-UP
4	Abdominal lesion	Abdominal and thymic uptake	Abdominal recurrence	Histology Imaging F-UP
5	Liver lesion	Liver and colonic uptake	Liver recurrence	Histology Imaging F-UP

F-UP, follow-up. In patient nos 1 and 2, both CT and FDG/PET gave false positive results because the patients were not found to have ACC recurrence at operation. In patient nos 3 and 4, FDG/PET showed thymic uptake that was considered to be physiological. In patient no. 5, FDG/PET showed a colonic uptake that was considered consistent with previous colonoscopy findings of inflammatory bowel disease.

abdominal ACC recurrences. FDG uptake of a liver lesion increases by 38 times the probability of being a true ACC recurrence. FDG uptake of an abdominal lesion increases by 52 times the probability of being a true ACC recurrence (Table 3). A list of false positive findings of PET/CT is given in Table 4.

In 26 patients (45.6%), CT and FDG PET/CT findings were superimposable (in two of them, both techniques had false positive results because local recurrence was finally excluded). When analyzing the 31 patients (54.4%) with discordant findings between the two imaging tests, CT showed a greater number of target lesions than FDG PET/CT in 23 patients. Conversely, FDG PET/CT showed additional target lesions not found by CT in four patients. Finally, in four patients FDG PET/CT and CT showed two different target lesions (Fig. 1). In seven of the 23 patients with target lesions at CT without corresponding FDG uptakes, ACC recurrence was excluded (two hepatic nodular hyperplasia, two unspecific pulmonary nodules, two post-surgical scars, and one bone aspecific lesion). In the eight patients with FDG PET/CT target lesions without corresponding CT findings, the additional lesions found by FDG PET/CT were demonstrated to be ACC recurrences.

The management strategy was changed based on PET/CT findings in 12 patients (21.1%) (Table 5). We did not treat eight patients with CT lesions not confirmed by PET. The following workup confirmed no ACC recurrence in seven of them and one patient had to be considered as a false negative of PET/CT. We changed the treatment plan in four out of eight patients who showed FDG PET/CT target lesions without corresponding CT findings. We gave a systemic treatment instead of surgery in one patient and planned a more extensive surgery in three patients, in whom surgical and pathologic reports demonstrated the existence of multiple recurrence sites. In the remaining four patients with discordant findings between techniques, we chose to base management on CT findings, but following investigations demonstrated the presence of ACC recurrence in the sites of FDG uptake.

Discussion

The role of FDG PET/CT in the post-operative monitoring of ACC patients is yet to be established. A single study evaluated the role of FDG PET/CT to diagnose ACC recurrence and showed that PET was more sensitive than CT in detecting local recurrence, while CT was more sensitive in detecting small lung or peritoneal metastases (9). As a consequence, no formal recommendation on incorporating this technique in the surveillance protocol

Figure 1

Discordant results between CT and FDG PET/CT scans: patients with a greater number of target lesions in CT than in FDG PET/CT scans are identified as CT > PET/CT; patients with a greater number of target lesions in FDG PET/CT than CT scans are identified as PET/CT > CT; patients with CT and FDG PET/CT scans showing target lesions in different districts are identified as CT ≠ PET/CT. Analysis is done per site of lesion.

of ACC patients following complete tumor removal has been provided. However, some expert centers add FDG PET/CT at 6-month intervals in the follow-up strategy (16).

In the present study, we have assessed retrospectively our experience at the San Luigi Hospital where FDG PET/CT has been used as a second-line test in patients with a potential ACC recurrence found by CT during post-surgical follow-up. Therefore, we did not make a formal comparison of FDG PET/CT vs CT to categorize patients as with or without ACC recurrence, but we assessed whether the addition of FDG PET/CT in selected cases

Table 5 Relevant characteristics of the patients whose management has been changed following FDG PET/CT results.

n	CT findings	PET/CT findings	Management change	Status at the last visit	Gold standard method	F-UP since index CT (months)
1	One lung lesion	No uptake	F-UP and not surgery	Disease free	Imaging F-UP	26
2	One abdominal lesion	No uptake	F-UP and not surgery	Disease free	Imaging F-UP	49
3	One liver lesion	No uptake	F-UP and not surgery	Disease free	Imaging F-UP	29
4	Three liver lesions	No uptake	F-UP and not surgery	Disease free	Imaging F-UP	66
5	Two lung lesions	No uptake	F-UP and not surgery	Disease free	Imaging F-UP	32
6	Two abdominal lesions	No uptake	F-UP and not surgery	Disease free	Imaging F-UP	10
7	One bone lesion	No uptake	F-UP and not surgery	Disease free	Imaging F-UP	56
8	One liver and one peri-renal lesion	No uptake	F-UP and not surgery	Disease free	Histology	24
9	One abdominal lesion	Multiple abdominal uptake	Chemotherapy and not surgery	Disease progression (multiple sites)	Imaging F-UP	8
10	One lung lesion	One abdominal uptake	Thoraco-abdominal instead of lung surgery	Disease progression (abdomen)	Histology	21
11	One peri-renal lesion	Two liver and one peri-renal uptake	Extended abdominal surgery instead of liver surgery	Disease progression (liver)	Imaging F-UP	7
12	One lung lesion	One peri-renal uptake	Thoraco-abdominal surgery instead of abdominal surgery	Disease progression (multiple sites)	Histology	10
					Imaging F-UP	

F-UP, follow-up. Patient no. 8 had an abdominal recurrence at 18 months and was radically operated on.

may refine the diagnosis of ACC recurrence and inform the management strategy. To this aim, we have compared the results of either FDG PET/CT or CT with a gold standard confirmation of recurrence (positive histopathology report of removed/biopsied lesions or radiological progression of target lesions at follow-up) to assess the diagnostic performance of both techniques at different body sites to correctly categorize presumed ACC recurrences.

Sensitivity of CT was overall greater than that of FDG PET/CT, and this may be partly expected due the specific inclusion criteria of the study requiring positivity of the CT scan (detection of new lesion(s) during follow-up). Sensitivity of CT was significantly greater than that of FDG PET/CT in the lungs and liver. The low sensitivity of FDG-PET for lung metastases is already known due to the limited FDG PET/CT resolution of lung nodules <5 mm (9). In our series, many lung metastases were small and frequently located in the inferior lobes, close to the lung bases, where nodules are less detectable due to respiratory movements, compared to nodules in the upper parts of the lung (19).

Specificity of FDG PET/CT was overall greater than that of CT, and the difference was at the limits of statistical significance in the liver. Moreover, FDG PET/CT had a greater LR+ than CT to identify liver and abdominal ACC recurrences. Thus, FDG PET/CT was of particular value in ruling out suspected ACC recurrences found by CT. FDG PET/CT findings informed patient management in 12 cases (21.1%) and the chosen strategy proved to be correct in all but one. In addition, four patients with discordant findings between the two techniques, all sites of pathological uptake by FDG PET/CT without a correspondent anatomical lesion at CT, were finally demonstrated to be true ACC recurrences. Results of FDG PET/CT were not considered to guide management in such patients, but the choice proved to be a mistake.

Strengths of the study are the rather large series considering the rarity of ACC, the central review of radiological material with FDG PET/CT scans done in a single center and the completeness of follow-up with an unequivocal demonstration of recurrence, while we have to disclose the limit of a retrospective analysis and lack of standardization of the time interval elapsed between index CT and FDG PET/CT scan. There are no formal recommendations on the optimal time interval between the two imaging procedures, and in previous work a time interval within 3 months was considered as acceptable (20). However, we should strive to achieve PET within 1 month from CT due to the possibility of fast

disease progression. This seems a plausible compromise between the need for the shortest delay possible and the need to face practical problems (i.e., PET availability, travel arrangement for patients living far from the referral center).

Although retrospective assessment of a decision-making process may be partly flawed, the study findings are of clinical relevance showing that the use of FDG PET/CT to confirm anatomical lesions suspected to be ACC recurrences may allow a better selection of patients to surgery. Owing to the limited efficacy of available medical treatments, surgical treatment of ACC recurrences still represents the best option to prolong patient survival whenever surgery can be done with radical intent, and proven that recurrence-free survival from primary surgery be of at least 1 year (21). FDG PET/CT was useful in differentiating liver nodular hyperplasia and post-surgery abdominal inflammatory reactions from ACC recurrence. As a matter of fact, FDG PET/CT pathological uptake of a liver or abdominal lesion increases by 38 or 52 times, respectively, the probability of a target lesion being a true ACC recurrence.

To conclude, we have showed that the use of FDG PET/CT as a second-line test in the post-operative surveillance of ACC patients following CT finding of a potential recurrence may have a significant impact on patient management, in particular for an appropriate selection of patients to surgery. Therefore, we suggest that FDG PET/CT becomes part of the post-operative workup protocol of ACC patients following a CT scan that has identified morphological lesions compatible with ACC recurrences. Despite limited availability of the technique and cost issues, this strategy seems particularly appealing also with the aim of reducing the psychological burden of repeated testing in such patients. It remains to be demonstrated whether the routine use of FDG PET/CT in addition to cross-sectional imaging in the post-operative follow-up of ACC patients may improve detection and, more importantly, treatment of recurrent disease.

Declaration of interest

M Terzolo received research grants and speaker honoraria by HRA Pharma and advisory honoraria by Attercor. There are no other conflicts of interest to disclose.

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Author contribution statement

A Ardito, E Pelosi, and M Terzolo for study concept and design. A Ardito, B Zaggia, and M Terzolo for patient management. E Pelosi, V Arena, and D Penna for FDG PET scan and analysis and analysis of CT scans. E Duregon for pathological analysis. A Ardito, C Massaglia, and V Basile for data collection and capture. P Perotti for database management and submission to EC. R Brambilla and F Vigna-Taglianti for statistical analysis. C Massaglia for manuscript drafting. All authors for critical input in the manuscript. M Terzolo for final manuscript review.

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