Positive Correlation Between [^{18}F]-fluorodeoxyglucose (FDG) Uptake and Tumor-proliferating Antigen Ki-67 Expression in Adrenocortical Carcinomas

Rossella Libe
Hopital Cochin https://orcid.org/0000-0003-2881-6362
Aurore Pais
Hopital Cochin
Florian Vialon
Hopital Cochin
Laurence Guignat
Hôpital Cochin: Hopital Cochin
Fideline Bonnet
Hôpital Cochin: Hopital Cochin
Olivier Huillard
Hôpital Cochin: Hopital Cochin
Guillaume Assié
Hôpital Cochin: Hopital Cochin
Martin Gaillard
Hôpital Cochin: Hopital Cochin
Bertrand Dousset
Hôpital Cochin: Hopital Cochin
Sébastien Gaujoux
Hôpital Pitié-Salpêtrière: Hopital Universitaire Pitie Salpetriere
Maxime Barat
Hôpital Cochin: Hopital Cochin
Anthony Dohan
Hôpital Cochin: Hopital Cochin
Mathilde Sibony
Hôpital Cochin: Hopital Cochin
Jérôme Bertherat
Hôpital Cochin: Hopital Cochin
Anne Segolene Cottereau
Hôpital Cochin: Hopital Cochin

Florence Tenenbaum
Hôpital Cochin: Hopital Cochin
Joël Coste
Hôpital Cochin: Hopital Cochin
Lionel Groussin (lionel.groussin@aphp.fr)
Hopital Cochin https://orcid.org/0000-0003-1476-475X

Short Report

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Abstract

Purpose

Adrenocortical carcinoma (ACC) is a rare endocrine malignancy, whose diagnosis is suspected by conventional radiology and hormonal investigations. 18F-fluorodeoxyglucose positron emission tomography ([^{18}F]-FDG PET) could help predict malignancy, but more consistent data are necessary to support future guidelines.

Methods

A cohort of 63 patients with histologically proven ACC (n=55) or metastatic ACC with steroid oversecretion (n=8) was assembled. All patients underwent a [^{18}F]-FDG PET and the maximum Standardized Uptake Value (SUVmax) and the adrenal-to-liver SUVmax ratio were calculated. The [^{18}F]-FDG PET parameters were compared with clinical, pathological and outcome data.

Results

A positive correlation between [^{18}F]-FDG PET parameters (SUVmax and adrenal-to-liver SUVmax ratio) and tumor size, ENSAT (European Network for the Study of Adrenal Tumors) staging, total Weiss score and the proliferation marker Ki67 was found. The strong correlation between SUVmax and Ki67 (r=0.47, *p=0.0009*) suggests a relationship between FDG uptake levels and tumor proliferation. Associations between outcome parameters (progression free or overall survival) and [^{18}F]-FDG PET parameters were weaker. Fifty-six out of 63 patients (89%) had an adrenal-to-liver SUVmax ≥1.45, a previously defined cutoff value to predict malignancy. Seven ACC (11%) had a lower uptake, with a Ki67 expression level statistically lower compared to other ACC.

Conclusion

This large cohort study shows that most ACC demonstrate high [^{18}F]-FDG uptake. However, the positive correlation observed between SUVmax and Ki67 expression levels seems to explain the possibility of identifying some ACC with a low [^{18}F]-FDG uptake and Ki67 ≤ 10%.

Introduction

Adrenocortical carcinoma (ACC) is a rare endocrine malignancy with an annual incidence rate of 0.5-2 cases per million people, with an overall poor prognosis [1, 2]. ACC can be suspected by the combination of radiological features on computed tomography (CT), and an abnormal steroid excretion profile [3].With the widespread use of imaging, the recognition of ACC among adrenal incidentalomas represents a common challenge in clinical practice. When an adrenal tumor does not meet the typical radiological criteria of benignity, other diagnostic tools are necessary. As stated in the European Society of Endocrinology guidelines [4] and in recommendations from oncologists [5], 18F-fluorodeoxyglucose

positron emission tomography ([^{18}F]-FDG PET) may help in the assessment of indeterminate adrenal masses. However, the evidence is considered insufficient to make a strong recommendation [6]. Despite this limitation, studies suggested that the adrenal-to-liver maximum Standardized Uptake Value (SUVmax) ratio is a good parameter for differentiation of ACC from benign adrenal lesion [7–10]. In the present study, we report the up-to-date largest cohort of ACC explored with [^{18}F]-FDG PET, and we investigate the relationship between clinicopathological and outcome data with [^{18}F]-FDG uptake.

Materials And Methods

Patients

We retrieved clinical, hormonal, radiological and histopathological data of a cohort of 63 patients diagnosed with ACC between 2007 and 2018. Patients were managed according to French [11] and European guidelines [4]. Fifty- five patients had a histologically proven ACC and eight had steroid oversecretion with a metastatic ACC corresponding to stage 4 of the ENSAT (European Network for the Study of Adrenal Tumors) classification. Figure 1 shows the study design.

[^{18}F]-FDG PET /CT

[^{18}F]-FDG PET/Computed Tomography (CT) was performed preoperatively or during the initial evaluation for non-operated patients, on a Gemini TF 16 (Philips Medical System) that combines a helical dual slice CT and a PET machine, with an emission scan of 3 min duration per bed position. 18-F-FDG (5 MBq/kg) was administrated intravenously, after at least 6 hours of fasting and if blood glucose level was below 150 mg/dL. Imaging was performed 60 min later. The SUVmax of the adrenal lesion and the liver SUVmax, used as a background, were measured. Then, the adrenal-to-liver SUVmax ratio was calculated.

Pathological parameters

For operated ACC, the following histopathological characteristics were obtained: tumor size, Weiss score with the detail of the 9 items, immunohistochemistry (IHC) results for the proliferation marker Ki67, p53, beta-catenin, and cyclin E.

Statistical Analysis

Major characteristics of the study cohort are given as means ± SD or frequencies. Univariate analyses were performed using nonparametric tests (chi-squared, Wilcoxon test). Spearman’s rank order correlation test (and partial Spearman’s rank order correlation) was used to investigate the correlation between FDG PET measures and other outcome predictors.

Overall and progression-free survival curves were estimated by the Kaplan–Meier method and were compared with the use of the Cox proportional-hazards model (proportional-hazards assumptions were

checked with the use of Schoenfeld residuals and graphic methods).

Results

Patients

The main characteristics of the patients are summarized in Table 1. Symptoms of adrenal steroids hypersecretion (42.8%) was the most common type of clinical presentation. Over half of the patients (54%) had a localized tumor larger than 5 cm (ENSAT stage 2). Among the 55 operated patients, 41 (75%) underwent an open surgery. Forty-eight (87.3%) operated patients had a complete resection (R0). The Ki67 labeling index was available for 46 out of the 55 operated patients. High expression of Ki67 (> 10%) and an excessive number of mitosis (> 5), both criteria associated with poorer survival, were present respectively in 61% and 78% of the patients. The median follow-up period was 3.3 years (range 8 days-11.7 years) from the diagnosis of ACC. Mean SUVmax and mean adrenal-to-liver SUVmax ratios ± standard deviation were 12.6 ± 6.9 and 5.2 ± 3.2, respectively.

Adrenal-to-liver SUVmax ratios and Weiss scores

As the adrenal-to-liver SUVmax ratio is considered to have the best diagnostic performance for characterizing adrenal tumors, this parameter is shown in Fig. 2 in relation to Weiss scores obtained for the 55 operated ACC. The indicated threshold value of 1.45 represents the lowest published cutoff ratio to diagnose ACC with a sensitivity of 100% [7]. In accordance, the ratio was ≥ 1.45 for the 8 non-operated metastatic ACC and for most of the operated patients (48/55, 87%). Conversely, 7 patients (representing 13% of the operated ACC, and 11% of all ACC) had an adrenal-to-liver SUVmax ratio < 1.45, between 0.7 and 1.36, four of them with a ratio less than 1. Among these 7 patients, the Ki67 was available for 6. Five out of these 6 patients (83%) had a Ki67 ≤ 10%, whereas only 13 out of 39 patients (32.5%) with an adrenal-to-liver SUVmax ≥ 1.45 had a Ki67 ≤ 10%. The difference was statistically significant ($p < 0.03$). Despite a low adrenal-to-liver SUVmax ratio two patients died from their metastatic ACC after 4 months or 3 years, respectively.

Correlation of [^{18}F]-FDG PET parameters with clinical and histological criteria

We next assessed whether the metabolic cancer activity derived from [^{18}F]-FDG PET uptake correlates with disease histology and/or clinical outcomes. Among the analyzed criteria (Fig. 1), a statistically significant positive correlation was found between tumor SUVmax or adrenal-to-liver SUVmax ratio and five clinical or histological parameters (Table 2). Considering individually the nine items of the Weiss score, a positive correlation was only found between tumor SUVmax and capsular invasion ($p = 0.05$).

The strongest linear relationship was observed between the proliferation marker Ki67 and the tumor SUVmax (r = 0.47, $p = 0.0009$) or the adrenal-to-liver SUVmax ratio (r = 0.45, $p = 0.0015$). The significant correlation between adrenal-to-liver SUVmax ratio and Ki67 is shown in Fig. 3. The Ki67 threshold value at 10% represents the known cutoff value predicting ACC with a worse prognosis. Indeed, only 2 out of 18

(11%) patients with Ki67 < 10% died from their metastatic ACC compared to 15 out of 28 (53.5%) patients with Ki67 > 10% (*p < 0.004).*

To illustrate the relationship between [^{18}F]-FDG PET and the Ki67 we chose images from patients with three different uptake intensity correlating with an increased proliferating marker (Fig. 4).

Tumor SUVmax and adrenal-to-liver SUVmax ratio were associated with reduced overall survival, albeit not achieving significance (hazard ratios [HR] for death, 1.04 per unit; 95% confidence interval [CI], 0.99 to 1.10, *p = 0.16*; and HR = 1.10, 95% CI 0.98 to 1.23, *p = 0.11* respectively). Associations of tumor SUVmax and adrenal-to-liver SUVmax ratio with progression free survival were weaker (HR = 1.03, 95% CI 0.96 to 1.20, *p = 0.42* and HR = 1.05, 95% CI 0.90 to 1.24, *p = 0.38* respectively).

Discussion

[^{18}F]-FDG PET is mainly used in patients with adrenal masses and a history of extra-adrenal malignancy because of its high sensitivity (97%) and specificity (91%) to suspect adrenal metastases [12]. The diagnostic performance of [^{18}F]-FDG PET in adrenal incidentalomas to predict malignancy has been less studied, explaining why current guidelines on adrenal tumors management cannot be evidence-based [1, 2, 4]. The two largest series studying this question included 35 and 37 ACC, respectively [10, 13]. Despite these limitations, current data suggest that [^{18}F]-FDG PET has a good sensitivity to recognize ACC with few false negative results [7, 13]. In [^{18}F]-FDG PETanalysis, the adrenal-to-liver SUVmax ratio was found to have a lower false-positive rate than adrenal SUVmax to differentiate between adrenocortical adenoma and ACC [7, 12]. Thus, the adrenal-to-liver SUVmax ratio is considered the diagnostic criteria to use, even if there is variability in the reported ratios between 1.29 and 2.5 [7–10, 13–16].

The present paper, concerning a cohort of 63 proven ACC, demonstrate a positive correlation between clinical-pathological parameters, in particular Ki67 expression, and [^{18}F]-FDG uptake. In accordance with a previous study we did not observe a correlation between steroid oversecretion and [^{18}F]-FDG uptake [17]. Instead, significant correlations between adrenal-to-liver SUVmax ratios and tumor sizes or ENSAT stages were observed, contrary to a previous study with 37 ACC [18]. Considering the pathological parameters, a significant correlation was found between adrenal-to-liver SUVmax ratio and total Weiss score, as previously reported [8]. Capsular invasion was positively correlated with SUVmax, whereas no correlation was observed with the other Weiss items, confirming the data by Tessonier *et al* [18]. The positive correlations concerning size, ENSAT stage, Weiss score and Ki67 corroborate the idea of a relationship between [^{18}F]-FDG uptake and tumor proliferation [19]. More specifically a correlation between Ki67 expression and [^{18}F]-FDG uptake has been described in different types of malignancy [20–24].

Considering the outcome data, the associations with the progression free or overall survival were weaker in our cohort, in agreement with recent works including ENSAT stages 1-2-3-4 ACC [18, 25].

The strong positive correlation between Ki67 expression and [^{18}F]-FDG uptake seems to have implications for [^{18}F]-FDG PET use in clinical practice. Indeed, we observed 7 ACC (11%) with an adrenal-to-liver SUVmax ratio lower than 1.45, a previously defined threshold ratio [7]. These low ratios did not correlated with lower Weiss scores or lower ENSAT stages, but a Ki67 ≤ 10% was present in most of these ACC. Even considering the lowest published ratio at 1.29 [10], four ACC of the present series would have still been false-negative [^{18}F]-FDG PET imaging. Some other malignancies have demonstrated low or absent [^{18}F]-FDG uptake, possibly due to low glucose metabolism or low cellularity [26].

In conclusion, this large cohort of ACCs shows that most ACC demonstrate high uptake of [^{18}F]-FDG. The positive correlation observed between SUVmax and Ki67 explains the possibility of identifying some ACC with a low [^{18}F]-FDG uptake.

Declarations

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Conflicts of interest/competing interests

The authors disclose no potential conflicts of interest related to the present work.

Authors contributions

All authors contributed to the study conception and design. Material preparation, data collection were performed by Rossella Libé, Aurore Pais, Florian Vialon, Laurence Guignat, Fideline Bonnet, Olivier Huillard, Guillaume Assié, Martin Gaillard, Bertrand Dousset, Sébastien Gaujoux, Maxime Barat, Anthony Dohan, Mathilde Sibony, Jérôme Bertherat, Anne Segolene Cottereau, Florence Tenenbaum and Lionel Groussin. Statistical analysis was performed by Joël Coste. The first draft of the manuscript was written by Rossella Libé, Aurore Pais and Lionel Groussin and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Helsinki declaration and its latest amendments or comparable ethics standards. All patients that participated in the study provided their informed consent, and the study received the approval from the local ethics committee for Cochin Hospital publications (Number AAA-2020-08049).

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Tables

Table 1: Main characteristics of the patients

	Number of patients (%)
Gender	
Female	38 (60)
Male	25 (40)
Clinical presentation	
Incidentaloma	20 (31.7)
Adrenal steroid hypersecretion	27 (42.8)
Palpable abdominal mass	16 (25.5)
ENSAT stage	
1	6 (9.5)
2	34 (54)
3	6 (9.5)
4	17 (27)
Operated patients (n=55)	
Laparoscopy	14 (25)
Open surgery	41 (75)
Resection status (n=55)*	
R0	48 (87.3)
R1	4 (7.2)
R2	1 (1.8)
RX	2 (3.7)
Mean tumor size (cm) ± SD	10 ± 5
(range)	(2.3-22)
Weiss score (n=55)	
3	6 (11)
4	5 (9.1)
5	4 (7.3)
6	10 (18.2)
7	11 (20)
8	10 (18.2)

9	9 (16.3)
Ki67 % (n=46)	
≤10	18 (39)
10-19	9 (19.5)
≥20	19 (41.5)
Number of mitosis (n=55)	
≤5	12 (22)
>5	43 (78)

*** R0: complete resection; R1: microscopic residual tumor; R2: macroscopic residual tumor; RX: resection cannot be assessed**

Table 2: Correlation between clinical/histological parameters and [^{18}F]-FDG PET parameters

Clinical/histological parameters	Adrenal SUVmax		Adrenal/liver SUVmax ratio	
	r	*p*	r	*p*
Tumor size	0.38	*0.0018*	0.43	*0.0004*
ENSAT stage	0.30	*0.017*	0.35	*0.005*
total Weiss score	0.28	*0.03*	0.27	*0.04*
Ki67 %	0.47	*0.0009*	0.45	*0.0015*
Cyclin E IHC	0.46	*0.004*	0.31	*0.05*
Capsular invasion	0.26	*0.05*	0.24	*0.07*

Figures

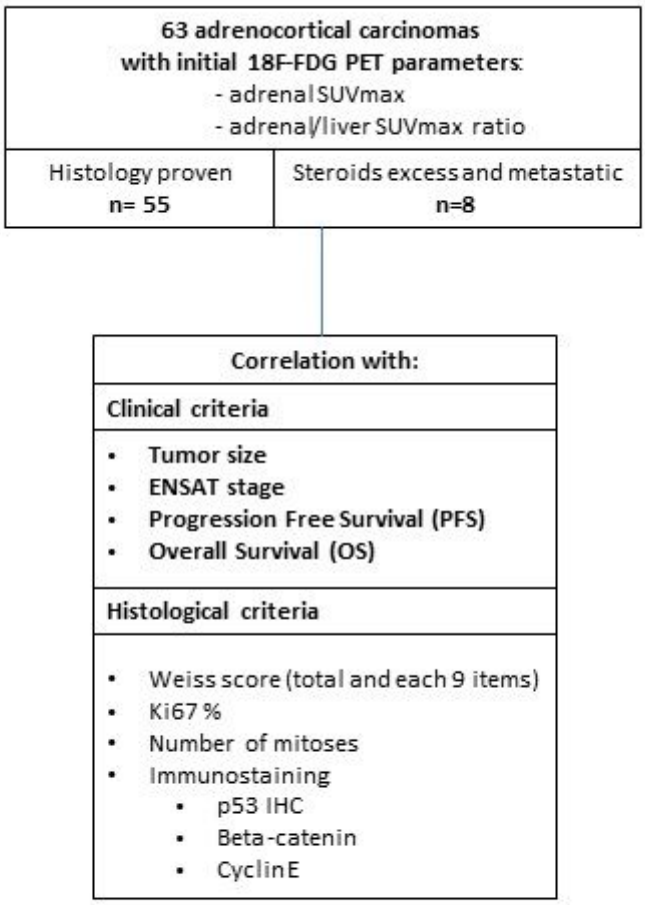


Fig.1

Figure 1

Patients population and analyzes description

Flow-chart of the study design. All the 63 ACC patients included in the study performed an [^{18}F]-FDG PET. Fifty five patients had a histologically proven ACC and eight had steroid oversecretion with a metastatic ACC corresponding to stage 4 of the ENSAT classification. Correlations between adrenal SUVmax and adrenal-to-liver SUVmax ratios and clinical/histological criteria were performed.

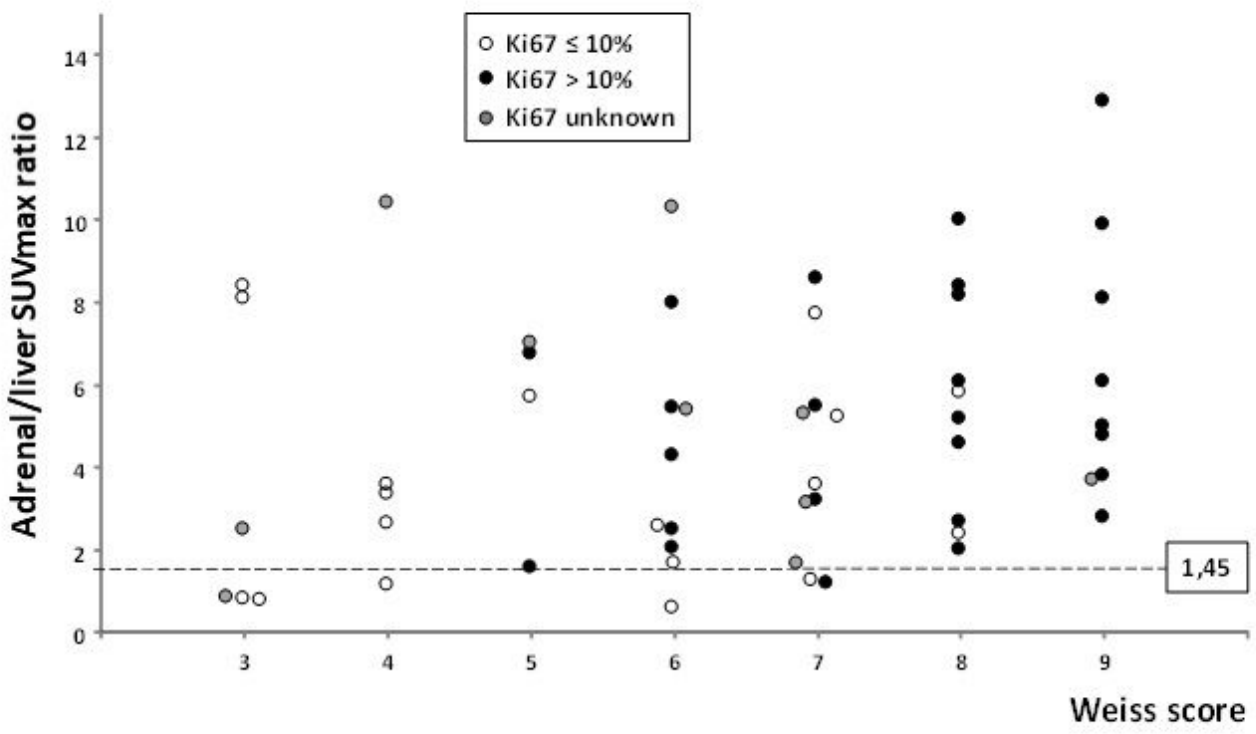


Fig.2

Figure 2

[^{18}F]-FDG PET and Weiss score.

[^{18}F]-FDG PET uptake is expressed as adrenal-to-liver SUVmax ratio. Weiss scores ≥ 3 defining adrenocortical carcinomas are represented. ACC with an immunohistochemical expression of Ki67 below or above the prognostic cutoff value of 10% are distinguished. The adrenal-to-liver SUVmax ratio threshold value of 1.45 represents the lowest published ratio that detects ACC with 100 % sensitivity.

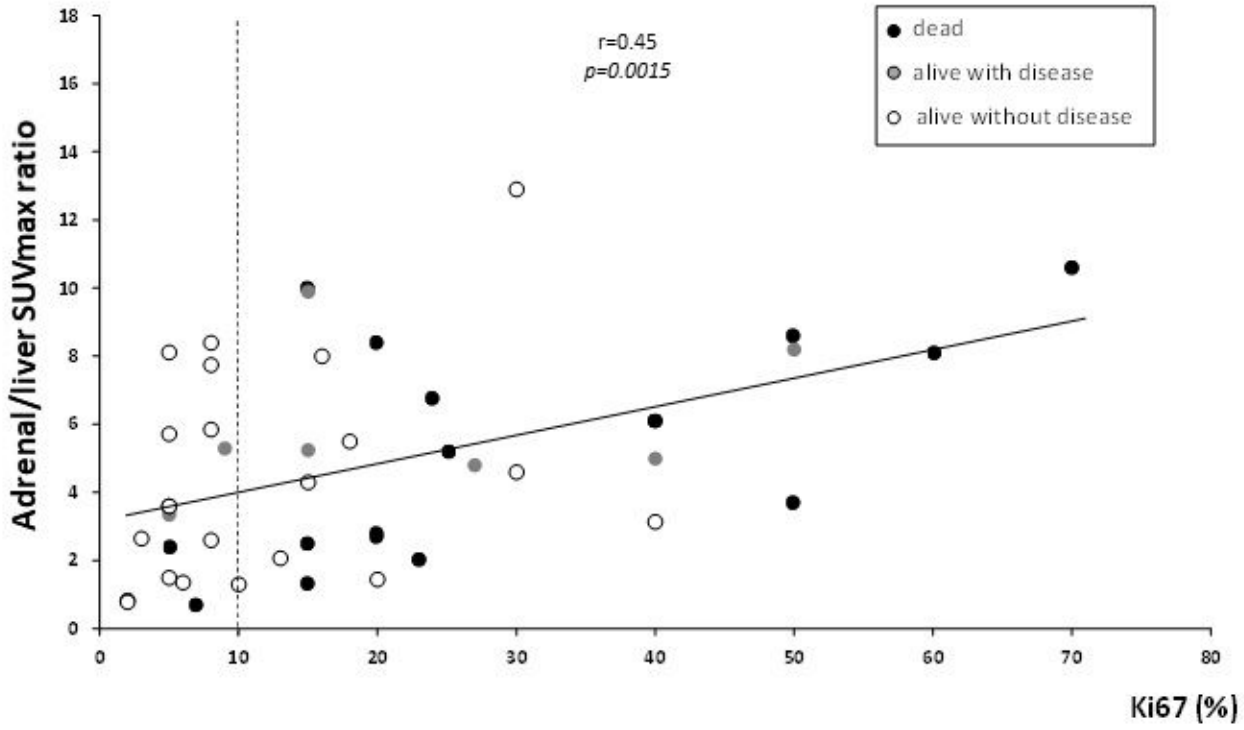
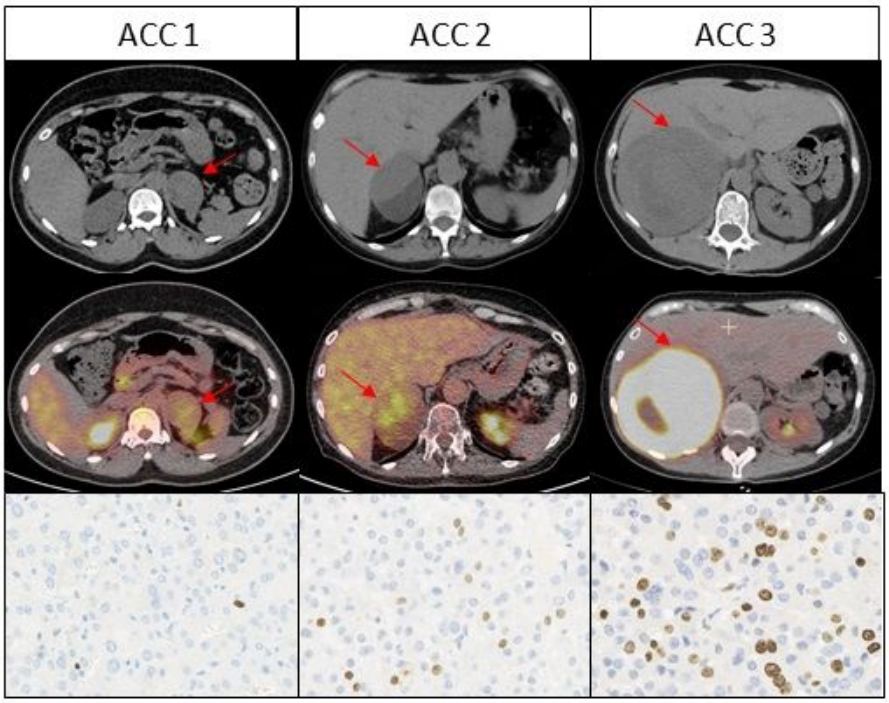


Fig.3

Figure 3

Correlation of [^{18}F]-FDG PET uptake with the proliferating marker Ki67.

[^{18}F]-FDG PET uptake expressed as adrenal-to-liver SUVmax ratio. Ki67 expressed as percentage of positively stained tumor cells. The three possible disease status at last follow-up are represented.



Adrenal SUVmax	2.5	4.9	16.8
Adrenal/liver SUVmax ratio	0.83	1.3	12.9
Weiss score	3	4	9
Ki67	2 %	10 %	30 %

Fig.4

Figure 4

Relationship between [^{18}F]-FDG PET uptake and Ki67 in three patients with ACC.

Computed tomography scans showing three ACC measuring respectively 4.5, 7 and 17 cm. The second patient had two components mass. [^{18}F]-FDG PET uptake was localized to the anterior component corresponding to the malignant adrenocortical neoplasm. Histological appearance with nuclear Ki67 immunostaining.