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Predicitve Value of FDG Uptake in the Remaining Adrenal Gland Following Adrenalectomy for Adrenocortical Cancer

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ABSTRACT

Following initial surgery, patients with adrenocortical carcinoma (ACC) are commonly treated with the adrenolytic substance mitotane in an adjuvant or therapeutic setting. Treatment responses, however, are variable. The objective of the study was to investigate a possible correlation between FDG-PET activity of the remaining adrenal gland and therapeutic response of mitotane treatment. This is a retrospective study enrolling patients from two German centers with operated ACC and minimal information on PET-CT scanning. Eighty-two ACC patients after adrenalectomy were included (66 treated with mitotane and 16 without medical therapy). FDG uptake of the contralateral adrenal gland, liver and mediastinum was analyzed from a total of 291 PET/CT scans (median 4 scans per patient) and correlated with clinical annotations including overall and recurrence free survival. The majority of patients (81 %) displayed a temporary increase in adrenal FDG uptake within the first 18 months following surgery, which was not associated with a morphological correlate for potential malignancy. This increase was mainly present in patients treated with mitotane (51/61, 84 %) but less frequent in the control group (4/7, 57 %). No direct correlation with mitotane plasma levels were evident. Patients following R0 resection with high adrenal uptake showed a tendency towards better clinical outcome without reaching a significance value (HR 1.41; CI 0.42–4.75; p = 0.059). FDG update of the contralateral adrenal gland may not be misinterpreted as sign of malignancy but might be rather associated with a trend towards better clinical outcome.

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Introduction

Adrenocortical cancer (ACC) is a rare tumor entity with an overall poor prognosis [1]. The heterogeneous course requires personalized therapeutic approaches that include surgery of the primary tumor, local ablation of single metastases, adrenolytic medical approaches and/or systemic chemotherapies [2]. Both in adjuvant setting and in advanced ACC, mitotane is treatment of first choice - alone or in combination with cytotoxic drugs [3, 4]. While some histological markers [5] and information from molecular profiling [6, 7] can provide prognostic information, therapeutic decisions often rely on imaging at initial diagnosis or during follow-up.

Positron emission tomography (PET) in combination with computed tomography (CT) is gaining increasing attraction as imaging modalities for the clinical care of ACC patients. As in other tumor entities, fluorine-18 fluorodeoxyglucose (F-18 FDG) PET/(CT) is used for both primary diagnosis as well as for follow-up after surgery or during systemic treatment [8, 9]. By quantifying the metabolic activity, PET/CT offers valuable advantages at diagnosis and for monitoring of therapy compared to the sole assessment of tumor morphology by means of CT or MRI. For differential diagnosis, the additional information of PET imaging can help to distinguish between benign and malignant adrenal tumors [10, 11]. In general, FDG uptake is regarded as having some prognostic value as it reflects the proliferative properties of the tumor tissue. For ACC, intensity of FDG uptake of the primary tumor appears to be related to survival of affected patients [12, 13]. In the context of systemic chemotherapy, therapeutic responses might be determined earlier based on the metabolic activity of the tumor in comparison to changes in size or morphology [8, 9].

As ACC patients often receive FDG PET/CT as additional imaging tool in the course of their initial diagnosis and during follow-up [2], FDG accumulation of the remaining adrenal gland following unilateral adrenalectomy has been documented in earlier studies [14, 15] and might lead in less experienced centers to the misdiagnosis of another adrenal malignancy. However, the relationship of this observation to the clinical course of the individual patient has not been studied in detail. In fact, there are several reasons that could potentially explain this phenomenon: First, surgical resection of an endocrine active adrenal tumor will initiate reactivation of the hypothalamus-pituitary-adrenal axis and growth of the contralateral adrenal gland. While this compensatory adrenal growth has mainly been studied in animal models [16–18], it is likely also to occur in humans. Secondly, therapy with the adrenolytic substance mitotane is known to affect the remaining adrenal gland to a similar extent as adrenocortical cancer cells [19] and results in adrenal insufficiency [20]. Thereby, mitotane induced cell death followed by local inflammation could lead to local FDG accumulation. Thirdly, the contra-lateral adrenal gland can be the target of hematological metastatic spread of the initial tumor or the origin of a secondary tumor in cases of hereditary syndromes [21]. In these cases, FDG uptake would indicate the presence of malignant disease, which would likely be of clinical relevance. Finally, also healthy organs enrich FDG to a variable extent. As for the adrenal gland maximum Standard Uptake Values (SUVmax) vary considerably between 0.95 and 2.46 [22] and between 0.82 and 3.65, respectively [23].

In the current study, we have made use of a cohort of ACC patients being followed with FDG PET imaging in the course of their disease to correlate these data with clinical courses, treatment modalities and outcome parameters.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Patients and Methods

Patients

Patients were enrolled at the University Hospitals of Munich and Würzburg (Germany) as part of the registry of the European Network for the Study of Adrenal Tumors (ENSAT, www.ensat.org) following written informed consent. The study protocol was approved by the ethics committees of the University of Munich and of the University of Würzburg, respectively. For the retrospective data analysis, inclusion criteria were histologically confirmed diagnosis of ACC and the availability of at least one PET/CT following unilateral adrenalectomy. The mitotane group consisted of patients who had received mitotane therapy for a period of at least 3 months following surgery while patients were included in the control group who had never received mitotane. Basic clinical annotations including tumor recurrence and survival as well as mitotane plasma levels (for the mitotane group) were documented and correlated with the findings from PET/CTs before and within the first 18 months after surgery and/or the start of mitotane treatment.

PET/CT protocols

At the Munich center, PET/CTs were carried out with a "General Electric Discovery 690" PET/CT device (GE Healthcare, Pollards Wood, United Kingdom) and were performed between 55 and 75 min after administration of a body weight adapted activity of 18-FDG. In addition, intravenous contrast agent, 20 mg furosemide and 20 mg butylscopulamine were administered. The patients were fasting for at least 4 h at the time of the examination and had blood glucose levels between 4 and 7 mmol/l. Attenuation correction was performed using diagnostic CT. Images were examined using the Hermes Hybrid Viewer (Hermes Medical Solutions, Stockholm, Sweden).

At the Würzburg center, examinations were carried out with a Siemens Biograph mCT 64 PET/CT device (Siemens Medical Solutions, Germany) and performed 60 min after administration of 307

Mbq 18-FDG on average. Blood glucose levels were <9 mmol/l at the time of examination. The anatomical correlation and attenuation correction was performed using a low-dose CT or a diagnostic full-dose CT with or without contrast agent. The reconstruction and evaluation of the images was carried out with the help of "Siemens E-soft" software.

FDG uptake was quantified using the Standard Uptake Value (SUV). In the remaining adrenal gland, tracer uptake was determined using SUVmax. One or more spherical volumes of interest (VOI) in variable sizes >1 cm were used as measuring ranges. The size was based on the extent of a visible lesion or the adrenal gland, respectively. In cases, where the adrenal gland could not be distinguished from the background by PET imaging alone, the SUVmax was determined in the area corresponding to the morphological position of the adrenal gland. Special care was taken not to include any physiological accumulations from adjacent organs, for example from the liver or kidney, into the measuring area.

In accordance with EANM guidelines [24], for each examination the SUVmean of the liver and the mediastinum were determined to include physiological uptake. In the liver, a sphere with a diameter of 3 cm was used as VOI to determine the SUVmean. The measuring site was always the right lobe of the liver, in an area with as few vessels as possible without metastases or other tumors. In the mediastinum, a sphere with a diameter of 2 cm was used as VOI to quantize the SUVmean. The measuring site was always the right atrium of the heart, in a central area without the involvement of cardiac tissue. To allow for inter-individual comparability, from the SUVmax of the adrenal gland and the SUVmean of the liver and the mediastinal blood pool the respective ratios (SUVmax/SUVmean) were calculated.

Statistical evaluation

Descriptive data are provided using absolute and relative frequency, mean, median and standard deviations, as appropriate. The chi-squared test was used to compare distribution of nominal scaled data. The Mann–Whitney U-test was used to compare non-parametric data between patients or patient groups, while the Wilcoxon sign-rank test was utilized to compare non-parametric data in connected samples. Survival curves were determined by Kaplan–Meier analysis and compared by log-rank test. Cox regression analysis was used to estimate the hazard ratios. Statistical significance was set as a p-value <0.05 using the SPSS Software Version 24 (SPSS, Inc., Chicago, IL, USA).

Results

Patient cohorts

From a total of 82 included patients, 66 were enrolled into the mitotane group and 16 in the control group, respectively. Overall, patients were aged between 27 and 87 years. All tumor stages (ENSAT I-IV [25]) were present with stage I in 8 patients (9.8%), stage II in 45 patients (54.9%), stage III in 15 patients (18.3%), and stage IV in 11 patients (13.4%) while remaining three patients (3.7%) had an unknown stage at diagnosis. A total of 291 PET/CT data sets were examined with a median of 4 examinations per patients during the observation period of a median of 10 months. In 14 patients

(5 in the mitotane group and 9 in the control group), only 1 PET/CT data set was available, so that these were excluded from further analysis of uptake progressions. A summary of patient characteristics is provided in ▶ Table 1.

Median duration of follow-up was 10.3 months, which was similar in the mitotane-group (10.5 months) and in the control-group (9.2 months, p = 0.512). During this interval, 27 (48.2%) of 55 R0 resected patients experienced disease recurrence with 23 (28.0%) in the mitotane-group and 4 (30.8%) in the control-group (p = 0.340). Moreover, during this time, 8 (9.8%) of the overall cohort of 82 patients died with 6 (9.1%) in the mitotane-group and 2 (12.5%) in the control group (p = 0.247).

FDG uptake in the liver and mediastinum

Considering the uptake of the liver, there were significant differences in the mean values between the two groups, which concerned the time points of 3 months [mitotane group vs. control, 2.92 (2.18–3.88) vs. 2.17 (1.67–2.48), p < 0.01], 6 months [2.97 (1.42–4.30) vs. 2.28 (1.71–2.90), p < 0.001], and 9 months [3.17 (2.00–4.24) vs. 2.60 (2.01–3.06), p < 0.01] (▶ Fig. 1a) after surgery, respectively. While it is plausible, that mitotane treatment might have contributed to the observed increase in hepatic SUV, no correlation with mitotane plasma levels were evident (3 months: r = 0.281, p = 0.148; 6 months: r = 0.071, p = 0.661; 9 months r = −0.142, p = 0.409) (▶ Supplemental Fig. 1S) In contrast, for the mediastinum, no significant difference in SUV was detectable between the two groups at 3 months [mitotane group vs. control, 1.86 (1.37–2.91), vs. 1.57 (1.02–1.93), p = 0.105], 6 months [1.72 (0.42–2.88) vs. 1.49 (1.23–2.11), p = 0.244], and 9 months [1.82 (1.06–2.59) vs. 1.78 (1.43–2.39), p = 0.744] (▶ Fig. 1b), respectively. In consideration of the less variable mediastinal FDG uptake, this value was further utilized for normalization of the SUVmax of the adrenal gland by calculation of the ratio SUV adrenal gland/SUV mediastinum.

Adrenal FDG uptake

In a subgroup of patients, FDG-PET was performed also prior surgery. In these patients, uptake in the adrenal gland contralateral to the ACC before surgery was not different between the two groups [mitotane group (n = 9), 1.36 (0.56–1.68) vs. control group (n = 2), 1.72 (1.02–2.42), p = 0.727]. During the course of their disease, overall 55/68 patients (81%) displayed a temporary increase in adrenal FDG uptake, which was defined as an increase of 0.5 above the lowest of all individual values. More specifically, this observation tended to be more prevalent in the mitotane group with 51/61 patients (84%) in comparison to the control group (4/7, 57%), although this difference was not found to be statistically significant (p = 0.288). In 58% of the patients, adrenal FDG uptake returned to baseline values within 18 months after surgery, while in the remaining patients, adrenal FDG uptake decreased without reaching baseline values (24%) or did not decrease within the observation period of 18 months (18%).

As summarized in ▶ Fig. 1c, the mean values of adrenal uptake between the patients receiving mitotane were not significant different from those of the control group at any time point. In most instances [42/61 patients (69%)], the peak in adrenal uptakes was found in the time interval between 3 and 6 months after the start

► Table 1 Characteristics of patient cohorts.

Characteristics	Mitotane group	Control group	p-Value
Age (years)			
Median (range)	56 (27–81)	53 (30–87)	0.847
Sex - no. (%)			
male	28 (42.4)	8 (50)	
female	38 (57.6)	8 (50)	0.584
Tumor stage - no. (%)			
I	6 (9.1)	2 (12.5)	
II	35 (53.0)	10 (62.5)	
III	13 (19.7)	2 (12.5)	
IV	10 (15.2)	1 (6.3)	
uncategorized	2 (3)	1 (6.3)	0.763
Resection status (%)			
R0	42 (63.6)	13 (81.3)	
non-R0	24 (36.4)	3 (18.8)	0.179
Polychemotherapy - no. (%)			
nono	31 (47.0)	15 (93.8)	
yes	35 (53.0)	1 (6.2)	0.001
Blood mitotane level			
No. of analyzed samples	208	0	
Median (range) - mg/l	13.1 (0–42.2)	n.d.	
No. of PET/CTs			
Total	254	37	
Median per patient (range)	4 (1–7)	1.5 (1–6)	
Progression free survival non-R0[†]- d			
Median (range)	188 (30–2 937)	– [*] (72–1 091)	
Recurrence free survival R0[†]- d			
Median (range)	396 (20–2 898)	– [*] (81–2 370)	
Overall survival non-R0[†]- d			
Median (range)	– [*] (238–3 529)	105 (102–1 091)	
Overall survival R0[†]- d			
Median (range)	2 378 (201–3 805)	– [*] (234–2 370)	

[*] <50 % events in observation period; [†] n (R0 Patients >1 PET/CT): mitotane group 42, control group 13; n (non-R0 patients >1 PET/CT): mitotane group 24, control group 3; n.d., not determined.

of mitotane therapy. In relation to surgery, this occurred in 28/47 patients (60 %) of the mitotane group and 3/7 (43 %) patients of the control group (p = 0.404). The highest maximum value occurred in both groups 6 months after surgery.

Temporary increase and peak adrenal uptakes were determined in all patients who had received more than one PET/CT (mitotane group 61/66 (92 %); control group 7/16 (44 %)). In the mitotane group, 29 of 57 patients (51 %) had at least one higher value in the first 18 months of therapy than the highest measured value before surgery. In the control group, this was true in 4 out of 16 patients (27 %, p = 0.094). In the mitotane group, however, significantly higher values were observed 3 months [2.14 (0.65–6.04), p = 0.002] and 6 months [2.39 (1.02–7.23), p = 0.018] after the start of mitotane treatment in comparison to baseline [1.26 (0.56–1.68)]. These differences were not significant in the control group {3 months [1.61 (1.24–2.01), p = 0.317] and 6 months [2.03 (1.40–3.21), p = n.d.] vs. baseline [1.72 (1.02–2.42)]}. When comparing the mean values of mitotane plasma levels and adrenal uptake, there was no indication of any dependence of the increased uptake on the level of plasma mitotane levels (r = − 0.028, p = 0.683).

None of the 291 PET/CTs examined provided indication of tumor development in the remaining adrenal gland. Specifically, in no case suspicious increases in adrenal FDG uptake were associated with morphological correlates in the CT scan of the current or follow-up examinations.

Correlation of adrenal FDG uptake with survival in patients treated with mitotane

To assess, whether adrenal FDG uptake in patients treated with mitotane might have a prognostic impact, different measures were investigated: Peak as well as mean values of normalized adrenal SUVmax were used to group patients in those with high uptake (above the median uptake) and low uptake (below or equal the median uptake). Similarly, the area under the curve of normalized adrenal SUVmax was calculated and patients were grouped in those with high and low uptake. For those analyses, patients were further grouped in those following R0 and non-R0 resection.

Overall, in comparison patients with R0 vs. non-R0 resection status, there were no differences in postoperative FDG uptake at any time point. Based on peak normalized adrenal SUVmax values, patients following R0 resection (n = 37) tended to have longer recurrence free survival (HR 1.41; CI 0.42–4.75; p = 0.059) when FDG uptake was above the median, while overall survival was not different (HR 1.62; CI 0.15–17.15; p = 0.770). Non-R0 resected patients (n = 23) had similar progression free (HR 2.27; CI 0.26–19.67; p = 0.232) and overall survival (HR 0.00; CI 0.00–3.698E + 149; p = 0.124) independent of adrenal FDG uptake (► **Fig. 2**). Similar tendencies were found for overall survival, where higher adrenal FDG uptake tended to be associated with better outcome (data not shown). In all cases, however, no significant differences were evident.

Discussion

FDG-PET imaging has become a corner stone in the follow-up of ACC patients and often provides the basis of treatment decisions. Herein, we provide a comprehensive description of FDG uptake in
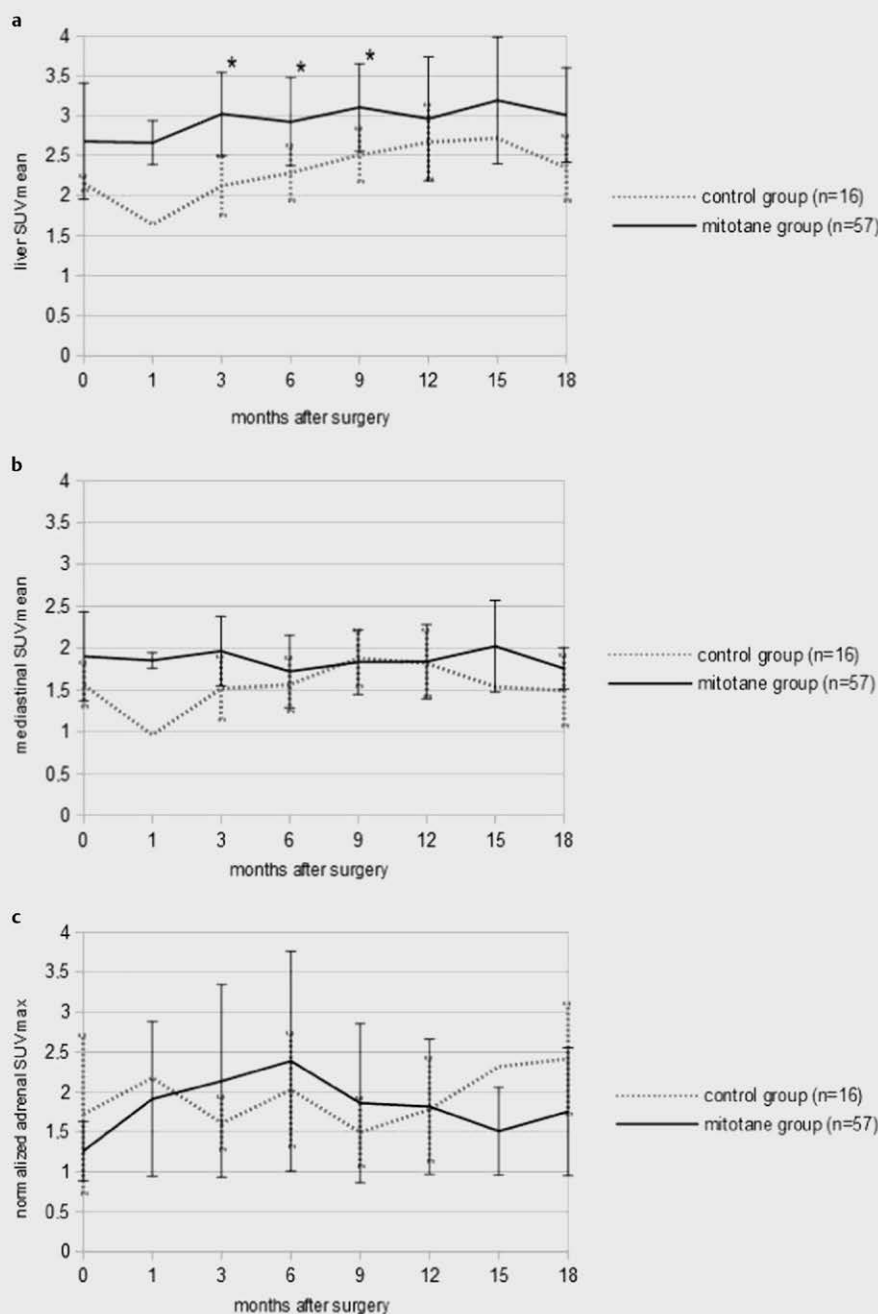
▶**Fig. 1** Time course of FDG uptake in the liver **a**, mediastinum **b**, and normalized adrenal SUVmax (SUV adrenal gland/SUV mediastinum) **c** in patients during mitotane treatment and control patients.

ACC patients following initial surgery in relation to mitotane therapy and clinical outcome. The current investigation provides more detailed results on the FDG uptake of the remaining adrenal in ACC patients than any previous studies. However, the detection of FDG uptake in the remaining adrenal gland in a patient following adrenal surgery seems to be a common finding that should not alarm affected patients and their physicians and seem not to require changes in the follow-up algorithm.

According to our current findings, increased uptake values of the adrenal are neither an obligatory finding following surgery nor during mitotane therapy. However, a large proportion of patients are characterized by a temporarily increase in adrenal uptake. Patients from both the mitotane and control group were affected to varying degrees by this phenomenon. A common factor for both groups that could impact adrenal FDG uptake is unilateral adrenalectomy. Reactive changes in contralateral adrenal gland were previously described in animal models and concerned only the mor-
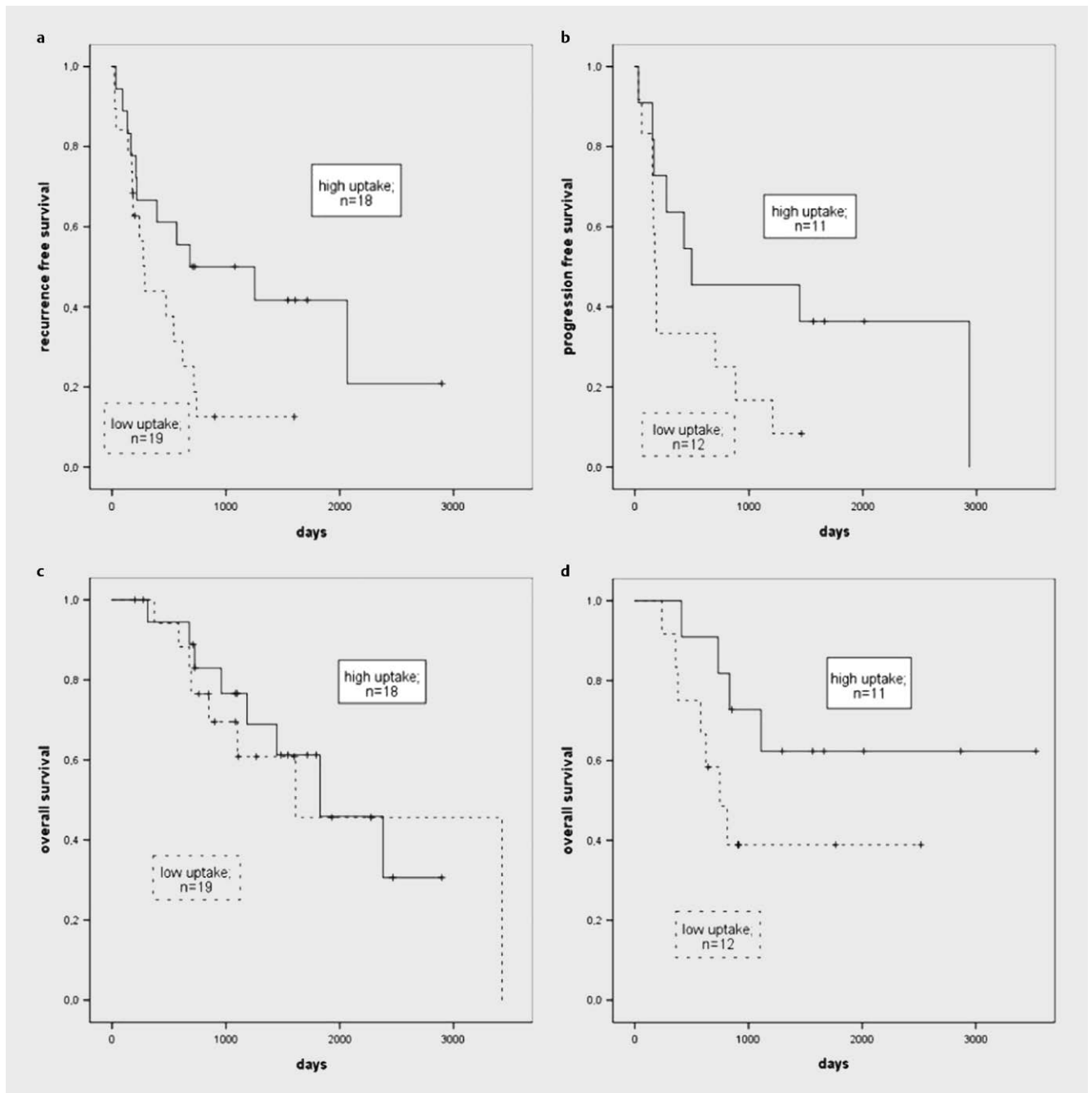
▶**Fig. 2** Survival of mitotane treated patients in relation to peak normalized adrenal SUVmax related survival. Recurrence free survival of R0 resected patients (HR 1.41; CI 0.42–4.75; p = 0.059. **a** Progression free survival of non-R0 resected patients (HR 2.27; CI 0.26–19.67; p = 0.097. **b** Overall survival in R0 resected patients (HR 1.62; CI 0.15–17.15; p = 0.770. **c** Overall survival of non R0 resected patients (HR 0.00; CI 0.00–3.698E + 149; p = 0.124. **d** Continuous line, high uptake > median uptake vs. dotted line, low uptake ≤ median uptake.

phology, but not the signaling behavior in PET [17]. Compensatory adrenal growth response following unilateral adrenalectomy is tightly controlled by both humoral and neuronal factors that are dependent upon a neural reflex arc with afferent nerve connections from one adrenal gland to the hypothalamus and an efferent limb back to the other adrenal [26]. In addition, there is indication in the literature that post-secretory cleavage of the N-terminus of POMC is also required for the proper initiation of compensatory growth

[18]. Autonomous secretion of glucocorticoids by an adrenal tumor results in suppression of the HPA axis and atrophy of the contralateral adrenal cortex. Following resection of this tumor, ACTH secretion resumes inducing a growth signal on the remaining adrenal gland. However, depending on the duration and extent of glucocorticoid excess, normalization of secondary/tertiary adrenal insufficiency can vary widely [27]. It is therefore possible, that those variables have precluded to find a consistent pattern in FDG uptake

in our control group and it might be worthwhile to implement a larger number of patients that would allow to investigate subgroups with early and late normalization of adrenal insufficiency.

Within the current dataset, we fail to demonstrate significant differences regarding the clinical outcome based on the FDG uptake in the remaining adrenal gland in patients during mitotane therapy. However, it is interesting to note, that by trend the patient group with the higher median uptake has a better recurrence free and overall survival. As maximum FDG uptake in comparison to baseline was more prominent in the mitotane treated group of patients, the adrenal destructing properties of mitotane are likely to contribute to this phenomenon. Our initial hypothesis, that the remaining adrenal could be used as a "sentinel" tissue to quantify mitotane-induced action on adrenocortical cancer cells cannot clearly be supported on the basis of the current data set. Reasons for this outcome – in addition to a false hypothesis – can be a patient group that is too small or too diverse to allow for the detection of significant differences. A further weakness of the current dataset concerns the retrospective study design and inclusion of patients from two different study sites.

Our study further suggests that the FDG uptake of the liver in the case of mitotane therapy is higher than in patients without mitotane therapy. It could be speculated, that this difference reflects hepatic metabolic processes induced by mitotane. Indeed, increase in cholestasis parameters is commonly observed in patients treated by mitotane. We could not ascertain a significant correlation between mitotane plasma levels and the extent of FDG uptake in the liver. However, considering the long half-live and complex pharmacodynamics properties of mitotane, effects on the hepatocytes that could affect FDG uptake might not be reflected by plasma levels at the same time point. Independent of its cause, the liver SUVmean does not appear as the most suitable parameter for calculating an adrenal uptake ratio. The extent of this influence on the interpretation of SUV values cannot be determined from this study. However, since a certain effect seems to exist, it should be considered in the interpretation of adrenal uptake in patients under mitotane therapy.

In summary, FDG uptake in the contralateral adrenal gland in patients who had undergone surgery for ACC is a common finding that is more distinct in the context of mitotane treatment. While there is only a tendency to an association with better clinical outcome, this phenomenon is unlikely to reflect the presence of malignant disease.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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