HHS Public Access

Author manuscript

Eur J Endocrinol. Author manuscript; available in PMC 2021 December 01.

Published in final edited form as:

Eur J Endocrinol. 2020 December ; 183(6): 539–550. doi:10.1530/EJE-20-0532.

Functional imaging with ^{11}C-metomidate PET for subtype diagnosis in primary aldosteronism

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Abstract

Objective: Endocrine Society guidelines recommend adrenal venous sampling (AVS) in primary aldosteronism (PA) if adrenalectomy is considered. We tested whether functional imaging of adrenal cortex with ^{11}C-metomidate (^{11}C-MTO) could offer a noninvasive alternative to AVS in the subtype classification of PA.

Design: We prospectively recruited 58 patients with confirmed PA who were eligible for adrenal surgery.

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Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EJE-20-0532.

Methods: Subjects underwent AVS and ^{11}C-MTO-PET without dexamethasone pretreatment in random order. The lateralization of ^{11}C-MTO-PET and adrenal CT were compared with AVS in all subjects and in a prespecified adrenalectomy subgroup in which the diagnosis was confirmed with immunohistochemical staining for CYP11B2.

Results: In the whole study population, the concordance of AVS and ^{11}C-MTO-PET was 51% and did not differ from that of AVS and adrenal CT (53%). The concordance of AVS and ^{11}C-MTO-PET was 55% in unilateral and 44% in bilateral PA. In receiver operating characteristics analysis, the maximum standardized uptake value ratio of 1.16 in ^{11}C-MTO-PET had an AUC of 0.507 (P = n.s.) to predict allocation to adrenalectomy or medical therapy with sensitivity of 55% and specificity of 44%. In the prespecified adrenalectomy subgroup, AVS and ^{11}C-MTO-PET were concordant in 10 of 19 subjects with CYP11B2-positive adenoma and in 6 of 10 with CYP11B2-positivity without an adenoma.

Conclusions: The concordance of ^{11}C-MTO-PET with AVS was clinically suboptimal, and did not outperform adrenal CT. In a subgroup with CYP11B2-positive adenoma, ^{11}C-MTO-PET identified 53% of cases. ^{11}C-MTO-PET appeared to be inferior to AVS for subtype classification of PA.

Introduction

Untreated primary aldosteronism (PA) increases the risk of mortality and cardiovascular, renal, and metabolic events beyond the risk caused by essential hypertension of comparable severity (1, 2, 3). Targeted treatments with adrenalectomy or medical therapy can prevent these adverse events and possibly provide a reversal of end-organ damage. However, in large series, antihypertensive medical therapy with a mineralocorticoid receptor antagonist (MRA) appeared to be inferior to adrenal surgery in reducing the risk of mortality, cardiovascular events, atrial fibrillation and decline of renal function, and quality of life (4, 5, 6, 7).

Determination of the optimal treatment for PA critically relies on subtype classification (1, 8). Most patients with PA are middle-aged or older and anatomical imaging with adrenal CT cannot distinguish unilateral aldosterone-producing adenomas (APAs) from nonfunctioning adrenal nodules, lateralization of aldosterone secretion from hyperplastic adrenal glands, or aldosterone-producing cell clusters (APCCs) that become more prevalent with age (9, 10). Therefore, the guidelines (8) recommend PA subtyping with bilateral adrenal venous sampling (AVS) in patients who are considered for adrenal surgery.

In experienced centers the diagnostic performance of AVS is excellent (8, 11, 12). The disadvantages include technical difficulties in non-specialized centers, potential vascular complications, and relatively high costs from the procedure and laboratory measurements (1). Currently, the standardized procedure and interpretation of AVS results are under discussion (1, 13).

^{11}C-metomidate PET (^{11}C-MTO-PET) CT is a potentially promising method since ^{11}C-metomidate traces 11β-hydroxylase (CYP11B2) activity in the adrenal cortex (14, 15). Recent case series of PA patients suggest that ^{11}C-MTO-PET may provide clinical benefit in PA subtype classification (16, 17).

In the present prospective study, our objective was to evaluate the diagnostic power of ^{11}C-MTO-PET imaging compared with AVS in establishing or excluding lateralization of aldosterone production in patients with confirmed PA. A secondary prespecified objective included analysis of the performance of ^{11}C-MTO-PET compared with AVS to detect lateralization in the subgroup of adrenalectomy patients in whom biochemical and medical outcome, as well as immunohistochemical analysis of aldosterone synthase (CYP11B2) of the adrenal samples, were available.

Subjects and Methods

Study design and participants

We recruited 58 eligible consecutive patients with PA who were referred to endocrinology units in Helsinki, Tampere, and Turku University Hospitals between February 2012 and December 2015. Patients fulfilling the criteria for confirmed PA according to the 2008 Endocrine Society guidelines (18) who were willing and eligible for possible adrenalectomy were included (Fig. 1). Inclusion criteria were age between 20 and 70 years, good general health enabling possible adrenalectomy, and a BMI of less than 35 kg/m^2. The exclusion criteria are presented in the Supplementary material (see section on supplementary materials given at the end of this article). A prespecified post hoc, blinded adrenal CT analysis was performed by a single experienced specialist in abdominal radiology (E.L.).

All subjects underwent AVS and ^{11}C-MTO-PET imaging in random order. Subjects with lateralization of aldosterone secretion in AVS were allocated to adrenal surgery (adrenalectomy group). In case of unsuccessful AVS, concordant findings suggesting single adrenal adenoma on ^{11}C-MTO-PET and adrenal CT justified adrenal surgery. The postoperative outcome was evaluated about 3 months after adrenalectomy. For those treated with medical therapy (medical therapy group), medicine and blood pressure data were collected after lateralization studies for comparison. We applied retrospectively the PASO consensus criteria for a surgical cure (19). The detailed blood pressure, daily defined dose (DDD) of antihypertensive medication, and biochemical cut points are described in the PASO study (19).

All subjects provided written informed consent. The study protocol was approved by the ethics committee of Turku University Hospital and the study was registered in the ClinicalTrials.gov database (NCT01567111). The study was undertaken in accordance with the Declaration of Helsinki. Patients received written information describing AVS and ^{11}C-MTO-PET procedures, including benefits and predictable complications.

Methods

^{11}C-metomidate positron emission tomography

All PET scans were performed in Turku PET Centre and the detailed description of the imaging is shown in the Supplementary material.

Images were analyzed with Advantage Workstation (version 4.7, GE Healthcare). PET lateralization was defined as metabolic activity localized to an anatomic adenoma compared

to anatomic adenomas without activity and/or >15% difference in SUV_{max} values between the adrenal glands. In some patients, clear anatomic adenomas could not be visualized, but there was a difference in ^{11}C-MTO uptake between the adrenal glands, or similar adrenal gland activity with clear anatomic adenoma also showing metabolic activity was found.

Follow-up ^{11}C-metomidate PET CT using dexamethasone suppression

According to previous studies, cortisol production (CYP11B1 activity) by cortical tumor may cause positive ^{11}C-MTO uptake in PET CT (15, 16). To test the reproducibility of the PET scans, we investigated the ^{11}C-MTO-PET CT during dexamethasone (DXM) pretreatment (0.5 mg every 6 h for 3 days) in a subgroup of seven patients.

Adrenal venous sampling

All AVS studies were conducted at Tampere University Hospital. Cosyntropin infusion and detailed methodology are described in the Supplementary material.

The selectivity of AVS on both sides was confirmed by an adrenal vein to peripheral cortisol ratio of greater than 5:1. An aldosterone to cortisol ratio greater than 4:1 on the dominant side compared with the non-dominant side confirmed the diagnosis of unilateral hyperaldosteronism. Ratios between 3:1 and 4:1 presented a zone of overlap, where lateralization was interpreted as positive according to a contralateral suppression index of <1.0.

Pathological and immunohistochemical analysis

Diagnostic H&E stained adrenal slides were reviewed centrally in the Helsinki University Hospital by a single pathologist with special expertise in endocrine pathology (HL). One or two representative blocks per case were selected with the following criteria: (a) adenoma coupled with normal adrenal cortex and (b) hyperplasia presenting with a dominant nodule. Immunohistochemical labeling was performed with previously described primary antibodies CYP11B1 (11β-hydroxylase, dilution 1:5) and CYP11B2 (aldosterone synthase, dilution 1:3000) (20). Each sample was categorized as APA or non-APA based on immunohistochemistry, as described in Fig. 2 (21, 22, 23). For detailed immunohistochemical methods, please see the Supplementary material.

Statistical analysis

Power calculation for the study and detailed statistical methods are presented in the Supplementary material. We analyzed all patients who completed the follow-up (Fig. 1). The test performance characteristics of AVS, CT, and ^{11}C-MTO-PET to lateralize adrenal aldosterone secretion were analyzed in the whole study population and in a prespecified subgroup of patients who underwent adrenalectomy. A receiver operating characteristics (ROC) curve was constructed from the pairs of sensitivity and specificity measured at each SUV_{max} ratio between dominant and non-dominant adrenal SUV_{max}. The ROC analysis was conducted, including all subjects and using allocation to the operation or medical therapy as the standard.

Results

Altogether, 55 subjects were included in the study (Fig. 1). A total of 34 displayed significant lateralization of aldosterone production and underwent unilateral adrenalectomy. The remaining 20 subjects without lateralization received medical therapy. Based on AVS, surgery was recommended to one subject who opted for medical therapy due to discordant lateralization studies and was included in the medical therapy group. Table 1 displays the baseline characteristics for all subjects in the study and clinical, biochemical data at follow-up during medical therapy or after adrenalectomy. Fourteen subjects had adequately controlled diabetes and four had the previous history of stable cardiovascular disease.

Clinical outcome in the medical therapy group

A total of 21 patients with PA were treated with medical therapy. Use of MRA increased from 29 to 95% in the medical therapy group at follow-up. The number of antihypertensive medications and their DDD remained constant at follow-up. Compared with the adrenalectomy group, the number of medications and the DDD were significantly higher in the medical therapy group ($P < 0.001$ for both). Systolic blood pressure decreased, and plasma potassium concentration increased significantly ($P = 0.013$ and $P = 0.028$) but diastolic blood pressure did not change ($P = 0.062$) from the baseline (Table 1). With medical therapy diastolic blood pressure decreased less than after adrenalectomy ($P = 0.004$) but no difference was found in systolic blood pressure decrease between the groups (Table 1).

Clinical, biochemical, and immunohistochemical outcome of adrenalectomized patients

The characteristics before and after operation in the 34 adrenalectomized patients are shown in Table 1. Blood pressure, the number of antihypertensive medications and DDD decreased, and plasma potassium concentration increased significantly after adrenalectomy. Of the 34 operated subjects, 10 (29%) were able to stop all antihypertensive medications, 12 (35%) used one drug, and none used MRAs.

Individual clinical and biochemical complete, partial, and absent cure responses (19) are shown in Table 2. Biochemical cure could be determined in 32 of the 34 operated subjects. None in the adrenalectomy group showed complete absence of clinical or biochemical cure and those with absent response according to the consensus criteria showed clinically meaningful improvement in either plasma aldosterone concentration, blood pressure, or DDD that did not reach the limit of the consensus guideline (19).

The immunohistochemical diagnosis was APA in 68% and non-APA in 32% of the cases (Table 2). Based on the immunohistochemical reevaluation of the adrenalectomy samples, the histological H&E classification between adenoma and hyperplasia changed in seven out of 34 (20.6%) samples (Supplementary data). Twenty-five out of 34 samples were found with a median of three APCCs. These subjects had a similar cure rate to those with a non-APA or adenoma.

Adrenal ^{11}C-MTO-PET concordance with adrenal venous sampling

The primary objective of the study was to compare the lateralization between ^{11}C-MTO-PET and AVS (Fig. 3). In the ROC analysis, the SUV_{max} ratio of dominant vs non-dominant adrenal in ^{11}C-MTO-PET, the area under the curve (AUC) could not significantly predict subject allocation to the adrenalectomy vs medical therapy groups. The cut point of 1.16 for the SUV_{max} ratio of dominant vs non-dominant adrenal yielded a sensitivity of 55% and specificity of 44%. The AUC for the blinded adrenal CT report for lateralization or no lateralization did not reach statistical significance in the ROC analysis.

In the whole study population, AVS and ^{11}C-MTO-PET demonstrated concordance (lateralization to the same side or no lateralization) in 24/47 (51%) subjects (Fig. 4). Of the discordant studies between AVS and ^{11}C-MTO-PET, we found a false negative result in 11/47 (23%), contralateral side lateralization in 2/47 (4%), and false positive lateralization of bilateral disease in 10/47 (21%) of them. In the adrenalectomy and medical therapy subgroups, concordance for AVS and ^{11}C-MTO-PET was 55 and 44%, respectively.

^{11}C-MTO-PET concordance with adrenal venous sampling in the adrenalectomy group

As a secondary objective, we analyzed the concordance between AVS and ^{11}C-MTO-PET in the adrenalectomy group. Among patients with CYP11B2-positive APA, the concordance between the AVS and ^{11}C-MTO-PET studies was 53% (Table 2). Those with non-APA showed 60% concordance between AVS and ^{11}C-MTO-PET. In two cases of APA, ^{11}C-MTO-PET lateralized to the contralateral side and in 11 studies (7 APAs and 4 non-APAs) showed no lateralization. In these subjects with discordant lateralization, the decision for adrenalectomy was based on AVS lateralization, and all demonstrated either complete or partial clinical and biochemical improvement after adrenalectomy.

Adrenal CT concordance with ^{11}C-MTO-PET

A total of 53 subjects had both ^{11}C-MTO-PET and adrenal CT available. The overall concordance of this secondary outcome between the two methods was 55%. The statistical difference between concordance of ^{11}C-MTO-PET with AVS or CT was not significant.

Concordance of all lateralization studies

Of 47 subjects with AVS, ^{11}C-MTO-PET, and CT data available, only 32% displayed concordance for right, left, or no lateralization in all three investigations (Fig. 4). The success rates for AVS and ^{11}C-MTO-PET were 88.0 and 94.8%, respectively. Figure 5 shows as an example two individual cases, one with discordant and one with concordant AVS and ^{11}C-MTO-PET lateralization findings together with the immunohistochemical CYP11B2 staining after adrenalectomy.

Reanalysis of ^{11}C-MTO-PET with dexamethasone pretreatment

We performed a second ^{11}C-MTO-PET study for five subjects with discordant and two subjects with concordant AVS and ^{11}C-MTO-PET findings after DXM pretreatment of 0.5 mg every 6 h for 3 days before the scan. All seven subjects had a non-lateralizing lateralization index (LI) of 1.58 ± 0.33 (range, 1.16–2.14) in AVS and were in the medical

treatment group. The ^{11}C-MTO-PET outcome changed only in one subject after DXM in whom SUV_{max}-ratio decreased from 1.18 to a non-lateralizing value of 1.09. The mean SUV_{max} values on the right (15.1 vs 9.5 g/mL) and left (23.9 vs 19.3 g/mL) sides were statistically lower ($P < 0.05$) and the SUV-ratio higher (2.2 vs 5.4, $P < 0.05$) after DXM pretreatment. When we compared the CT findings in these seven subjects, three had discordant CT in both investigations, and two had consistent CT with AVS and two with ^{11}C-MTO-PET.

Discussion

The present prospective clinical trial evaluates the lateralization accuracy of ^{11}C-MTO-PET in patients with PA based on AVS lateralization and outcome after adrenalectomy. Our main finding is that the ^{11}C-MTO-PET is discrepant from AVS in half of the subjects with confirmed PA, and thus ^{11}C-MTO-PET does not provide a non-inferior method to ascertain the subtype diagnosis in PA. Although the definite diagnosis remains uncertain in subjects with medical therapy and on those without an APA histology, we identified a prespecified subgroup of subjects with CYP11B2-positive APA, in whom ^{11}C-MTO-PET identified only 53% of cases correctly. Therefore, the identification of subtypes in PA is not reliably facilitated with ^{11}C-MTO-PET.

Our main result contradicts two previous publications (16, 17). In the study by Burton et al. (16), 35 subjects with PA of whom 22 were operated underwent ^{11}C-MTO-PET. They found the SUV_{max} ratio cutoff of 1.25:1 to provide 87% specificity and 76% sensitivity in distinguishing unilateral and bilateral PA. O´Shea et al. (17) presented a case series of 15 patients of whom only 4 underwent adrenalectomy. Their study design did not allow comparison of the lateralization methods but concluded that ^{11}C-MTO-PET provided useful information to aid clinical decision-making. In our ROC analysis (Fig. 3), the SUV_{max} ratio of dominant vs non-dominant adrenal could not significantly predict subject allocation to adrenalectomy vs medical therapy group. In contrast, the observed optimal cut point of 1.16:1 yielded a sensitivity of 55% and a specificity of 44% – test characteristics not suitable to support clinical treatment decision making.

The major differences between the present and the two previous investigations (16, 17) are in the study design. We present here the largest prospective multicenter study with prespecified primary and secondary endpoints, whereas Burton et al. (16) reported a single-center case series consisting of within-patient comparisons of diagnostic techniques, and O´Shea et al. (17) presented a case series based on clinical evaluation or retrospective audit. The Supplementary Table highlights other differences between these thee investigations in study design, patient selection, conduction of AVS and ^{11}C-MTO-PET, and evaluation of outcome. Importantly, patient inclusion in our study was based on current guidelines (18), and spironolactone was discontinued for at least 6 weeks before all examinations. Burton et al. (16) presented the outcome of cases classified according to the prescan diagnosis, but the ten cases classified as bilateral PA did not undergo confirmatory testing, and spironolactone was not systematically discontinued before the examinations. We base the ROC evaluation on allocation to adrenalectomy or medical therapy because all subjects in the adrenalectomy group displayed significant CYP11B2 staining in immunohistochemical examination and at

least partial clinical or biochemical cure. Furthermore, adrenalectomy was based on lateralization in AVS when successfully performed. Four patients were operated according to our prespecified study plan despite unsuccessful AVS because they had concordant ^{11}C-MTO-PET and CT findings. Therefore, the risk of bias is probably lower than in many lateralization studies in the past.

Like AVS, ^{11}C-MTO-PET is not without methodological challenges (please see the Supplementary material). DXM pretreatment has been used in previous studies (16, 17) to suppress background activity as ^{11}C-metomidate traces also 11-hydroxylase (CYP11B1) activity in the adrenal cortex (14, 15, 24). We performed the studies without DXM pretreatment in subjects with confirmed PA because supraphysiological glucocorticoids may cause well-known side effects even with short-term use, and also simplify the protocol. After the report by Burton et al. (16), we repeated another ^{11}C-MTO-PET scan during DXM pretreatment in seven subjects who were allocated to the medical therapy group. Although this group without lateralization in AVS presents the hard to classify patient population in all lateralization studies, the results of the PET scans without and with DXM were concordant in six of seven subjects. Although the absolute SUV values decreased with DXM pretreatment, the SUV_{max} difference or the SUV_{max} ratio between the adrenal glands or the report by the nuclear medicine specialist did not change the interpretation without or with DXM. Burton et al. (16) did not discontinue MRAs systematically, which may affect metomidate uptake of the adrenal cortex. They tested the impact of DXM pretreatment vs no pretreatment on six subjects and in agreement with our study found DXM to somewhat decrease the background adrenal activity compared with the APA activity (16). We instead reached the opposite conclusion that DXM pretreatment does not improve the diagnostic ability of ^{11}C-MTO-PET in bilateral PA. However, we cannot exclude the possibility that the discrepant lateralization results in six subjects in the adrenalectomy group could have been more consistent with DXM pretreatment.

The poor concordance of AVS and adrenal CT is well characterized (25). The SPARTACUS study and other studies have questioned whether AVS is required to recognize the optimal subgroup of patients with PA who benefit from adrenalectomy (26, 27). Their study is in contrast to our findings and many other studies showing AVS to be superior in predicting lateralization and operation outcome (11, 28, 29, 30, 31). Furthermore, in a long-term follow-up study, AVS-guided adrenalectomy cured biochemically 96% of patients with PA (28). In our analysis, the concordance between ^{11}C-MTO-PET and adrenal CT was surprisingly low both in the lateralizing (55%) and non-lateralizing (44%) groups. When we compared all three localization methods together, the concordance of AVS, ^{11}C-MTO-PET, and adrenal CT was 32%,that is, less than one would expect by chance. This highlights the fact that all these methods detect various aspects of either adrenal anatomy or function. A sufficiently powered trial where all patients would undergo both AVS and ^{11}C-MTO-PET and would be randomly allocated to operation according to AVS or ^{11}C-MTO-PET, could settle the discrepant results found so far.

Discordant lateralization studies present a situation not desired by patients or clinicians. In our study in two subjects, AVS and ^{11}C-MTO-PET suggested lateralization to the opposite sides. After adrenalectomy, both subjects presented with CYP11B2-positive APA. Overall,

our results suggest that AVS, despite its obstacles, should remain as the gold standard to guide subtype allocation in PA.

Immunohistochemical analysis of the steroidogenic enzyme aldosterone synthase (CYP11B2) agrees with the view that unilateral non-APA is more common than previously stated. Subjects with hyperplasia may have a somewhat lower cure rate after the operation and a risk of later recurrence of hyperaldosteronism. A large multicenter study investigated adrenals from patients with absent and partial biochemical success and demonstrated a higher prevalence of hyperplasia (49% vs 21%; $P = 0.004$) compared with those adrenals from matched patients with PA with the complete biochemical success (32). APCCs were a common finding in our study but whether they autonomously secrete aldosterone remains debated (33, 34, 35). Based on the cure rate of subjects with non-APAs, we speculate that hyperplasia and APCCs may represent a significant source of unilateral aldosterone excess. In such patients, AVS provides reliable lateralization, but the use of a radiolabel tracer in PET imaging does not reliably sort outpatients with bilateral asymmetrical PA who benefit from adrenalectomy.

Unilateral adrenalectomy may be more effective in preventing adverse outcomes when compared with lifelong MRA therapy to block the aldosterone excess (4, 5, 36, 37, 38). Whether surgical outcome in lateralizing non-APA is superior to medical therapy, in the long run, remains unclear but in this subtype of PA at least biochemical and clinical improvements are also seen (39, 40, 41, 42, 43, 44). Accordingly, in the present study, we detected a significantly better outcome in both systolic and diastolic blood pressure, DDD, and the quantity of antihypertensive medication used in the adrenalectomy vs medical therapy group despite less severe PA at baseline in the latter, which suggest a more advantageous change in the cardiovascular risk profile after adrenalectomy.

Our study has limitations that deserve discussion. The cure rate was evaluated once, and long-term follow-up data are not available. Some subjects in the adrenalectomy group did not show improvement in both biochemical and clinical outcomes. However, the strict PASO cure criteria (45) have been questioned because up to 70% of the subjects whose treatment was defined as ‘no clear success’ by these criteria demonstrated a blood pressure decrease that was considered significant in terms of reducing vascular risk (46). When evaluating clinically significant benefit, we were able to observe at least a partial benefit of adrenalectomy in all subjects.

In summary, our study presents prospective data that ^{11}C-MTO-PET had lower sensitivity and specificity to detect lateralization when compared with AVS. The subgroups with CYP11B2-positive APA, CYP11B2-positive non-APA or no lateralization in AVS had low clinical benefit from the addition of ^{11}C-MTO-PET. Furthermore, performing three lateralization tests decreases the likelihood of concordance to less than would be predicted by chance. Hopefully, future advances will lead to easier, more accessible, sensitive and specific diagnostic methods to complement or replace AVS in the subtype diagnosis of PA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Professor W Y Young, Mayo Clinic, Rochester, WY, for his valuable comments to the manuscript.

Funding

This work was supported by a research grant from the Jalmari and Rauha Ahokas Foundation (N M), Helsinki University Hospital research grants (VTR TYH2018111, N M and TYH2013243, M V), Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital (VTR 9X046, I P), and Pirkanmaa Regional Fund of the Finnish Cultural Foundation (I P).

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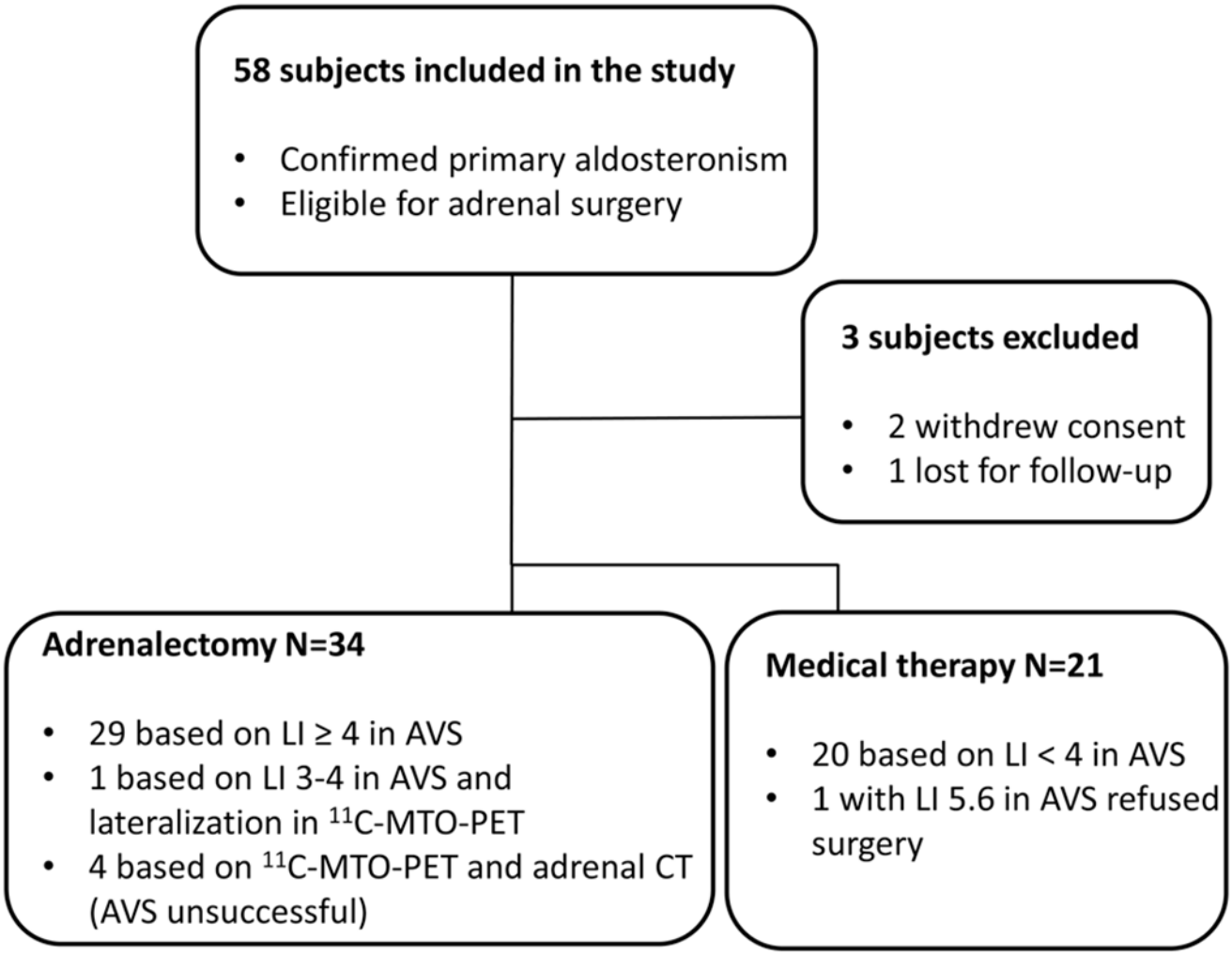

Figure 1.
Patient selection, excluded subjects, and allocation to adrenalectomy or medical therapy. AVS, adrenal venous sampling; ^{11}C-MTO-PET, ^{11}C-metomidate positron emission tomography; LI, lateralization index.

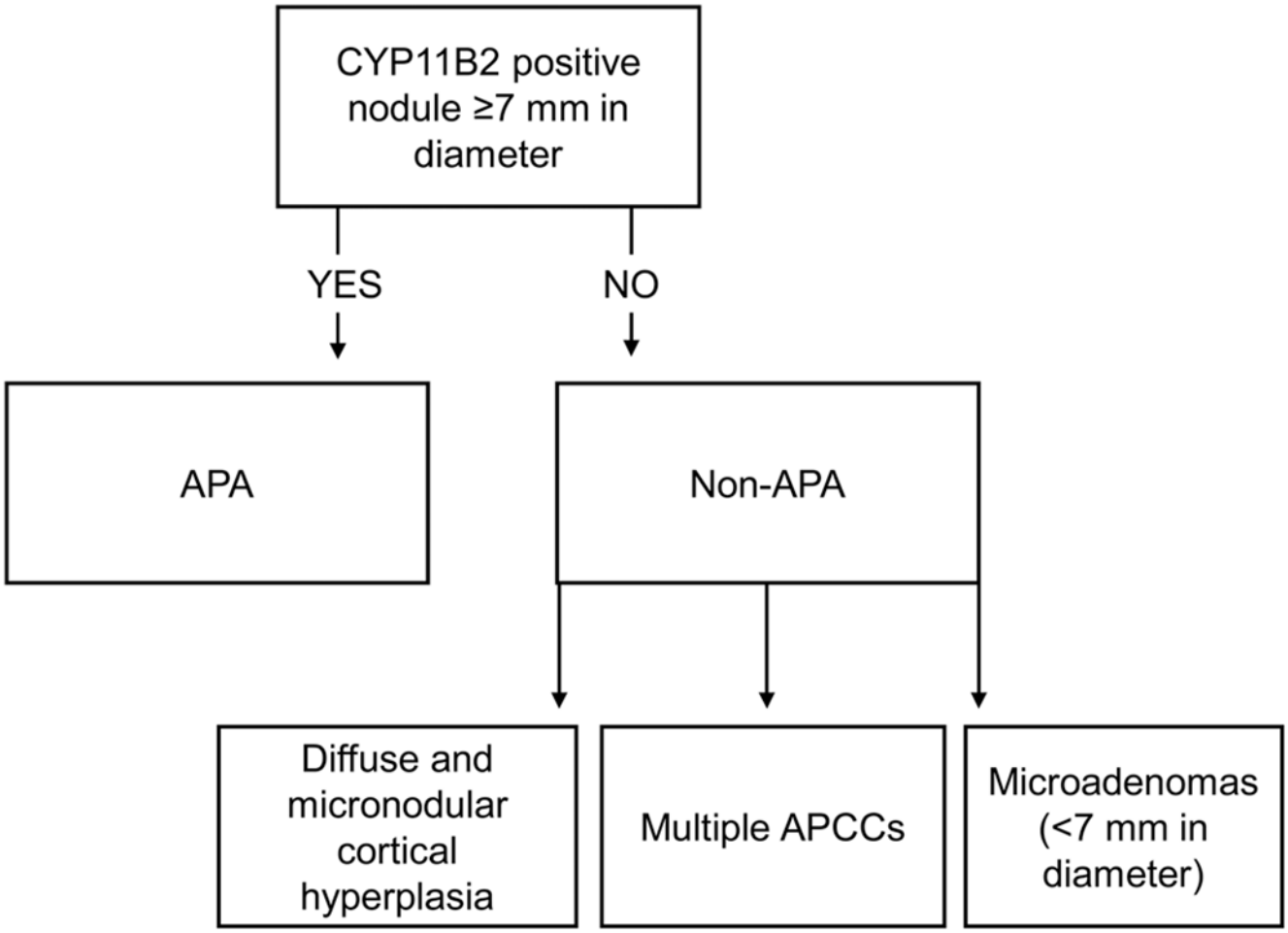

Figure 2.
CYP11B2-based categorization of adrenal gland samples.

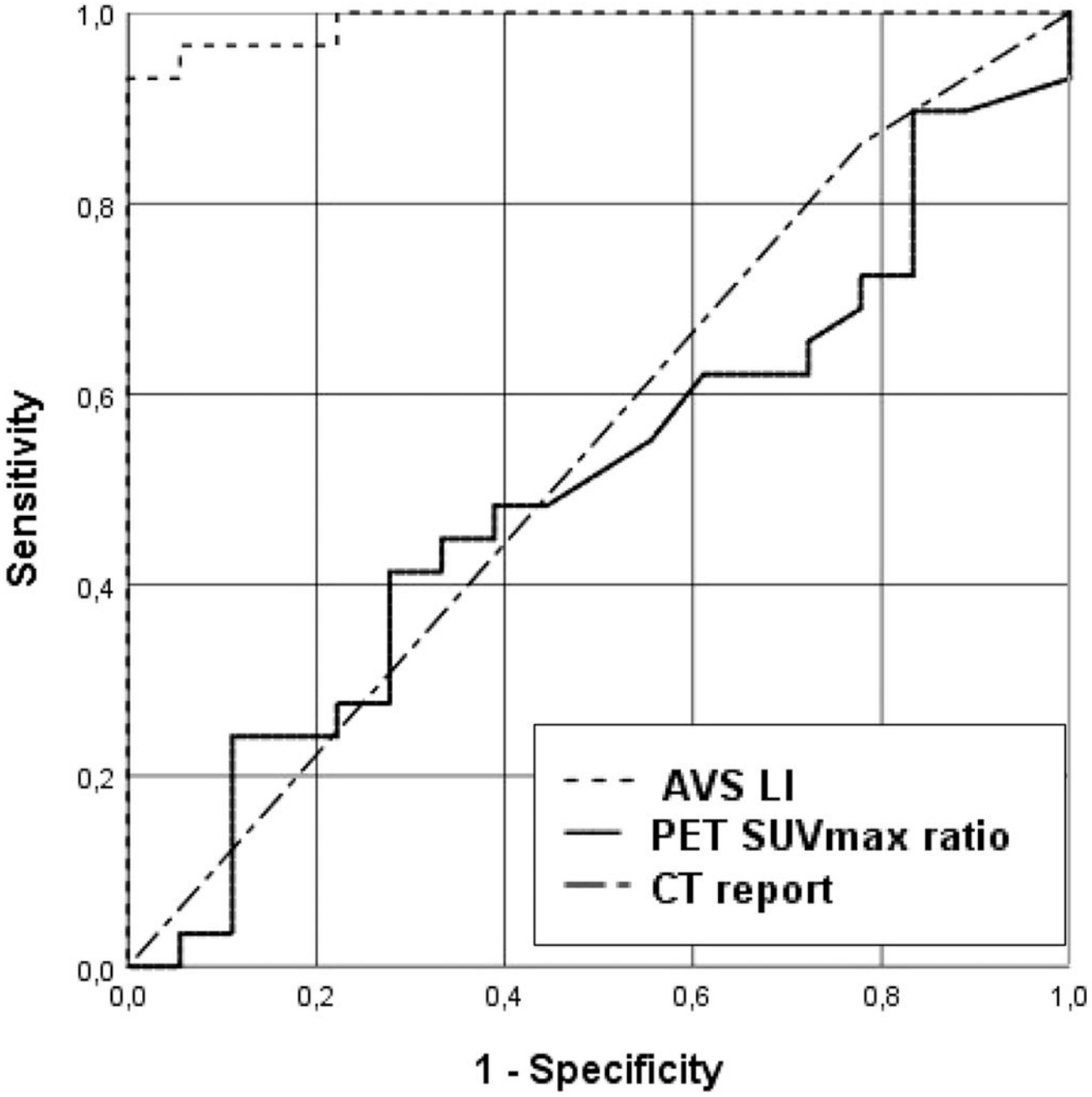

Figure 3.

Receiver operating characteristics (ROC) analysis. Pairs of sensitivity and specificity were calculated using ^{11}C-metomidate positron emission tomography (^{11}C-MTO-PET) SUV_{max} ratio (AUC = 0.507, $P = 0.939$), Lateralization index (LI) for adrenal venous sampling (AVS) (AUC = 0.990, $P < 0.001$), and adrenal computed tomography radiology report (lateralizing or bilateral/no findings, AUC = 0.542, $P = 0.63$) to predict subject allocation to adrenalectomy vs medical therapy groups ($n = 48$). SUV, standardized uptake value.

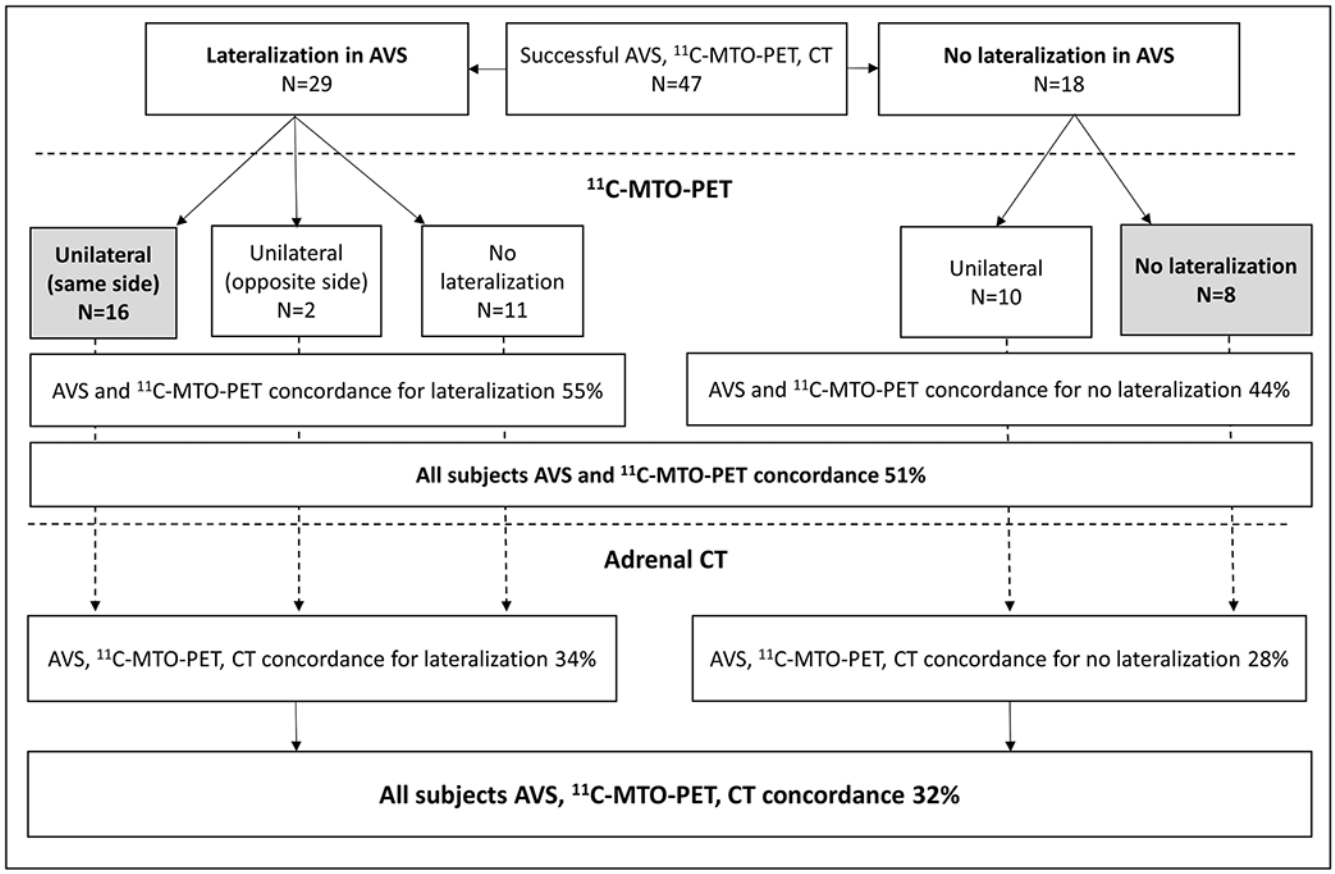

Figure 4.

Study subjects divided into those with lateralizing (lateralization index, LI ≥ 4) or non-lateralizing adrenal venous sampling (AVS) result. The middle row shows the ^{11}C-metomidate positron emission tomography (^{11}C-MTO-PET) outcome and the lower row the adrenal CT outcome. Of all subjects, 15 demonstrated concordance uniformly in AVS, ^{11}C-MTO-PET, and CT. Numbers or percentages are given for each possible outcome.

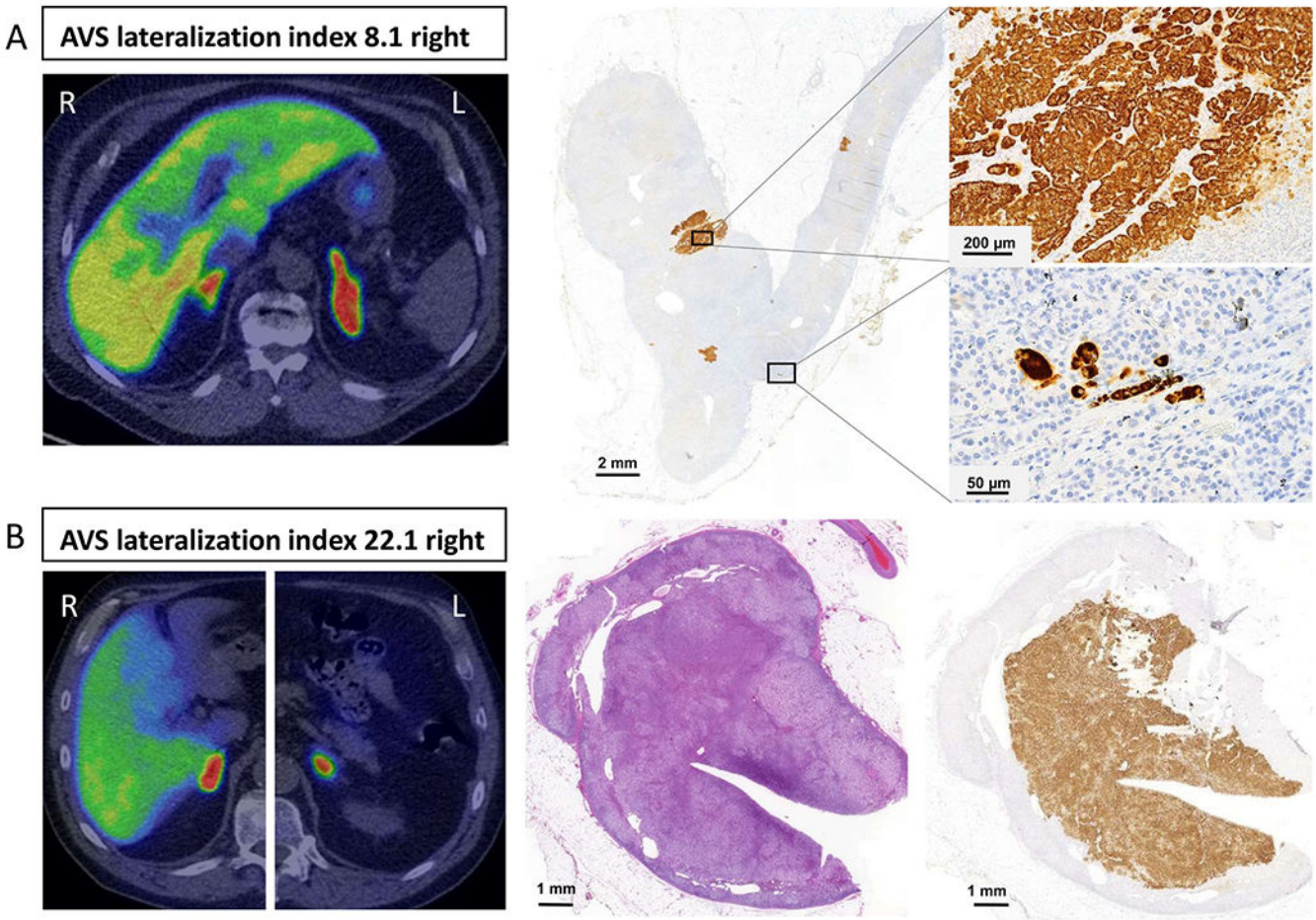

Figure 5.

Two patients who underwent right adrenalectomy with complete biochemical cure. In both cases, the operation was based on adrenal venous sampling (AVS) lateralizing to the right. In the upper panel (Case A) the ^{11}C-metomidate positron emission tomography (^{11}C-MTO-PET) was discordant with AVS showing increased activity in the left (L) adrenal, whereas the AVS lateralized to the right. After adrenalectomy, immunohistochemistry revealed multiple small CYP11B2-positive focuses. In the lower panel (Case B), ^{11}C-MTO-PET was concordant with AVS lateralization to the right (R) adrenal. In a histological examination of the right adrenal, the H&E stain revealed a cortical adenoma that was confirmed as an APA with CYP11B2-immunostain.

Table 1

Patient characteristics. Data are presented as number, mean and standard deviation, or median and interquartile range. SUVmax indicates the standardized uptake value (SUV) of the dominant adrenal and SUVmax-ratio indicates the ratio between the dominant and non-dominant adrenal gland in 11C-metomidate positron emission CT. Follow-up data were evaluated about 3 months after adrenalectomy or at a follow-up visit after intensification of the medical therapy.

	All subjects	Medical therapy baseline	Medical therapy follow-up	Adrenalectomy baseline	After adrenalectomy follow-up
Number (male/female)	55 (40/15)	21 (17/4)	–	34 (23/11)	–
Age (years)	54.7 ± 8.5	55.2 ± 7.8	–	54.3 ± 9.0	–
BMI (kg/m^2)	30.5 ± 5.3	31.1 ± 5.0	–	30.2 ± 5.6	–
Systolic BP (mmHG)	154 ± 19	153 ± 22	139 ± 13	155 ± 18	133 ± 12***
Diastolic BP (mmHG)	94 ± 10	95 ± 10	88 ± 10	94 ± 10	80 ± 8***
Duration of treated hypertension (years)	12 (7.8–25)	22 (8.8–25)	–	10 (5.8–16.3)*	–
Antihypertension medication, DDD	4.5 (2.7–6.0)	4.5 (2.9–6.3)	4.3 (3.3–5.3)	4.0 (2.5–5.8)	2.0 (0–3.3)***
Antihypertension medication (*n*)	2.7 (2–6)	3 (2–3)	3 (2–3)	2.5 (2–3.25)	1 (0–2)***
Serum aldosterone (pmol/L)	685 (467–1010)	567(421–871)	–	765 (519–1217)	82 (30–208)***
PRA (pmol/L/min)	0.2 (<0.2–0.2)	<0.2 (<0.2–0.2)	–	<0.2 (<0.2–0.2)	0.6 (0.2–2.1)*
ARR, PRA	2825 (1767–4701)	2600 (1630–4007)	–	3440 (1950–4773)	140 (25–567)***
DRC (mU/L)	5.0 (2.5–10.1)	8.5 (5.5–16.8)	–	2.5 (1.7–3.2)	10 (5–21)*
ARR, DRC	117 (65–338)	91 (34–119)	–	338 (93–1771)	12.3 (6.0–21.4)
24 h U-aldosterone (nmol)	60 (51–96)	59 (50–68)	–	70 (55–112)	11 (8–24)*
Plasma potassium (mmol/L)	2.95 ± 0.41	3.14 ± 0.44	4.35 ± 0.21	2.86 ± 0.38**	4.05 ± 0.47***
SUV_{max} (g/mL)	23.7 ± 8.8	21.7 ± 12.2	–	25.4 ± 9.2	–
SUV_{max} ratio	1.49 (1–6.39)	1.51 (1.00–6.39)		1.48 (1–3.83)	–
Lateralization index	27.37 (1.07–159.23)	1.95 (1.07–4.55)		43.47 (3.00–159.23)***	–
Contralateral suppression index	1.29 (0.02–4.21)	2.47 (1.19–4.21)		0.52 (0.02–1.51)***	–

Asterisks indicate significant differences between medical therapy vs adrenalectomy at baseline or before vs postadrenalectomy in the adrenalectomy group:

*$P < 0.05$,

**$P < 0.01$,

***$P < 0.001$.

ARR, aldosterone-renin ratio; BP, blood pressure; DDD, daily defined dose; DRC, direct renin concentration; PRA, plasma renin activity; SUV, standardized uptake value.

Table 2

Individual data of the adrenalectomy group showing the results from immunohistochemical analysis, histological size of an APA, adrenal venous sampling (AVS), ^{11}C-metomidate (^{11}C-MTO) positron emission tomography (PET), and biochemical and clinical improvement according to (19).

Histology based on CYP11B2	APA size, mm	Operation side	APCC, *n*	AVS, LI	AVS, side	SUV_{max} Right	SUV_{max} Left	SUV_{max} ratio	PET, side	PET finding	AVS vs PET	Biochemical improvement	Clinical improvement
APA	13	Left	1	159.9	L	6.7	25.8	3.38	L	Adenoma	**Concordant**	Complete	Partial
APA	12	Left	2	NA	NA	8.8	20	2.28	L	Adenoma	NA	Complete	Complete
APA	15	Left	0	23.4	L	9	19.6	2.19	L	Adenoma	**Concordant**	Complete	Complete
APA	14	Left	1	59.5	L	23.2	47.8	2.06	L	Adenoma	**Concordant**	Complete	Complete
APA	14	Left	0	151.8	L	11	21.7	1.98	L	Adenoma	**Concordant**	Complete	Partial
Non-APA	-	Right	4	34.7	R	46.4	23.6	1.97	R	Adenoma	**Concordant**	Absent *	Partial
Non-APA	-	Right	5	NA	NA	25.7	13.5	1.9	R	Adenoma	NA	Complete	Partial
APA	29	Right	1	105.5	R	37.9	21.5	1.76	R	Adenoma	**Concordant**	Complete	Partial
Non-APA	-	Left	2	7.2	L	9.2	16.2	1.66	L	Adenoma	**Concordant**	Complete	Absent #
APA	7	Left	0	NA	NA	14.1	22.2	1.57	L	Hyperplasia L	NA	Complete	Absent #
Non-APA	-	Right	4	3	R	17.1	11.1	1.54	R	Hyperplasia R	**Concordant**	Complete	Partial
Non-APA	-	Left	5	5.3	L	13.8	20.6	1.49	L	Adenoma	**Concordant**	Complete	Partial
Non-APA	-	Left	0	5.2	L	12.7	17.7	1.39	L	Hyperplasia L	**Concordant**	Partial	Partial
APA	16	Left	0	66.4	L	20.9	28.9	1.38	L	Adenoma	**Concordant**	Complete	Complete
APA	10	Right	1	128.9	R	26.3	19.3	1.36	R	Adenoma	**Concordant**	Complete	Partial
APA	13	Right	0	54.2	R	17.7	24	1.36	L	Hyperplasia L	Discordant	Not done	Partial *
APA	8	Right	3	13.3	R	22.6	17.4	1.3	R	Adenoma (suspicion)	**Concordant**	Complete	Partial
APA	13	Right	2	29.2	R	17.4	13.9	1.25	R	Adenoma	**Concordant**	Complete	Complete
APA	12	Left	0	14.2	L	42.1	34	1.24	R	Adenoma R/ Hyperplasia L	Discordant	Not done	Partial *
APA	7	Right	1	NA	NA	28.7	34.2	1.19	L	Adenoma L/ Hyperplasia R	NA	Partial	Partial
APA	-	Left	2	19.6	L	25.6	30.3	1.18	L	Adenoma	**Concordant**	Complete	Complete
Non-APA	-	Left	5	36.6	L	20.6	24	1.17	L	Hyperplasia L	**Concordant**	Complete	Complete
APA	14	Left	4	8.4	L	29.2	33.5	1.15	None	No activity difference	Discordant	Complete	Complete

Histology based on CYP11B2	APA size, mm	Operation side	APCC, *n*	AVS, LI	AVS, side	SUV_{max} Right	SUV_{max} Left	SUV_{max} ratio	PET, side	PET finding	AVS vs PET	Biochemical improvement	Clinical improvement
APA	15	Right	0	6.3	R	51.4	44.7	1.15	None	Hyperplasia both sides	Discordant	Partial	Partial
APA	18	Left	2	4.8	L	18.5	20	1.08	None	Hyperplasia both sides	Discordant	Complete	Complete
Non-APA	-	Left	5	10.7	L	36.5	39.1	1.07	None	No activity difference	Discordant	Partial	Partial
Non-APA	-	Right	8	5.9	R	15.4	14.5	1.06	None	No activity difference	Discordant	Complete	Complete
APA	-	Left	3	9	L	29.4	28.3	1.04	None	No activity difference	Discordant	Complete	Partial
Non-APA	-	Right	4	13	R	20.1	19.4	1.04	None	No activity difference	Discordant	Complete	Complete
APA	20	Left	1	95.6	L	20.4	21.1	1.03	None	No activity difference	Discordant	Complete	Partial
APA	12	Left	4	88.5	L	31.2	32.2	1.03	None	Hyperplasia both sides	Discordant	Complete	Complete
Non-APA	-	Right	5	8.1	R	23.5	24.3	1.03	None	No activity difference	Discordant	Complete	Partial
APA	9	Left	2	4.3	L	34.8	34.9	1	None	Hyperplasia both sides	Discordant	Partial	Partial
APA	14	Right	0	132.5	R	NA	NA	NA	NA	NA	NA	Complete	Partial

Data are organized according to descending SUV_{max}-ratios.

*Subjects with contralateral findings in AVS and ^{11}C-MTO-PET.

#Subjects with absent clinical or biochemical improvement by PASO criteria (ref. (19)) all showed improvement that did not meet the criteria.

AVS, adrenal venous sampling; L, left; LI, lateralization index; NA, not applicable; R, right; SUV, standardized uptake value.