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ORIGINAL SCIENTIFIC REPORT

Outcomes of Adrenal Venous Sampling in Patients with Bilateral Adrenal Masses and ACTH-Independent Cushing's Syndrome

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Abstract

Background Management of patients with bilateral adrenal masses and ACTH-independent Cushing's syndrome (AICS) is challenging, as bilateral adrenalectomy can lead to steroid dependence and lifelong risk of adrenal crisis. Adrenal venous sampling (AVS) has been previously reported to facilitate lateralization for guiding adrenalectomy. The aim of the current study was to investigate the utility of AVS using protocol from study by Young et al. in the management of patients with bilateral adrenal masses and AICS.

Methods and design A retrospective review of all patients with bilateral adrenal masses and AICS who underwent AVS from 2008 to 2016 was performed. AVS for cortisol and epinephrine was performed with dexamethasone suppression. The adrenal vein to peripheral vein cortisol ratios and side-to-side cortisol lateralization ratios were calculated.

Results AVS was successful in 8 of 9 patients. All 8 patients had AVS results indicating bilateral cortisol hypersecretion. Six patients underwent adrenalectomy: 3 had unilateral adrenalectomy of the larger size mass, 2 had bilateral adrenalectomy (both sides >4 cm.) and 1 had stepwise bilateral adrenalectomy. Final pathology revealed macronodular adrenal hyperplasia in all 6 patients that underwent surgery.

Conclusion AVS was useful in excluding a unilateral adenoma as the source of AICS in this study of patients with bilateral adrenal masses and AICS. However, adrenal mass size influenced surgical decision making more than AVS results. More data are needed before AVS can be advocated as essential for management of patients with bilateral adrenal masses and AICS.

Introduction

Adrenal incidentalomas (AIs) are defined as clinically silent adrenal masses >1 cm in size and are detected in up to 10% of patients during imaging procedures performed for unrelated conditions [1, 2]. The incidence of AI is increasing because of extensive utilization of CT and MRI imaging modalities [3]. Up to 20% of AIs secrete hormones, and subclinical Cushing's syndrome (SCS) is the most frequent hormonal abnormality, with a prevalence of 5–20% [4]. SCS remains a poorly defined clinical entity [5], usually diagnosed in a patient with an adrenal adenoma and biochemical evidence of autonomous ACTH- independent CS (AICS), but without a clear cushingoid

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phenotype [2]. Patients with SCS may have several metabolic disorders including hypertension, dyslipidemia, impaired glucose tolerance, type 2 diabetes mellitus (T2DM), atherosclerosis, and an increased risk for vertebral fractures [2]. In a prospective randomized controlled trial of 45 patients with SCS, comparing surgical management to conservative management, surgical management was associated with significant improvement or resolution of T2DM (62.5%), hypertension (67%), hyperlipidemia (37.5%), and obesity (50%) [4]. Deterioration in these metabolic markers was found in patients who were managed conservatively, indicating that laparoscopic adrenalectomy was superior to conservative management for SCS [4].

Although patients with unilateral adrenal masses and SCS may be managed by unilateral adrenalectomy, management of the rare patient with bilateral adrenal masses and AICS is not as straightforward, as these patients may present with one of several clinical scenarios, including: (1) unilateral cortisol-secreting adenoma with a contralateral non-functioning cortical adenoma; (2) bilateral cortisol-secreting adenomas; (3) bilateral macronodular adrenal hyperplasia (BMAH); or (4) primary pigmented nodular adrenocortical disease (PPNAD) [6]. The distinction between a functioning or non-functioning adrenal mass cannot be ascertained by CT or MRI. Functional imaging modalities such as 6β-^{131}Iodomethyl-19-norcholesterol (NP-59) scintigraphy have been previously utilized to guide management in cases of bilateral adrenal masses and AICS [7]. However, this imaging modality is no longer available in the USA [6]. In a recent study, ^{18}FDG PET/CT detected cortisol-secreting adenomas with a sensitivity of 50.0% and specificity of 81.8% [8]. However, significant overlap in the SUV values between functioning and non-functioning adrenal adenomas limited its discriminatory ability [8].

In the absence of a good clinical test to differentiate between cortisol-secreting and non-secreting adenomas in patients with bilateral adrenal masses and AICS, bilateral adrenalectomy ensures cure of AICS, but leads to permanent corticosteroid dependence and a lifelong risk of adrenal crisis [9]. Bilateral adrenalectomy is associated with increased mortality, even among well-educated patients [10]. Therefore, if feasible, diagnosis of a unilateral cortisol-secreting adenoma and treatment with unilateral adrenalectomy is preferable to avoid bilateral adrenalectomy.

Adrenal venous sampling (AVS) has been reported in a single institutional series (n = 10) to aid in successful localization of cortisol-secreting adrenal adenomas in patients with bilateral adrenal masses and AICS [6]. Since the original report by Young et al., several referring endocrinologists at our institution have utilized AVS, using protocol from study by Young et al., for cases of bilateral adrenal masses and AICS. The goal of the current study was to retrospectively investigate the utility and outcomes of AVS in guiding management of patients with bilateral adrenal masses and AICS at our institution.

Methods

Patient selection

After institutional QI (#ID564) approval, we performed a retrospective review of all patients with bilateral adrenal masses and AICS who underwent AVS at the University of Pittsburgh Medical Center from 2008 to 2016. We included all patients who met the following inclusion criteria: (1) CT findings of bilateral adrenal masses; (2) low basal ACTH; and (3) concordantly positive results of 2 or more different screening tests for Cushing's syndrome (CS) based on 2008 clinical practice guidelines [11] (Table 1). Data were collected on demographics, imaging, AVS results, and management of the included patients. Continuous variables were summarized as means (±standard deviation) or medians (range). Categorical data were summarized as frequencies and percentages.

Protocol for AVS procedure

Patients received 0.5 mg oral dose of dexamethasone every 6 h for 24 h prior to AVS, and on the day of the procedure for a total of 2 days. All successful AVS procedures were performed by one of two dedicated interventional radiologists with special expertise in AVS. AVS was performed without ACTH infusion. The right (R) common femoral vein was used for access. Sequential sampling of both adrenal veins (AV) was performed. Samples were obtained for testing of epinephrine and cortisol from both AVs and the external iliac vein (peripheral vein, PV). Multiple samples were obtained to ensure adequate sampling. Figure 1 shows images of the adrenal CT scans along with right and left adrenal vein catheterization of case 1.

Interpretation of AVS results

Catheterization of an AV was considered successful if plasma epinephrine (Epi) concentration in the AV was 100 pg/ml above the PV (AV–PV >100 pg/ml), per protocol by Young et al. [6]. Cortisol gradients were then calculated by computing the AV/PV ratios. Only the AV cortisol values from samples with Epi levels >100 pg/ml above the PV were included in the analysis. We calculated the AV/PV ratio for each adrenal gland using the mean of the values. Side-to-side (higher cortisol/lower cortisol)

Table 1 Patient characteristics and CT findings

Case no.	Age (years)	Sex	Clinical presentation	AVS-Mean PV Cortisol post DEX	BMI kg/m^2	Pre-op HTN	Pre-op DM	CT findings	Right				Left			
									Size (cm)	HU-unenhanced	AW	RW	Size (cm)	HU-unenhanced	AW	RW
1	51	F	Subclinical	2.9	25	y	Y	Nodules	3.7	− 6.5	NA	NA	4.1	− 5	NA	NA
2	62	F	Subclinical	2.6	26.7	y	Y	Hyperplasia	1.6	1.9	58.2	64.3	1.7	3.2	73	65.2
3	65	F	Subclinical	2.7	29.9	y	Y	Nodules	1.6,2.9	2.5	91.2	88.5	2.9,1.8	24	72.9	59.6
4	73	F	Subclinical	2.4	21.8	y	Y	Hyperplasia	2.3	− 14	NA	NA	3.3	− 0.2	NA	NA
5	60	F	Subclinical	13	40	y	N	R adenoma, L mild hyperplasia	2.4	2	NA	NA	2.3	1	NA	NA
6	59	F	Subclinical	3.3	39	y	N	Hyperplasia	1.9	NA	NA	NA	3.4	N/A	NA	NA
7	67	F	Subclinical	9	38.2	y	Y	Bilateral Lobulated Adrenals	4.3	− 2	NA	NA	5.1	0.3	NA	NA
8	70	F	Subclinical	18.4	26.3	N	Y	Bilateral Hyperplasia	5.5	− 1.5	65.8	66.7	6.9	5.9	66.9	63.3

For multiple nodules in the same adrenal gland, HU of the largest nodule is reported

AW absolute washout; *RW* relative washout; *HU* hounsfield units

cortisol lateralization ratios (CLR) were also calculated. The data were analyzed using criteria from study by Young et al. of an AV/PV cortisol ratio of >6.5 on one side and ≤3.3 on the contralateral side, and CLR ≥ 2.3 to indicate a unilateral cortisol-secreting adenoma. A CLR of ≤2 was used to indicate bilateral cortisol hypersecretion [6].

Results

Nine patients with bilateral adrenal masses and AICS met inclusion criteria and were included in the current study. The median age of all patients was 62 years (range 51–73 years), and all patients were women. Mean body mass index was 31.4 (range 21.8–39.9 kg/m^2). All patients presented with biochemical evidence of SCS (normal 24 h. urine free cortisol). Cross-sectional imaging with CT was performed, and review of the imaging reports revealed bilateral single or multiple adenomas in 2 patients, unilateral adenoma with contralateral hyperplasia in 1 patient, bilateral adenomas with hyperplasia in 2 patients, bilateral hyperplasia in 1 patient, unilateral nodular hyperplasia and contralateral hyperplasia in 1 patient, and bilateral lobulated adrenals in 1 patient. Tables 1 and 2 provide further details on these patients.

Successful catheterization for AVS was achieved in 8 patients (Fig. 2). One patient with unsuccessful catheterization had significant comorbidities and passed away from unrelated reasons. The remainder of the analysis will focus on the 8 patients who underwent successful catheterization. Dexamethasone (DEX)-suppressed PV cortisol levels were greater than 1.8 μg/dl in all 8 patients (normal <1.8) and >5 μg/dl in 3 patients. There were no cases in our series with unilateral cortisol hypersecretion, as none had an AV/PV cortisol ratio on one side of >6.5 with simultaneous contralateral AV/PV cortisol ratio of ≤3.3 or a CLR of ≥2.3. Seven patients had CLR ratios of ≤2, suggesting bilateral cortisol hypersecretion. The AV/PV cortisol ratios bilaterally were ≥4.1 in 3 of these patients and ≥1.9 in all 7 cases. One patient (case 4) had a bilateral AV/PV cortisol ratio of ≥4.1, with a CLR that was 2.2, again suggesting bilateral cortisol hypersecretion. Therefore, all 8 patients had findings consistent with bilateral cortisol hypersecretion. Of the 8 patients with bilateral cortisol hypersecretion by AVS, 3 underwent unilateral adrenalectomy, 2 patients underwent bilateral adrenalectomy, and 1 patient (case 2) underwent stepwise bilateral adrenalectomy (right followed by left, 5 months later, due to non-resolution of SCS). Follow-up to assess remission for the 4 patients that underwent initial unilateral adrenalectomy revealed 1 remission, 1 patient who required a second adrenalectomy, and no follow-up data for 2 cases. Two patients (case 4 and 5) did not undergo surgical resection and were followed or

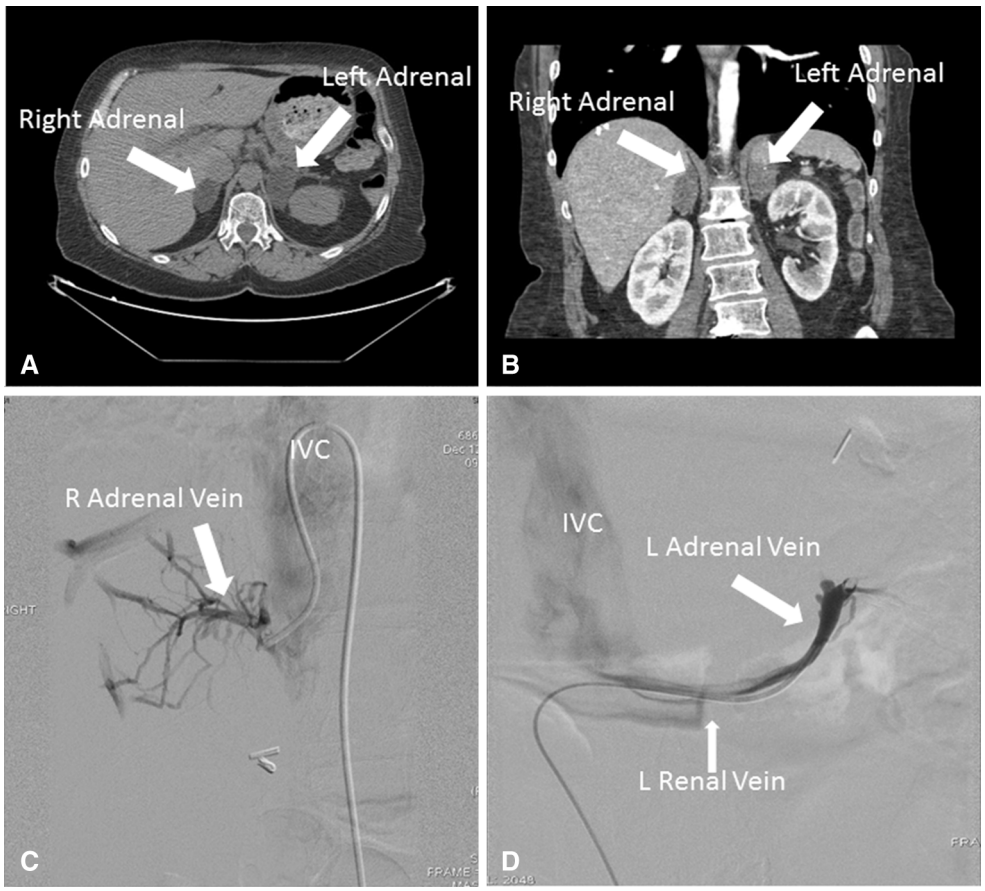

Fig. 1 Representative CT and AVS images (case 1). **a** Axial CT scan image of right and left adrenal glands **b** Coronal CT scan image of right and left adrenal glands **c** Right adrenal vein catheterization **d** Left adrenal vein catheterization

given medical therapy. The pathology results for all 6 patients that had an adrenalectomy revealed macronodular adrenal cortical hyperplasia (MAH) (Fig. 2).

Two patients (case 1 and 6) who underwent unilateral adrenalectomy had the larger sized adrenal mass resected. The AV/PV cortisol ratios were higher on the side with the larger mass on CT in these two cases. Unilateral adrenalectomy was chosen in these cases because of patient preference for avoiding the development of permanent AI and because they lacked severe symptoms of CS. The third patient (case 3) who underwent a unilateral adrenalectomy had bilateral multiple nodules with an aggregate size 0.2 cm greater on the left (L aggregate size 4.7 cm) compared to right (R aggregate size 4.5 cm). The AVS sampling showed the AV/PV cortisol ratio to be higher on the R side than the L. This patient underwent R adrenalectomy. Follow-up was available for 1 patient (case 6) who underwent a unilateral adrenalectomy. This patient was in remission with improvement in hypertension and normal 1 mg DEX suppression test at 2.5 years after surgery.

Two patients (case 7 and 8) underwent bilateral adrenalectomy because they had adrenal nodules >4 cm bilaterally, as well as AVS data indicating bilateral cortisol hypersecretion. A third patient (case 2) first underwent R adrenalectomy followed by a L adrenalectomy, 5 months later. In this case, the size of both adrenal nodules was relatively equal (0.1 cm difference, L > R) and the AV/PV cortisol ratio on the R side was greater than the L. Therefore, concordance between larger adrenal mass size and higher AV/PV cortisol ratio was found to be present in 50% of cases (case 1, 5, 6, and 8).

These data demonstrate that in our series of patients who underwent successful AVS, all failed to lateralize to one side, based on criteria from study by Young et al. In the 6 of 8 patients who underwent surgery (3 bilateral, 3 unilateral), all had MAH on pathological analysis, which is known to be associated with bilateral cortisol hypersecretion. A bilateral AV/PV cortisol ratio $\geq$1.9, with a CLR $\leq$2, was associated with MAH (Fig. 3).

Table 2 Patient management

Case no.	Age (years)	Sex	Mean cortisol levels on AVS			Surgery	Adrenal tissue wt in grams (R, L)	Pathology
			R AV/PV ratio	L AV/PV ratio	CLR			
1	51	F	3.1	3.8	1.2	L robotic assisted laparoscopic adrenalectomy	44	Macronodular adrenal cortical hyperplasia (MAH)
*2	62	F	13.3	7.7	1.7	Stepwise Bilateral laparoscopic adrenalectomy R first, then L, 5 months later	14.1,19	MAH
*3	65	F	12.5	7.3	1.7	Right adrenalectomy	25.2	Adrenal cortical adenoma, infarcted in background of MAH
4	73	F	19.8	8.9	2.2	No surgery-medical therapy	N/A	N/A
5	60	F	2.3	1.7	1.3	No surgery with serial f/u at outside facility	N/A	N/A
*6	59	F	6	9.9	1.6	Left sided adrenalectomy	31.6	MAH
7	67	F	5.4	2.9	1.9	Bilateral adrenalectomy	36,57	MAH
8	70	F	1.9	2.3	1.2	Bilateral adrenalectomy	32,94	MAH

Young's criteria for unilateral adenoma: AV/PV ratio >6.5 on one side and ≤3.3 on opposite side and CLR ≥2.3. No patients met these criteria

Young's criteria for bilateral cortisol hypersecretion: AV/PV ratio >4.1 bilaterally and CLR <2. Three patients indicated by* above met both of these criteria; 3 had AV/PV ratios >1.9. Seven patients had CLR <2. One patient had CLR of 2.2 and AV/PV ratio of >4.1 bilaterally. Eight patients were therefore classified as having results most consistent with bilateral secretion

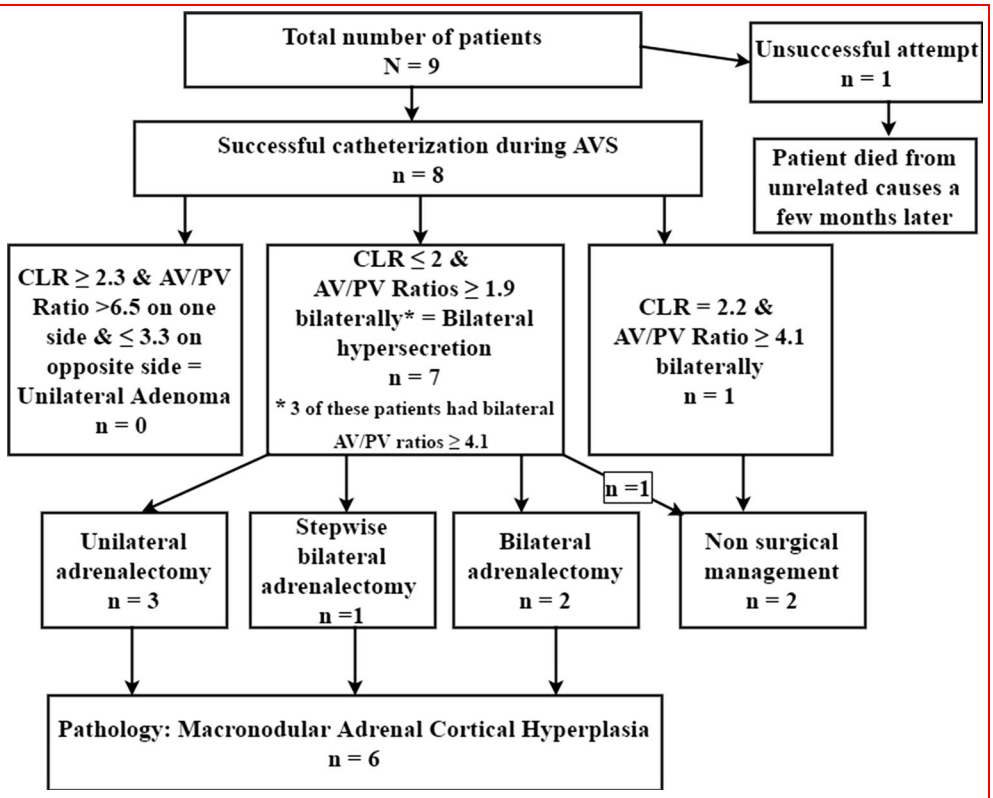

Fig. 2 Flow diagram depicting patient management: Six patients who underwent surgery had bilateral cortisol hypersecretion on AVS, and pathology revealed macronodular adrenal cortical hyperplasia (MAH). Unilateral adrenalectomy was the initial management in 4 cases: 1 had remission, 1 required a second adrenalectomy, and no follow-up data was available in 2 cases

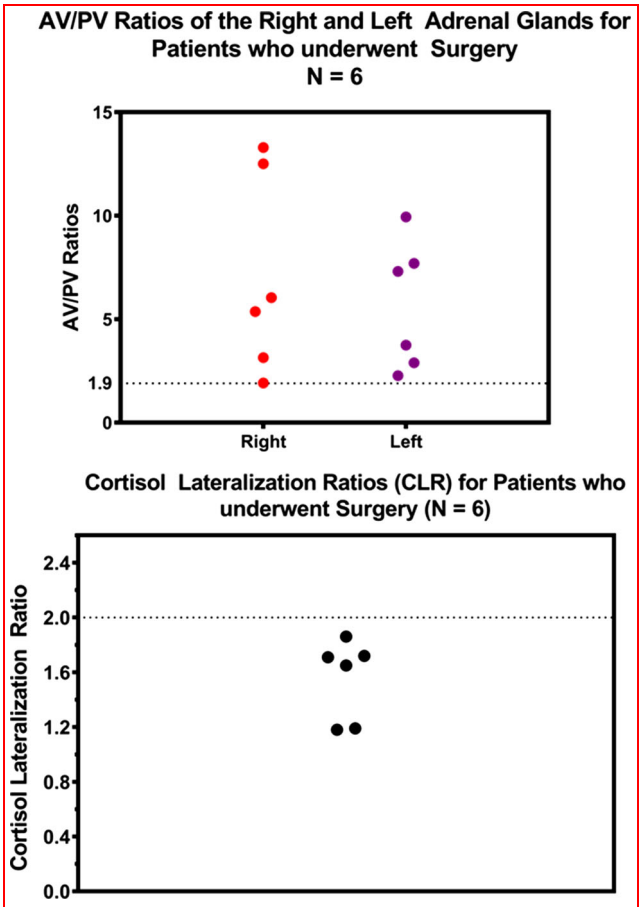

Fig. 3 Adrenal vein sampling results for patients who underwent surgical resection. All patients in the current study had AVS data consistent with bilateral cortisol hypersecretion. Concordance of adrenal mass size and higher AV/PV cortisol ratio was present in 4 of 8 cases

Discussion

Management of patients with bilateral adrenal masses and AICS poses a significant challenge, as the surgeon is faced with the dilemma of which adrenal gland to remove and the general desire to avoid bilateral adrenalectomy. AVS has been previously shown to aid in localization in these patients and to aid in surgical management. The goal of our study was to determine whether performing AVS using Young et al. protocol was useful in surgical decision making [6]. To the best of our knowledge, this is the second study to evaluate the utility of AVS in guiding management of patients with bilateral adrenal masses and AICS. Our study suggests that AVS, using Young et al. criteria, was useful in excluding a unilateral cortisol-secreting adenoma. No case in our series was found to have a unilateral source of cortisol by AVS, and the pathology results of the 6 cases that underwent surgery confirmed MAH. In our series, the absence of the combination of an AV/PV cortisol ratio of >6.5 on one side with a contralateral ratio ≤3.3 was useful to exclude a unilateral functioning adenoma. A CLR of ≤2, as well as a bilateral AV/PV cortisol ratio of ≥1.9, was predictive of MAH.

Previously, Young et al. reported that of patients with bilateral adrenal masses and AICS undergoing AVS, unilateral localization was achieved in 5 of 10 of the patients [6]. The protocol used in the current study was similar to that used by Young et al. However, our results differ in that none of our patients who underwent successful AVS were identified as having a unilateral source of cortisol hypersecretion. There were several differences in patient characteristics and inclusion criteria when our study is compared to the previous study. In study by Young et al., CT findings were described as "bilateral adrenal masses," without mention of the presence of hyperplasia or multiple nodules on one or more sides. This might indicate that only CT findings of bilateral solitary adenomas were included. However, 3 of 10 patients in his study had BMAH on final path and 5 of 10 also had bilateral hypersecretion by AVS. One could conclude from his results that radiologic assessment by CT may not be reliable for diagnosing BMAH versus adenoma and therefore AVS might be useful for excluding a unilateral source in cases with bilateral adrenal masses on CT. Analysis of CT findings in the current study revealed that the adrenal masses in many cases included evidence of hyperplasia or multiple nodules on one or both sides. Therefore, the radiologic findings in the current study may have been more predictive of BMAH when compared to cases in Young et al. study. Furthermore, all 10 patients in the study by Young et al. had DEX suppressed cortisol levels of >5 μg/dl, as opposed to 3 of 9 cases in our study. Seven of 10 patients in Young et al. study were classified as having SCS, versus all 9 in our study. Additionally, final pathologic analysis revealed bilateral adenomas in 7 out of 10 patients in Young et al. study, whereas all 6 patients that underwent surgery in our study were found to have MAH. Therefore, the inclusion of cases with more severe CS in Young et al. study likely explains the greater number of unilateral adrenal adenomas found in that study and the high number of BMAH patients in the current study. This is consistent with prior reports showing that the degree of CS is often milder in patients with BMAH [9].

There are several series [9, 10] showing that resection of the larger adrenal mass in patients with BMAH results in clinical improvement of CS. In theory, unilateral adrenalectomy provides de-bulking of the hypersecreting gland mass which achieves lower cortisol production. In one prospective study, unilateral adrenalectomy of the larger mass in 7 patients with BMAH led to improvement in AICS in all patients, with improvement in hypertension and DM in 100% and 80% of patients, respectively [9]. In

another multi-institutional retrospective study, 15 patients with BMAH and CS underwent unilateral adrenalectomy of the larger mass, and 100% of the patients achieved remission of CS and had significant improvement in metabolic parameters [10]. Therefore, unilateral adrenalectomy of the larger adrenal mass was chosen instead of bilateral adrenalectomy in many of our patients. We do not have follow-up data in enough of our cases to comment on the success rate of unilateral adrenalectomy for patients with BMAH. The small sample size is a limitation of the current and previous studies. Multiple endocrinologists from our institution and outside institution were involved in decision making in the stated cases; therefore, we are unable to determine why in some of these cases more aggressive management with bilateral adrenalectomy was sought rather than medical management even though all patients were diagnosed with SCS.

In conclusion, in this small series, AVS was useful for excluding a unilateral source of cortisol hypersecretion in patients with bilateral adrenal masses and AICS. All patients had AVS data consistent with bilateral cortisol hypersecretion, and in those who underwent surgery, pathology results revealed MAH. CT findings that included adrenal hyperplasia or multiple nodules on one or both sides within the adrenal masses were consistently associated with bilateral cortisol hypersecretion by AVS and MAH. Surgical management was strongly influenced by adrenal mass size. However, AVS may have influenced surgical decision making in some cases particularly when minimal difference in size was noted in adrenal mass sizes. Because of the rarity of this condition and very limited data using AVS, future multi-institutional registries of patients with bilateral adrenal masses and AICS are needed before AVS can be advocated as a useful tool in the management of these patients.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

References

1. Young WF (2007) Clinical practice. The incidentally discovered adrenal mass. N Engl J Med 356:601–610. https://doi.org/10.1056/NEJMcp065470
2. Terzolo M, Pia A, Reimondo G (2011) Subclinical Cushing's syndrome: definition and management. Clin Endocrinol 76:12–18. https://doi.org/10.1111/j.1365-2265.2011.04253.x
3. Kloos RT, Gross MD, Francis IR, Korobkin M (1995) Incidentally discovered adrenal masses. Endocrine Review 16:460–484
4. Toniato A, Merante-Boschin I, Opocher G, Pelizzo MR, Schiavi F, Ballotta E (2009) Surgical versus conservative management for subclinical cushing syndrome in adrenal incidentalomas: a prospective randomized study. Ann Surg 249:388–391. https://doi.org/10.1097/SLA.0b013e31819a47d2
5. Zeiger MA, Siegelman SS, Hamrahian AH (2011) Medical and surgical evaluation and treatment of adrenal incidentalomas. J Clin Endocrinol Metab 96:2004–2015. https://doi.org/10.1210/jc.2011-0085
6. Young WF Jr, du Plessis H, Thompson GB, Grant CS, Farley DR, Richards ML et al (2007) The clinical conundrum of corticotropin-independent autonomous cortisol secretion in patients with bilateral adrenal masses. World J Surg 32:856–862. https://doi.org/10.1007/s00268-007-9332-8
7. Sarkar SD, Cohen EL, Beierwaltes WH, Ice RD, Cooper R, Gold EN (1977) A new and superior adrenal imaging agent, 131I-6beta-iodomethyl-19-nor-cholesterol (NP-59): evaluation in humans. J Clin Endocrinol Metab 45:353–362. https://doi.org/10.1210/jcem-45-2-353
8. Patel D, Gara SK, Ellis RJ, Boufraqech M, Nilubol N, Millo C et al (2015) FDG PET/CT scan and functional adrenal tumors: a pilot study for lateralization. World J Surg 40:683–689. https://doi.org/10.1007/s00268-015-3242-y
9. Iacobone M, Albiger N, Scaroni C, Mantero F, Fassina A, Viel G et al (2008) The role of unilateral adrenalectomy in ACTH-independent macronodular adrenal hyperplasia (AIMAH). World J Surg 32:882–889. https://doi.org/10.1007/s00268-007-9408-5
10. Debillon E, Velayoudom-Cephise F-L, Salenave S, Caron P, Chaffanjon P, Wagner T et al (2015) Unilateral adrenalectomy as a first-line treatment of cushing's syndrome in patients with primary bilateral macronodular adrenal hyperplasia. J Clin Endocrinol Metab 100:4417–4424. https://doi.org/10.1210/jc.2015-2662
11. Nieman LK, Biller BMK, Findling JW, Newell-Price J, Savage MO, Stewart PM et al (2008) The diagnosis of cushing's syndrome: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 93:1526–1540. https://doi.org/10.1210/jc.2008-0125