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Primary aldosteronism with nonlocalizing imaging ☆

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ABSTRACT

Background: Unilateral primary aldosteronism is surgically curable. The goal of this study was to examine outcomes based on preoperative imaging findings.

Methods: We performed a retrospective analysis of patients with primary aldosteronism who underwent adrenal vein sampling. Patients were classified by imaging as localized (unilateral adrenal mass) or nonlocalized (no mass/bilateral masses). Outcomes were assessed as complete, partial, or absent clinical success.

Results: Of 446 patients, 74.9% were localized. There were no significant demographic or biochemical differences between groups; however the imaged tumor size was larger (median 1.3 vs 1.2 cm, $P = .038$), and rates of lateralizing adrenal vein sampling were higher (79.0% vs 62.2%, $P < .001$) in the localized group. Of 289 patients who underwent adrenalectomy, adenoma was the most common finding in both groups (79.7% vs 80.3% respectively, $P = .447$), but median tumor size was larger in localized patients (1.5 vs 1.0 cm, $P < .001$). Equivalent rates of partial (94.6% vs 91.7%, $P = .456$) and complete (8.7% vs 9.8%, $P = .801$) clinical success were observed. At long-term follow-up, nonlocalized patients experienced partial reversal of clinical improvement.

Conclusion: Primary aldosteronism patients with nonlocalizing imaging but lateralizing adrenal vein sampling benefit from adrenalectomy. Regardless of imaging findings, adrenal vein sampling is indicated to determine whether patients may be surgically curable.

Introduction

Primary aldosteronism (PA) is the most common cause of secondary hypertension in the United States, affecting approximately 10% of the hypertensive population and up to 23% of patients with resistant hypertension.[1–3] Diagnosis is predicated on biochemical testing of plasma aldosterone (PAC) and plasma renin activity (PRA), where an aldosterone to renin ratio (ARR) of greater than 30 is highly suggestive of PA.[4]

After a biochemical diagnosis is confirmed, cross-sectional imaging studies are typically performed to determine the cause of PA.[5] PA may be unilateral in up to half of cases and amenable to surgical cure; causes include aldosterone-producing adenoma and unilateral adrenal hyperplasia.[6] Bilateral adrenal hyperplasia (BAH) is managed medically with mineralocorticoid antagonists and potassium supplementation.

Although cross-sectional imaging technology continues to improve, the diagnostic performance of computed tomography (CT) scan and magnetic resonance imaging (MRI) is highly variable in the detection of unilateral causes of PA and may be particularly limited in detection of small adenomas; moreover, imaging cannot differentiate between an incidental, nonfunctional adrenal adenoma and a functional tumor.[6]

Adrenal venous sampling (AVS) is considered the standard of care for subtype differentiation in PA because 40%–50% of patients might be inappropriately managed, based on imaging findings alone.[7,8] However, reliable AVS is not universally available, and many published studies are limited by selective AVS referral or high AVS failure rates. The goal of this study is to examine a large PA cohort evaluated with both AVS and imaging and to compare outcomes in patients, based on imaging findings.

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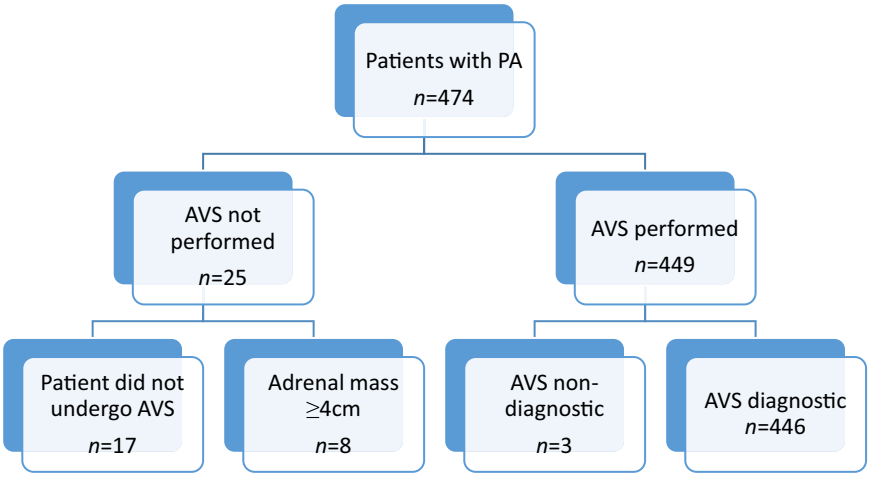


Fig 1. Consort diagram of study population.

Methods

Patients

Institutional review board approval was obtained from the University of Pennsylvania (Philadelphia). Patients who were evaluated at the Hospital of the University of Pennsylvania (1997–2017) with a diagnosis of PA and successful AVS were identified for inclusion in this study. A biochemical diagnosis of PA was defined as an elevated PAC in the setting of a suppressed PRA level, with an ARR of greater than 20 (ng/dL)/(ng/mL/hr). Confirmatory testing was performed at the discretion of the evaluating clinician, as clinically indicated, consistent with Endocrine Society Guidelines.[9] Of 474 patients identified, 446 (94.1%) underwent diagnostic AVS and were included in the final study population (Fig. 1). Of the 28 patients who were excluded from the final study cohort, only 3 had AVS attempted but unsuccessful. Eight patients' masses met size criteria for surgery, based on imaging (adrenal mass ≥4 cm) regardless of functional status, and 17 failed to undergo the recommended study.

Variables

Retrospective chart review was performed. Clinical and demographic data were analyzed. Standard blood pressure (BP) criteria were used, normal mean arterial pressure (MAP) was 70–110 mm Hg and hypertensive MAP was >110 mm Hg. Patients were classified by imaging as localized (unilateral adrenal mass with a normal contralateral adrenal gland) or nonlocalized (no mass or bilateral masses). Outcomes were assessed as complete, partial, or absent clinical success, consistent with the published definitions.[10] Hypokalemia was defined as serum potassium below normal levels, as assessed by individual laboratory normal range. Preoperative serum potassium levels were assessed on potassium supplementation. Postoperative serum potassium levels were assessed before hospital discharge, as described later in this report. Availability of postoperative renin and aldosterone levels was limited and was not assessed as a formal outcome measure.

Clinical management

Patients were managed with a multidisciplinary team consisting of surgery, nephrology, interventional radiology, and in consultation with the referring clinician. At the time of surgery, patients were maintained on continuous telemetry monitoring. Medication management was performed in consultation with nephrology and the referring physician, and medication regimens were tailored to the clinical situation. Potassium supplements were stopped at the time of surgery, and serum potassium levels were assessed daily while patients were admitted. On discharge, patients monitored and recorded blood pressure two to three times daily. Patients were evaluated two to three weeks postoperatively in the surgical clinic and at that time were transitioned to the care of nephrology or the referring physician for further management. Postoperative renin and aldosterone levels were evaluated at the discretion of the referring clinician.

AVS

AVS was performed using the modified Mayo protocol, as previously published.[11,12] AVS was considered technically successful with a selectivity index ([SI] defined as adrenal/caval cortisol) of ≥5. AVS was considered lateralizing with a lateralization index ([LI] defined as higher aldosterone/cortisol [A/C] ratio/lower A/C ratio) of ≥4. Patients with lateralizing AVS were referred for surgical management.

Statistics

Group comparisons were performed using the χ^2 test, Wilcoxon rank sum test, paired Student t test, or Fisher exact test, as appropriate. Univariate analysis was performed. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated to determine the relationship between imaging and the presence of an adenoma on final surgical pathology. Statistical analysis was performed using STATA 12.1 (STATA Corporation, College Station, TX). A P value of .05 was considered significant.

Results

Cohort characteristics

Of 446 patients with primary hyperaldosteronism and diagnostic AVS, 60% ($n = 268$) were male (Table I). The mean age was 53.5 ± 11.0 years, and median patient body mass index (BMI) was in the obese range, at 31.6 kg/m2 (IQR [interquartile range] 27.3–36.6). The median duration of patient-reported hypertension was 10.0 years (IQR 5.0–18.0), and patients were on a median number of 3 antihypertensive medications (IQR 2–4). At the time of evaluation, the majority 63.5% ($n = 283$) of patients were hypokalemic. The

Table I
Demographic and clinical characteristics of 446 patients with primary hyperaldosteronism and adrenal vein sampling

	N, median, or mean
Mean age, years (SD)	53.5 (11.0)
Male sex (%)	268 (60.1)
Median BMI, kg/m2 (IQR)	31.6 (27.3–36.6)
Median duration of hypertension, years (IQR)	10.0 (5.0–18.0)
Hypokalemia (%)	283 (63.5)
Median serum potassium level, mmol/l (IQR)	3.8 (3.4–4.2)
Median antihypertensive medications (IQR)	3 (2–4)
Mineralocorticoid receptor antagonist use (%)	265 (59.4)
Median PAC, ng/dl (IQR)	27.0 (17.8–40.9)
Median PRA, ng/ml/hr (IQR)	0.2 (0.1–0.4)
Median ARR, (ng/dl)/(ng/ml/hr) (IQR)	124.2 (67.5–233.5)
Tumor laterality on imaging	
Right (%)	111 (24.9)
Left (%)	223 (50.0)
Bilateral (%)	22 (4.9)
None (%)	90 (20.2)
Median tumor size on imaging, cm (IQR)	1.3 (1.1–1.9)
Lateralizing AVS (%)	333 (74.7)
Median lateralization index (IQR)	8.7 (3.3–20.8)

SD, standard deviation

median ARR was markedly elevated, at 124.2 (ng/dL)/(ng/mL/hr) (IQR 67.5–233.5).

On cross-sectional imaging, 74.9% ($n = 334$) patients had evidence of a unilateral mass. A total of 39 patients had unilateral masses less than 1 cm in size; the median tumor size in this subgroup was 0.8 cm. Bilateral masses were present in 4.9% ($n = 22$), and no masses were identified in 20.2% ($n = 90$). The median tumor size on imaging was 1.3 cm (IQR 1.1–1.9). AVS lateralized in 74.7% ($n = 333$) of patients, consistent with a unilateral source of aldosterone secretion. The median lateralization index was 8.7 (IQR 3.3–20.8).

Localization status

Patients were classified as localized ($n = 334$) or nonlocalized ($n = 112$) by cross-sectional imaging findings, and group comparisons were performed (Table II). There were no differences between localized and nonlocalized patients in age (mean 53.9 vs 52.4 years, respectively; $P = .236$) or sex distribution (male 60.8% vs 58.0%, $P = .608$). BMI trended toward lower values in the localized group as compared with the nonlocalized group (31.3 vs 34.5), although this did not achieve statistical significance ($P = .147$). The median duration of patient-reported hypertension was 10 years in both groups ($P = .519$), and there was no significant difference in the number of antihypertensive medications that patients were taking (3 medications in localized group vs 4 medications in nonlocalized group, $P = .140$).

Biochemical profiles were similar between groups, with the majority of patients having evidence of hypokalemia (75.4% in the localized group vs 73.4% in the nonlocalized group, $P = .706$), and the median ARR being similar between localized and nonlocalized patients (125.2 vs 118.9 [ng/dL]/[ng/mL/hr], $P = .499$).

In the localized group, AVS changed management in 29.6% ($n = 99$). AVS was discordant from imaging in 8.4% ($n = 28$), lateralizing to the contralateral side of the imaged mass. AVS was nonlateralizing in 21.3% ($n = 71$). The PPV of localization on imaging for lateralization to the ipsilateral side on AVS was 67.7%, with 81.0% sensitivity and 27.3% specificity. In patients 40 years of age or younger, a population in whom it has been suggested that AVS may not be necessary because of the higher predictive value of imaging, the PPV was 84.4%, with 77.6% sensitivity and 41.7% specificity.

Nonlocalized patients

Patients were considered nonlocalized if cross-sectional imaging identified bilateral adrenal masses (19.6%, $n = 22$), or no adrenal masses (80.4%, $n = 90$). The median tumor size detected on imaging was significantly larger in the localized group (1.3 cm) as compared with patients with bilateral tumors in the nonlocalized group (1.2 cm, $P = .038$). Patients with localization by imaging had significantly higher rates of lateralizing AVS (79.0% vs 62.2%, $P < .001$) and significantly higher median lateralization index levels (10.2 vs 5.0, $P < .001$) when compared with nonlocalized patients.

Operative findings

Of the 333 patients with lateralization on AVS, 289 underwent adrenalectomy at our institution; the remainder were excluded from the final analysis. The median lateralization index in the surgical cohort was 12.4 (IQR 6.5–24.2). Adrenalectomy was performed laparoscopically in 96.2% ($n = 278$) of cases; 5 cases were performed open, and 6 required conversion from laparoscopic to open surgery (Table III). Although the distribution of final surgical pathology was similar between localized and nonlocalized patients, with a single cortical adenoma being the most common finding in both groups (79.7% vs 80.3% respectively, $P = .447$), tumor size was significantly larger in the localized group (1.5 cm vs 1.0 cm, $P < .001$). A dominant adenoma in the setting of adrenal hyperplasia was present in 15.9% of localized patients vs 11.5% of nonlocalized patients; cortical hyperplasia without adenoma in 4.0% of localized and 8.2% of nonlocalized patients.

The combination of localization on preoperative imaging and lateralizing AVS had a 79% sensitivity but only 33% specificity for a cortical adenoma on final pathology (PPV 96%, NPV 8%). In patients 40 years of age or younger, the sensitivity was similar at 77%, with a PPV 97%; specificity was 50% and NPV was 8%.

Postoperative outcomes

Adrenalectomy was associated with a significant decrease in blood pressure and number of antihypertensive medications. In the surgical cohort, the mean MAP decreased 107.8 mm Hg preoperatively to 97.3 mm Hg 6 to 12 months after surgery ($P < .001$), and the mean number of antihypertensive medications similarly decreasing from 3.4 to 2.0 ($P < .001$) during the same period. Of note, at a median follow-up time of 24 months, the mean MAP stayed stable at 97.3 mm Hg, but the mean number of antihypertensive medications decreased slightly to 1.9. Although the overall rate of complete clinical success was relatively low (9%, $n = 26$), the overwhelming majority of patients (93.9%, $n = 155$) experienced partial clinical success.

Outcomes by localization status

Clinical outcomes were evaluated by localization status. Equivalent rates of complete clinical success (8.7% vs 9.8%, $P = .801$) were seen in localized and nonlocalized patients, respectively, and the majority of patients in both groups had long-term partial clinical success (94.6% vs 91.7%, $P = .456$). Within the cohort of 289 patients who underwent adrenalectomy, 76.5% ($n = 221$) were hypokalemic before surgery. Within the hypokalemic group, before hospital discharge, resolution of hypokalemia off potassium supplementation was observed in 90.5% ($n = 199$). There was no difference in rates of resolution of hypokalemia between the localized (89.1%) and nonlocalized (95.7%, $P = .260$) groups, and median serum potassium levels were equivalent (localized 3.8 mmol/L [IQR 3.4–4.2]; nonlocalized 3.9 mmol/L [IQR: 3.5–4.3], $P = .126$).

Table II
Group comparisons of clinical characteristics in localized and nonlocalized patients

	Localized ($n = 334$)	Nonlocalized ($n = 112$)	P value
Mean age, years (SD)	53.9 (10.8)	52.4 (11.4)	.236
Male sex (%)	203 (60.8)	65 (58.0)	.608
Median BMI, kg/m2 (IQR)	31.3 (27.2–35.9)	34.5 (27.8–37.8)	.147
Median duration of hypertension, years (IQR)	10 (7–20)	10 (5–16)	.519
Hypokalemia (%)	214 (75.4)	69 (73.4)	.706
Median serum potassium level, mmol/l (IQR)	3.8 (3.4–4.2)	3.9 (3.5–4.3)	.126
Median antihypertensive medications (IQR)	3 (2–4)	4 (2–5)	.140
Mineralocorticoid receptor antagonist use (%)	197 (66.8)	68 (72.3)	.314
Median PAC, ng/dl (IQR)	27.5 (18.0–41.0)	23.0 (17.0–39.9)	.228
Median PRA, ng/ml/hr (IQR)	0.2 (0.1–0.4)	0.2 (0.1–0.3)	.761
Median ARR, (ng/dl)/(ng/ml/hr) (IQR)	125.2 (70.6–232.0)	118.9 (58.3–233.5)	.499
Tumor laterality			<.001
Right (%)	111 (33.2)	–	
Left (%)	223 (66.8)	–	
Bilateral (%)	–	22 (19.6)	
None (%)	–	90 (80.4)	
Median tumor size on imaging, cm (IQR)	1.3 (1.1–1.9)	1.2 (0.9–1.5)	.038
Lateralizing AVS (%)	263 (79.0)	69 (62.2)	< .001
Median lateralization index (IQR)	10.2 (3.7–23.4)	5.0 (2.0–11.4)	< .001

SD, standard deviation

Table III
Operative findings in 289 patients undergoing adrenalectomy, by localization status

	Localized ($n = 228$)	Nonlocalized ($n = 61$)	P value
Operative approach			.706
Laparoscopic (%)	217 (95.2)	61 (100.0)	
Open (%)	5 (2.2)	0 (0.0)	
Laparoscopic converted to open (%)	6 (2.6)	0 (0.0)	
Median tumor size, cm (IQR)	1.5 (1.0–2.0)	1.0 (0.7–1.5)	< .001
Pathology			.447
Adenoma (%)	181 (79.7)	49 (80.3)	
Adenoma in the setting of hyperplasia (%)	36 (15.9)	7 (11.5)	
Nodular hyperplasia (%)	9 (4.0)	5 (8.2)	
Normal adrenal (%)	1 (0.4)	0 (0.0)	
Tumor laterality on pathology			.010
Right (%)	89 (39.0)	35 (57.8)	
Left (%)	139 (61.0)	26 (42.6)	

Within the group of 61 nonlocalized patients who underwent surgery, 4 required future potassium supplementation, likely because of the recurrence of PA; all 4 had initial resolution of hypokalemia. On the most recent follow-up, 2 of the 4 had resumed mineralocorticoid receptor antagonists.

Although there was no significant difference in preoperative MAPs between localized and nonlocalized patients (107.5 mm Hg vs 108.5 mm Hg, respectively; $P = .587$), localized patients required significantly fewer antihypertensive medications (3.3 vs 3.9, $P = .006$) to maintain this BP (Table IV). Both groups had improved BP control on fewer medications at the initial postoperative appointment, 2 weeks after surgery, and there was no significant difference between groups (Fig 2). From 6 to 12 months after surgery, however, the groups diverged. Although both groups maintained improved BP control (mean MAP 97.1 mm Hg in localized patients vs 98.1 mm Hg in nonlocalized patients, $P = .730$), localized patients required significantly fewer antihypertensive medications (1.3 vs 2.0, $P = .019$). This trend was even more prominent at long-term follow up, with localized patients maintaining or improving on BP control, with mean MAP 96.1 mm Hg, and nonlocalized patients experienced partial reversal of previous improvements, with a mean MAP increase to 101.3 mm Hg and a mean number of antihypertensive medications increasing to 2.4.

Discussion

It has been more than 60 years since Conn described PA in a report of a single case.[13] The understanding of the prevalence, pathophysiology, diagnosis, adrenal pathology, and treatment of PA has changed markedly in recent decades. PA was considered to be a rare cause of surgically correctable hypertension 50 years ago, accounting for as low as 0.05% of cases, and no more than 1% of cases of refractory hypertension.[14] Recent reports conclude that 10%–20% of patients with refractory hypertension have PA.[1,2] A multicenter Italian study reported that 11.2% of 1,125 consecutively screened patients referred for hypertension had PA.[3] Hypokalemia, once thought to be a cornerstone of the diagnosis of PA, has been found to be less common than previously believed. In the Italian study, <10% of patients were hypokalemic. This shift in understanding may contribute to increased prevalence of PA. In addition to now being recognized as a relatively common cause of hypertension, several studies have clearly documented that long-term end-organ damage is significantly increased in patients with PA compared with patients with essential hypertension.[15,16]

Because of the awareness of the increased prevalence and appreciation of the harmful effects of PA, minimally invasive procedures now allow surgical correction of PA to be accomplished with low morbidity and expense. The benefits of surgical correction of the abnormal biochemical profile in PA has been well documented by our group and others.[17–19] The decrease or elimination of antihypertensives significantly improves the quality of life for patients and decreases end-organ damage over time and is the most cost-effective strategy.[20,21] All studies identify early intervention in the course of the disease as a key variable to maximize beneficial outcomes.[17,19,22] Because PA is virtually never associated with malignant adrenal pathology, the only goal of surgical therapy is to re-

Table IV
Postoperative outcomes, by localization status

	Localized ($n = 231$)	Nonlocalized ($n = 61$)	P value
Preoperative			
Mean MAP, mm Hg (SD)	107.5 (13.2)	108.5 (14.5)	.587
Mean number AHM (SD)	3.3 (1.3)	3.9 (1.7)	.006
2 weeks postoperative			
Mean MAP, mm Hg (SD)	99.6 (11.3)	103.4 (11.7)	.112
Mean number AHM (SD)	1.8 (1.3)	2.0 (1.5)	.441
6–12 month follow-up			
Mean MAP, mm Hg (SD)	97.1 (9.7)	98.1 (9.4)	.730
Mean number AHM (SD)	1.8 (1.3)	2.8 (2.0)	.019
Long-term follow-up			
Median follow-up, months (IQR)	20.0 (6.0, 68.0)	33.0 (16.0, 50.0)	.292
Mean MAP, mm Hg (SD)	96.1 (10.1)	101.3 (13.7)	.014
Mean number AHM (SD)	1.7 (1.4)	2.4 (1.7)	.029
Resolution of hypokalemia (%)	155 (89.1)	44 (95.7)	.260
Median serum potassium level, mmol/l (IQR)	3.9 (3.7–4.3)	3.9 (3.7–4.2)	.733
Partial clinical success (%)	122 (94.6)	33 (91.7)	.456
Complete clinical success (%)	20 (8.7)	6 (9.8)	.801

SD, standard deviation; *AHM*, antihypertensive medications

verse the clinical profile. The two choices for treatment are medical management, which does not reverse long-term side effects and has associated medication side effects or surgical correction of PA.

After establishing the definitive biochemical diagnosis of PA, determining the pathologic processes in the adrenal tissue causing this abnormality is determined by a combination of cross-sectional imaging and AVS. Many groups, including our own, have reported that changes in surgical management when performing AVS after cross-sectional imaging can be as high as 50% of patients.[7,8] The most recent published guidelines from the Endocrine Society recommend performing AVS in all patients with PA except those younger than 35 years of age with an imaged adrenal mass >1.0 cm.[9] The primary focus of the current study is the specific patient population with PA who have no evidence of localizing adrenal abnormality on a CT scan. Although practice guidelines would recommend performing AVS for this group of patients, the reality of limited access to AVS and the assumption that this large group of patients have BAH after negative imaging by managing physicians means that this population defaults to medical management.

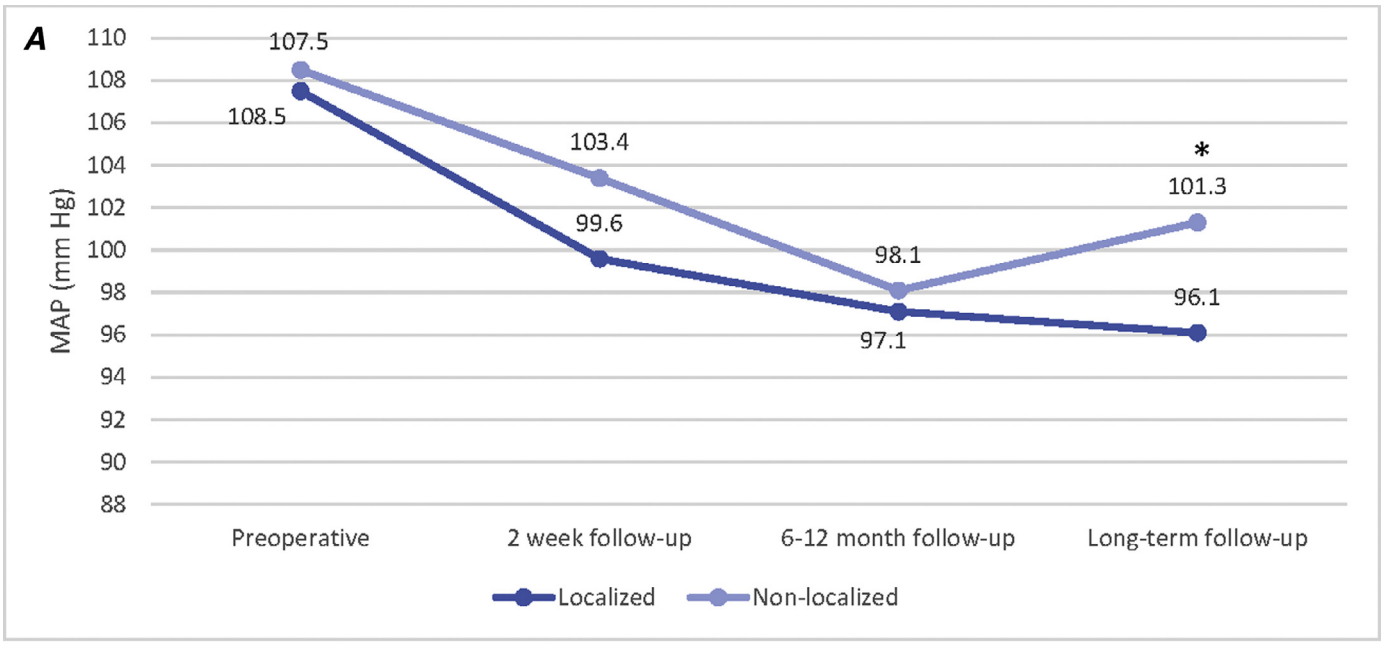
At our large referral center, 90 patients out of a population of 446 (20.2%) had definitive PA and no evidence of adrenal pathology on CT or MRI. In this group of 90 patients, 61 had lateralization on AVS, leading to successful minimally invasive adrenalectomy in all 61 patients. Greater than two-thirds of the imaging negative patients (67.8%) benefitted from AVS, which accounts for 13.7% of the total population. Although this number seems to be a relatively small subset of a large group of PA patients at a tertiary referral center, it bears emphasis that the majority of patients with PA are referred into our system by outside cardiologists, nephrologists, endocrinologists, and primary care physicians. It remains unknown how many patients with PA and negative imaging are never referred for AVS because of the assumption that these patients have BAH. If managing physicians were aware that more than two-thirds of imaging negative patients could benefit from minimally invasive surgery for a unilateral cause of PA, imaging negative patients would likely account for a higher proportion of the total cohort.

Analysis of the demographics, biochemical profile, clinical profile of hypertension, and treatment are essentially identical between the localized and nonlocalized groups of patients with PA (Table II). Somewhat surprising is the equivalence of pathologic findings of a distinct adenoma in patients who were localized (79.7%) versus nonlocalized (80.3%) as with negative imaging the pathologic diagnosis of unilateral hyperplasia would be expected to be significantly higher. The fact that the median tumor size is significantly smaller in the nonlocalized group ($P < .001$, Table III) is completely expected; however, the median tumor size of 1.0 cm may be surprising in patients with negative imaging.

One potential criticism of this study is that a more directed fine-cut CT or MRI imaging protocol could have possibly identified lesions in a portion of the nonlocalized group, as surgical pathology demonstrated that small tumors were present in this group. The response to that criticism would have 2 components. First, the negative imaging report that defines this patient population is the information given to referring physicians managing this patient population, and therefore initial referral decisions are based on nondedicated imaging. Second, the current study is not an imaging protocol in that no patient had additional cross-sectional imaging with an alternative technique, which also reflects our institutional bias to perform AVS on virtually all patients regardless of imaging results.

A second difference between these two patient populations is that, despite immediate equivalent postoperative benefit, the nonlocalized patients seem to derive less long-term benefit measured by need for antihypertensive medications at greater than 6 months postoperatively and becoming more divergent at later points. One possible explanation for this finding is that these are not equivalent patient populations. The nonlocalized patients required significantly more antihypertensives preoperatively and, although having reported similar duration, the disease may have had increased severity reflected only by number of medications. A second more interesting explanation may be that this image negative group has a subset of patients with asymmetric BAH. The pathology data suggest that there are twice as many patients with nodular hyperplasia without an adenoma in the nonlocalized group. One limitation of this study is that we do not have biochemical profiles on the patients with long-term follow-up to comment on the possible biochemical recurrence of PA. Recent data on the histology of PA suggest a polyclonal or multifocal process, even in patients who have a dominant aldosterone-producing adenoma. Staining for aldosterone synthase with CYP11B2 suggests multiple nests of increased aldosterone in the zona glomerulosa, with cases of a clear transition to a dominant adenoma.[23,24] Because we virtually never operate for BAH, we do not know whether a similar process is occurring bilaterally.

A recently reported randomized trial for patients with PA, comparing CT with AVS, argued that there is no benefit for AVS.[25] The SPARTACUS trial (Subtyping Primary Aldosteronism: A Randomized Trial Comparing Adrenal Vein Sampling and Computed Tomographic Scans) randomized 180 patients with PA and hy-



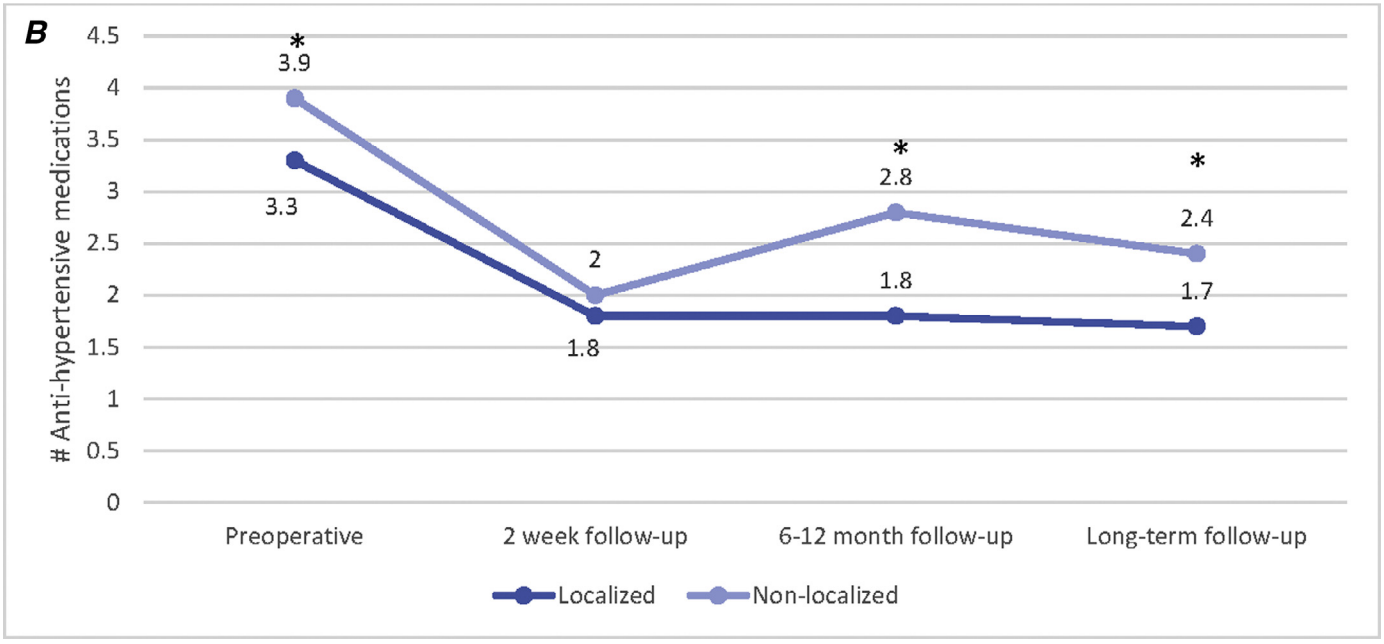


Fig 2. (*A*) Postoperative blood pressure and (*B*) antihypertensive medication outcomes, by localization status. Statistically significant difference between groups at individual time points is denoted by*.

pokalemia to either CT or AVS with no crossover. Exactly half of each arm ended up having surgery, with a slightly higher cure rate in the AVS arm. The authors concluded that there was no role for obtaining the expensive and challenging AVS in PA. This study has been criticized on many fronts. First, because it is a random assignment trial, each arm would have identical pathology, so the overall incidence of unilateral cause of PA should be the same. Given our data, one would expect that one-third of the 45 patients in the CT arm may have a positive AVS and benefit from surgery. There was a trend toward long-term benefit in the AVS arm, but the lack of significance is likely attributable to low patient number.

An Italian study, screening for PA in patients with refractory hypertension in 14 centers, included 5 locations where AVS was performed and 9 where it was not available.[3] In the centers where AVS was available the final pathologic diagnosis was 63% adenoma and 37% BAH. Conversely, in the centers with no AVS and imaging only, the findings were reversed, with only 32% adenomas and 68% BAH. Although nonrandomized, there is no reason to believe that the patient population at any of the locations would be different. These results support our contention that there are large populations with PA who have unilateral disease that are denied the prospect of beneficial surgery without AVS.

This study is inherently limited because of its retrospective nature. A subset of this study population has been previously published; this study adds 101 patients with diagnostic AVS, of whom 72 underwent adrenalectomy.[8] Outcomes were assessed as clinical resolution, and therefore the increase in antihypertensive medica-

tions observed in the nonlocalized cohort may reflect either essential hypertension or biochemical recurrence, as discussed earlier in this report. Furthermore, granular data on individual medications and dosages were not analyzed in this data set. These represent further potential areas of study.

In summary, more than two-thirds of patients with PA and negative cross-sectional imaging have clear lateralization on AVS and benefit from adrenalectomy. Although cross-sectional imaging is often recommended after initial biochemical diagnosis and AVS may be performed selectively based on imaging findings, this study indicates that all PA patients should be referred to a center performing AVS, regardless of imaging. Our group has argued that AVS may even precede CT as the initial diagnostic maneuver.[12] Although Endocrine Society guidelines agree with performing AVS in the large majority of these patients,[9] it is possible that negative imaging is equivalent to a diagnosis of BAH in the minds of managing physicians. This report provides objective data that image negative patients with PA should be referred to experienced centers for AVS.

In conclusion, PA accounts for a large portion of patients with refractory hypertension in the United States. These patients suffer significant morbidity even with medical management. Minimally invasive adrenalectomy is an extremely safe and well-tolerated procedure that has been shown to be highly beneficial. All patients with PA and negative imaging should have AVS to allow surgery in the subgroup of this population with unilateral disease.

References

1. Calhoun DA. Hyperaldosteronism as a common cause of resistant hypertension. *Ann Rev Med*. 2013;64:233–247.
2. Douma S, Petidis K, Doumas M, Papaefthimiou P, Triantafyllou A, Kartali N, et al. Prevalence of primary hyperaldosteronism in resistant hypertension: A retrospective observational study. *Lancet*. 2008;371:1921–1926.
3. Rossi GP, Bernini G, Caliumi C, Desideri G, Fabris B, Ferri C, et al. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. *J Am Coll Cardiol*. 2006;48:2293–2300.
4. Harris DA, Au-Yong I, Basnyat PS, Sadler GP, Wheeler MH. Review of surgical management of aldosterone secreting tumours of the adrenal cortex. *Eur J Surg Oncol*. 2003;29:467–474.
5. Zeiger MA, Thompson GB, Duh QY, Hamrahian AH, Angelos P, Elaraj D, et al. The American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons medical guidelines for the management of adrenal incidentalomas. *Endocr Pract*. 2009;15(Suppl 1):1–20.
6. Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, et al. Case detection, diagnosis, and treatment of patients with primary aldosteronism: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2008;93:3266–3281.
7. Mathur A, Kemp CD, Dutta U, Baid S, Ayala A, Chang RE, et al. Consequences of adrenal venous sampling in primary hyperaldosteronism and predictors of unilateral adrenal disease. *J Am Coll Surg*. 2010;211:384–390.
8. Wachtel H, Zaheer S, Shah PK, Trerotola SO, Karakousis GC, Roses RE, et al. Role of adrenal vein sampling in primary aldosteronism: Impact of imaging, localization, and age. *J Surg Oncol*. 2016;113:532–537.
9. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, et al. The management of primary aldosteronism: Case detection, diagnosis, and treatment: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;101:1889–1916.
10. Williams TA, Lenders JWM, Mulatero P, Burrello J, Rottenkolber M, Adolf C, et al. Outcomes after adrenalectomy for unilateral primary aldosteronism: An international consensus on outcome measures and analysis of remission rates in an international cohort. *Lancet Diabetes Endocrinol*. 2017;5:689–699.
11. Trerotola SO, Asmar M, Yan Y, Fraker DL, Cohen DL. Failure mode analysis in adrenal vein sampling: A single-center experience. *J Vasc Interv Radiol*. 2014;25:1611–1619.
12. Asmar M, Wachtel H, Yan Y, Fraker DL, Cohen D, Trerotola SO. Reversing the established order: Should adrenal venous sampling precede cross-sectional imaging in the evaluation of primary aldosteronism? *J Surg Oncol*. 2015;112:14—8.
13. Conn JW, Louis LH. Primary aldosteronism: A new clinical entity. *Trans Assoc Am Physicians*. 1955;68:215–231 discussion, 31–3.
14. Gyamlani G, Headley CM, Naseer A, Valaulikar GS, Geraci SA. Primary aldosteronism: Diagnosis and management. *Am J Med Sci*. 2016;352:391–398.
15. Tanabe A, Naruse M, Naruse K, Hase M, Yoshimoto T, Tanaka M, et al. Left ventricular hypertrophy is more prominent in patients with primary aldosteronism than in patients with other types of secondary hypertension. *Hypertens Res*. 1997;20:85–90.
16. Rossi GP, Bernini G, Desideri G, Fabris B, Ferri C, Giacchetti G, et al. Renal damage in primary aldosteronism: Results of the PAPY Study. *Hypertension*. 2006;48:232–238.
17. Wachtel H, Cerullo I, Bartlett EK, Kelz RR, Cohen DL, Karakousis GC, et al. Long-term blood pressure control in patients undergoing adrenalectomy for primary hyperaldosteronism. *Surgery*. 2014;156:1394–1402 discussion 402–3.
18. Hennings J, Andreasson S, Botling J, Hagg A, Sundin A, Hellman P. Long-term effects of surgical correction of adrenal hyperplasia and adenoma causing primary aldosteronism. *Langenbecks Arch Surg*. 2010;395:133–137.
19. Lumachi F, Ermani M, Basso SM, Armanini D, Iacobone M, Favia G. Long-term results of adrenalectomy in patients with aldosterone-producing adenomas: Multivariate analysis of factors affecting unresolved hypertension and review of the literature. *Am Surg*. 2005;71(10):864–869.
20. Velema M, Dekkers T, Hermus A, Timmers H, Lenders J, Groenewoud H, et al. Quality of life in primary aldosteronism: A comparative effectiveness study of adrenalectomy and medical treatment. *J Clin Endocrinol Metab*. 2018;103:16–24.
21. Lubitz CC, Economopoulos KP, Sy S, Johanson C, Kunzel HE, Reincke M, et al. Cost-effectiveness of screening for primary aldosteronism and subtype diagnosis in the resistant hypertensive patients. *Circ Cardiovasc Qual Outcomes*. 2015;8:621–630.
22. Zarnegar R, Young Jr WF, Lee J, Sweet MP, Kebebew E, Farley DR, et al. The aldosteronoma resolution score: Predicting complete resolution of hypertension after adrenalectomy for aldosteronoma. *Ann Surg*. 2008;247:511–518.
23. Gioco F, Seccia TM, Gomez-Sanchez EP, Rossi GP, Gomez-Sanchez CE. Adrenal histopathology in primary aldosteronism: Is it time for a change? *Hypertension*. 2015;66:724–730.
24. Nishimoto K, Koga M, Seki T, Oki K, Gomez-Sanchez EP, Gomez-Sanchez CE, et al. Immunohistochemistry of aldosterone synthase leads the way to the pathogenesis of primary aldosteronism. *Mol Cell Endocrinol*. 2017;441:124–133.
25. Dekkers T, Prejbisz A, Kool LJS, Groenewoud H, Velema M, Spiering W, et al. Adrenal vein sampling versus CT scan to determine treatment in primary aldosteronism: An outcome-based randomised diagnostic trial. *Lancet Diabetes Endocrinol*. 2016;4:739–746.

Discussion

Dr. Quan-Yang Duh (San Francisco, CA): It's a really wonderful study. I want to ask a question about the pathogenesis of the disease. Way back 30 or 40 years ago, the aldosteronomas that we saw were much bigger.

In fact, in our own institution, the patients who were treated for hyperaldosteronism surgically then had bigger tumors, like 1.5 or 2 centimeters. Nowadays, we see them much smaller. And the thinking is that we are making the diagnosis earlier, and therefore that's why they are smaller. But a competing hypothesis is that there's a broad spectrum of patients, and we were just seeing the more severe ones for surgery. Perhaps the nonlocalized patients are the ones with less severe disease.

With your data, can you tell me which one of those hypotheses is more likely, that there is a disease process in which the tumors get bigger and bigger, and you catch them in the later stages, or is it that there's a spectrum of disease, with patients that are different from the very beginning?

Dr. Heather Wachtel: I think it's a really interesting question and you are really getting to the crux of the physiology. I have been keeping our databases for only a short time, but we have actually seen a trend over time toward smaller tumors. When I first started, the median tumor size was 1.8 cm. It's now 1.5 cm in our operative patients. I was actually very surprised when I analyzed the data and there wasn't a discrepancy between the two groups

in terms of the duration of hypertension, since that's what I was expecting.

I think there's been some stellar work in parallel to what's happening with primary hyperparathyroidism, where we are catching the disease at earlier stages and potentially finding smaller tumors. But I also think there's this entity that we haven't really well characterized, which may potentially be asymmetric hyperplasia of the adrenal glands. We do see a trend toward lower lateralization index and they may be recurring a little bit earlier. I think if we carried out this study after another couple of years, we would find that more of these patients are recurring with nodularity on the contralateral side. So they probably had asymmetric hyperplasia, and removing one adrenal gland unmasked that and they are probably going to recur.

Honestly, I think we still made a difference for them and we have improved their blood pressure control. Dr Lubitz at MGH has done some fantastic work showing that this is cost-effective for patients even if they get a very small improvement in their blood pressure measurements.

So, I hope that we are still doing good by doing these operations, but I think that our understanding of this disease process will continue to evolve.

Dr. Barbra Miller (Ann Arbor, MI):

You have highlighted one of the limitations of your study, which is not having the biochemical data to document cure. We have found that information to be incredibly important. We presented our work at the IAES meeting in Basel over the summer, and we looked at what our criteria for cure were early on in 2005 and 2010. Now that the PASO criteria have come out, there's a very big difference in the cure rates contingent on definitions. And the key, I think, is the biochemical cure, not just the apparent clinical cure. We have got to document aldosterone and renin levels afterward, and we know those change over time, as well. It's important to follow things, out not only at 2weeks but 3 to 6 months and then finally at a year, because it will change over time.

As for some of your patients, I think you had eight, that had tumors that were greater than 4 centimeters, we have also found that you can have co-secretion of cortisol, especially as the tumors get bigger. This can throw off your AVS, so you have to consider that when you are thinking about which gland to take out, and whether or not you are going to actually cure their hyperaldosteronism. It may be coming from the other side and they may have bilateral secretion.

I wanted to know if you checked routinely what their cortisol levels were, or whether you did a dexamethasone suppression test?

My second question regards your documentation of the blood pressure and changes in medication. Just categorizing the number of medications doesn't take into account the dosage or the drug type. And I would encourage everyone as we go forward in reporting this information to truly understand what the impact is on blood pressure medication. The World Health Organization has a daily drug dosage calculator that you can use that takes all of that into account.

I will say that we have been doing IHC on our tumors, and a lot of the adenomas that are on the side that we take out actually don't have aldosterone-producing cells in them. They are elsewhere in that gland. So, just because there's an adenoma and they lateralized to that side doesn't mean that's exactly where the aldosterone is coming from.

Dr. Heather Wachtel: Those are very interesting and important points. In addressing your first question, we do routinely send all functional studies for any large adenomas where we don't have documentation of functional status. So, part of our routine workup for a functional study includes metanephrines to rule out pheochromocytoma, renin activity, and aldosterone levels, to investigate possible hyperaldosteronism. We also do cortisol and ACTH levels, and then, at the discretion of the referring clinician, we will work with them to perform a dexamethasone suppression test. We don't routinely order those ourselves.

We only send androgens selectively in conjunction with a suspicious clinical picture.

Dr. Barbra Miller (Ann Arbor, MI): But did any of your patients co-secrete cortisol?

Dr. Heather Wachtel: None of the patients in this study co-secreted cortisol. We actually have a separate database for our Cushing's patients as well.

Dr. Barbra Miller (Ann Arbor, MI): Do you check that in everybody?

Dr. Heather Wachtel: We check cortisol for every adrenal mass.

Dr. Barbra Miller (Ann Arbor, MI): But not dexamethasone suppression tests on everybody?

Dr. Heather Wachtel: Not dexamethasone suppression on everybody. We would not do that if they had a paired ACTH and cortisol which are completely normal and no clinical signs or symptoms of Cushing's syndrome.

Dr. Barbra Miller (Ann Arbor, MI): I would say that you are probably missing out on some of those patients, especially the ones with bigger adrenal masses.

Dr. Heather Wachtel: It's possible we may be, and I think that's an important point moving forward.