



Diagnostic Efficacy of CT/MR Imaging and Adrenal Vein Sampling for Localization of Aldosterone-producing Adrenal Adenomas in Primary Aldosteronism

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Abstract

Objective: To test the sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of CT/MR imaging and adrenal vein sampling (AVS) for diagnosis of aldosterone-producing adrenal adenoma (APA).

Material and method: Retrospective study of 14 patients with primary hyperaldosteronism (PAL) who underwent both CT/MR imaging and AVS between June 2007 and June 2012 were performed. The study included 7 male and 7 female patients. Review CT/MR findings of these cases and compared with AVS results were done.

Results: Five of fourteen patients (35%) had unilateral adrenal nodules on CT, and one of fourteen patients (7.1%) had bilateral adrenal nodules on CT[D1]. The remaining eight patients had no significant nodules in both adrenal glands.

Among 5 patients who had unilateral adrenal nodule detected from CT, 4 patients (80%) with nodule greater than 10 mm also presented with lateralization from AVS and finally pathological proven APA. The last patient with unilateral nodule showed small size less than 10 mm and had AVS results of bilateral lesion. Medical therapy was applied for this patient instead of surgical treatment.

In other group (8 of 14 patients, 57.1%), there was no significant nodule from CT or MRI and AVS results indicated bilateral lesions in two patients (25%). The rest of six patients found unilateral lesion on AVS which underwent adrenalectomy and histological revealed adrenal hyperplasia of all cases. Two of six patients concluded to be primary adrenal hyperplasia (PAH) or unilateral adrenal hyperplasia (UAH), which showed clinical cure after adenalectomy. The remaining four patients who showed no improvement of hypertension after adrenalectomy concluded to be bilateral adrenal hyperplasia (BAH).

The sensitivity, specificity, accuracy, PPV and NPV for detected adrenal adenoma by CT/MRI of our study were 66.67%, 87.50%, 78.57%, 80.00%, and 77.78%, respectively. The sensitivity, specificity, accuracy, PPV and NPV for detected adrenal adenoma by AVS at cut point AVS ratio at 2 were 100%, 50%, 71.43%, 60% and 100%, respectively.

Conclusion: In patient with suspected PAL who presented with unilateral adrenal nodule at least 10 mm in size detected by CT, these patient should be referred for adrenalectomy without need to performing AVS. The differentiation of subtype in patients with PAL is most reliably achieved with AVS which may reserve for patient who had no significant adrenal nodule from CT/MRI.

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Introduction

Primary aldosteronism (PAL) is defined as secondary hypertension accompanied by aldosterone hypersecretion leading to suppressed plasma renin, resulting in hypertension and usually hypokalemia. It is accounted for 3-15% of all hypertensive patients⁽¹⁾. Two most common causes of PAL include aldosterone-producing adrenal adenoma (APA, or Conn's syndrome) and bilateral adrenal hyperplasia (BAH) which account for over 95% of all cases⁽²⁾. It is important to differentiate between APA and BAH because of different in treatment techniques. APA should be treated surgically, whereas bilateral adrenal hyperplasia is best managed medically⁽³⁾. The rare entity of PAL is primary adrenal hyperplasia (PAH) or unilateral adrenal hyperplasia (UAH) which physiologically and biochemically mimics APA and also still has benefit from surgery⁽⁴⁾.

Several techniques have been used as the pre-operative identification of unilateral disease including APA and PAH, included computed tomography, MR imaging and adrenal venous sampling.

Computed tomography (CT) is the modality of choice for the detection of APA. It is a fast, easily accessible and non-invasive investigation with sensitivity, specificity and accuracy varying from 53-100%, 33-100% and 37-86%, respectively. The CT characteristics of adrenal adenoma is low density on CT scan (<10 Hounsfield units) due to high intracellular lipid content⁽²⁾. Many studies employ CT attenuation and washout value to differentiate adrenal adenoma and non adenoma⁽⁵⁾. However, up to 20% of APA has been reported as being smaller than 1 cm and CT scan might miss these nodules. In contrast, CT scan may identify a non secreting nodule in patients with BAH as an APA⁽⁶⁾.

Magnetic resonance imaging (MRI) has the

advantage of superior soft-tissue contrast resolution and lack of ionizing radiation. Disadvantages include higher cost, longer scanning time, poorer spatial resolution compared with CT⁽²⁾. Chemical shift imaging quantitatively assesses lipid content in tissue that has close relationship between lipid content and the functional aspect of adrenocortical lesions. It has been suggested that chemical shift image may enable better differentiation between APAs and nonfunctional adenomas from MRI than Hounsfield unit measurement from CT scan⁽⁷⁾. However, some studies⁽⁸⁾ suggested that chemical shift imaging could not help in the differentiation among functional and non functional adrenal adenoma, because both were found to contain lipid without significant differences in appearance⁽²⁾. Adrenal vein sampling (AVS) was initially described in 1967 to aid determination of the sub-type of primary aldosteronism and to differentiate between unilateral and bilateral production of aldosterone, with sensitivity approaching 100%^(1,2). However, this procedure is invasive, difficult technique especially the right renal vein catheterization and this procedure also requires long fluoroscopy time, which exposes patient to high radiation exposure. The success rate depends on the angiographer's experience and failure rate is as high as 30%⁽⁹⁾. And there are reported complications of AVS such as venous extravasations, hemorrhage and adrenal vein thrombosis⁽²⁾.

Aim of this study is try to compare efficacy of CT and/or MRI and AVS in differentiation of PAL.

Material and Methods

Retrospective analysis of all patients with secondary hypertension who were biochemically suspected to be PAL and underwent both CT/MR imaging and adrenal vein sampling in our hospital

from June 2007 to June 2012. Five patients were excluded from the study due to failure to identify right adrenal vein and three patients were excluded due to unavailability of CT or MRI. Total fourteen patients were included in this study.

Computed tomography was performed in all cases with standard, contiguous 5 mm slice thickness obtained using 16-channel (Sensation16, Siemens, Cleveland, OH) and 320-channel (Aquilion One Dynamic Volume CT, Toshiba Medical System, Tochigi-ken, Japan) CT scanners. All cases had pre contrast and post contrast enhanced CT imaging of adrenal glands. Two-mm slice thickness was generated in most of cases. Pre contrast studies were reviewed in which low density (<10 Hounsfield units) nodule indicated lipid rich adenoma. If adrenal adenoma was not diagnosed with pre contrast CT, contrast enhanced CT would be used to determine their enhancement. If relative washout value is more than 40% or absolute washout value is more than 60%, lipid poor adrenal adenoma is suggested. Morphology of both adrenal glands were analyzed and described as “normal” if the adrenal glands were normal, “plump” if its edges lose concavity and “nodule” if a circular adrenal lesion was detected. Size of nodule was recorded in millimeter (mm). A macronodule was a nodule that size is at least 10 mm.

One case underwent MR imaging for adrenal gland using 3 Tesla system (Achieva 3T, Philips Medical System, Best, the Netherlands) generally consists of axial T1 gradient echo in-phase and out-of-phase and axial T2-weighted with fat suppression sequences. Chemical shift imaging sequence was used to differentiate adrenal mass.

AVS was performed in all cases. Blood samples were obtained from bilateral adrenal veins and infe-

rior vena cava (IVC) for cortisol and aldosterone measurements. Successful AVS was determined by at least double elevation in adrenal vein cortisol levels compared with IVC level. Lateralization criteria or unilateral aldosterone hypersecretion were defined as followed (1) the ratio of adrenal vein aldosterone concentration to the homolateral cortisol concentration on the side with higher ratio over the contralateral aldosterone to cortisol ratio (AVS ratio) was greater than 2. (2) The aldosterone/cortisol (A/C) ratio of the non-dominant adrenal vein was less than that of the IVC⁽¹⁰⁾.

Definition of primary aldosteronism sub-type

1. Aldosterone-producing adenoma (APA) was defined by concordant results between the unilateral adrenal nodule detected by CT or MRI and lateralized aldosterone production as assessed by AVS which are finally pathological proven.

2. Primary adrenal hyperplasia (PAH)/Unilateral adrenal hyperplasia (UAH) was defined by normal, unilateral or bilateral plump on CT, and lateralized aldosterone production as assessed by AVS.

3. Bilateral adrenal hyperplasia (BAH) was defined by normal or bilateral CT abnormalities and bilateral aldosterone secretion or unilateral aldosterone secretion on AVS that clinical is not improvement after adrenalectomy⁽¹²⁾.

A final diagnosis of APA and PAH/UAH was considered proven, providing that all the following conditions were satisfied:

- 1) Histological proven of adenoma
- 2) Normalization of hypokalemia if present
- 3) Cure or improvement of hypertension. Cure of hypertension was defined as normal blood pressure level without treatment; improvement was defined as achievement of normal blood pressure with

a reduced number of drugs, compared with the number before adrenalectomy.

Patient characteristics were reported descriptive analysis. Efficacy of CT/MRI and AVS were evaluated and reported as sensitivity, specificity, accuracy, NPV and PPV.

Results

The medical records of 14 included patients were reviewed. There are 7 men and 7 women with mean age of 58 years for men (43-69 years) and 43 years for women (13-65 years).

Five of 14 patients (35%) had unilateral adrenal nodules on CT, and one of fourteen patients (7.1%) had bilateral adrenal nodules on CT. The remaining patients had no significant nodules in both adrenal glands (Fig 1).

In five patients who had unilateral adrenal nodules on CT, 4 patients (80%) had nodule greater than 10 mm and also had lateralization from AVS. These patients underwent adrenalectomy, which were pathological proven adrenal adenoma. Two of them had unilateral lipid rich adenoma (Fig 2). Other two had unilateral lipid poor adenoma. The last patient in this group who had unilateral nodule less than 10 mm from CT, AVS result indicates bilateral lesions (Fig 3). Medical therapy was applied for this patient instead of surgical treatment.

In other 8 patients (57.1%) which CT scan/MRI showed no detectable nodule, 2/8 patients had AVS result of bilateral diseases and received medical therapy with clinical improvement later. The other six patients found unilateral disease on AVS which underwent adrenalectomy and histological revealed adrenal hyperplasia. Two of 6 patients showed improvement of hypertension after adrenalectomy which diagnosis of UAH/PAH (Fig 4). The remaining

four patients were not improved after adrenalectomy.

The result of 4 of 8 patients (50%) may have inappropriate treatment from AVS when AVS cutoff ratio is at 2 (Fig 5).

The sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of CT/MRI to detect APA were 66.67%, 87.50%, 78.57%, 80.00%, and 77.78%, respectively. The sensitivity, specificity, accuracy, PPV and NPV of AVS at ratio cut point 2 to detect APA were 100%, 50%, 71.43%, 60% and 100%, respectively. When increased AVS ratio cut point to 4, the specificity, accuracy and PPV increased to 87.5%, 92.8%, and 85.7%, respectively (table 1).

Discussion

Patients with a bilateral source of excess aldosterone secretion should undergo pharmaceutical therapy⁽¹²⁾. AVS is a difficult procedure that may not be available in many general hospitals and typically require interpretation from experts so it may not always be the gold standard for diagnosing primary hyperaldosteronism. Our study showed that 22.7% of patients had incomplete AVS due to the difficulties in right adrenal vein catheterization similar to prior literatures^(9,10), the catheterization failure ranges from 10 to 30%.

To our understanding, CT is less sensitive in assessment of lesion localization compared to AVS, which can cause improper management in PAL. Two of 14 patients (14%) demonstrated no nodule from CT whereas AVS indicated lateralization. The patients were performed adrenalectomy and proven unilateral adrenal hyperplasia. However, our study showed lower percentage of inappropriate management in PAL than the prior literatures. Prior study

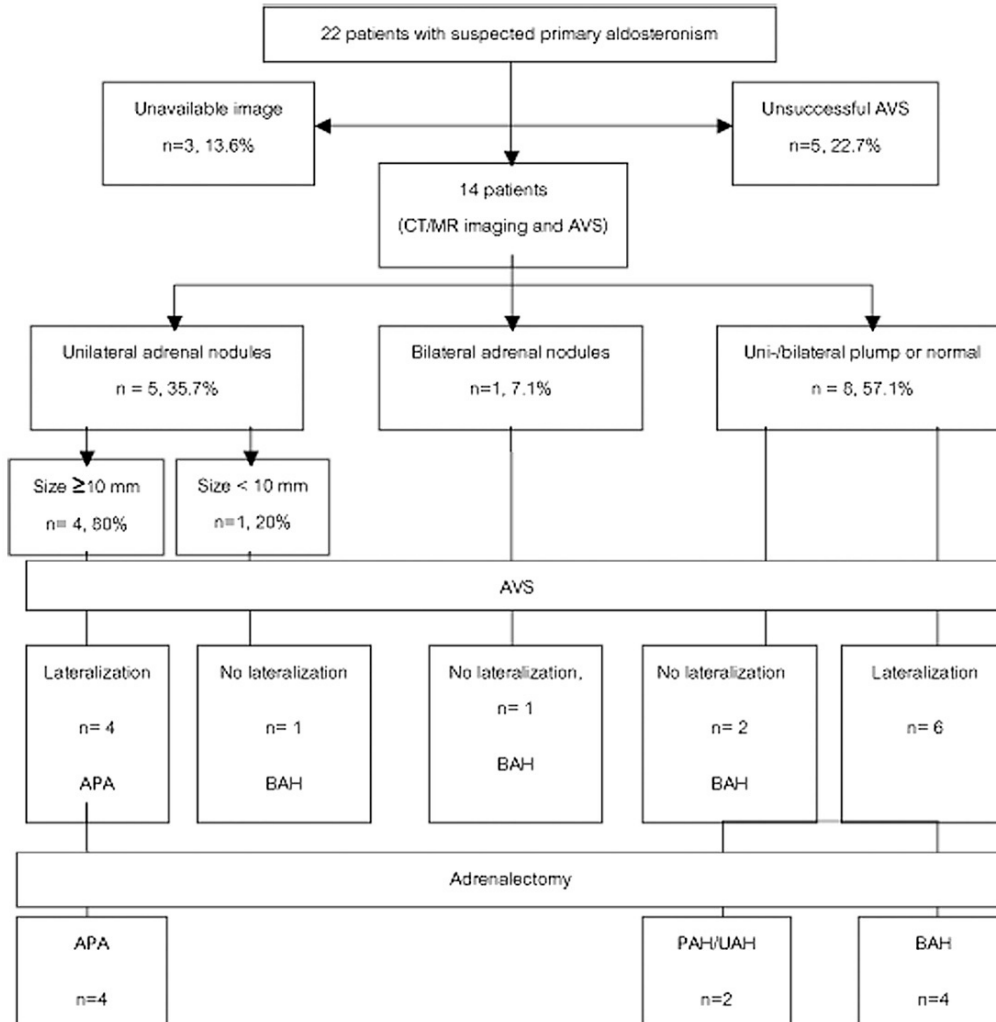


Fig.1 Summarized findings of computed tomography and adrenal vein sampling for causes of primary aldosteronism.

(APA, adenoma-producing aldosterone; AVS, adrenal vein sampling; BAH, bilateral adrenal hyperplasia; PAH, primary adrenal hyperplasia; UAH, unilateral adrenal hyperplasia)



Fig.2 A 65-years-old female with right adrenal adenoma. (A-C) Pre contrast axial CT reveals a 17x14-mm nodule at medial limb of right adrenal gland that attenuation is less than 10 HU, indicating lipid-rich adenoma. Coronal reformat (D) reveals right adrenal nodule.

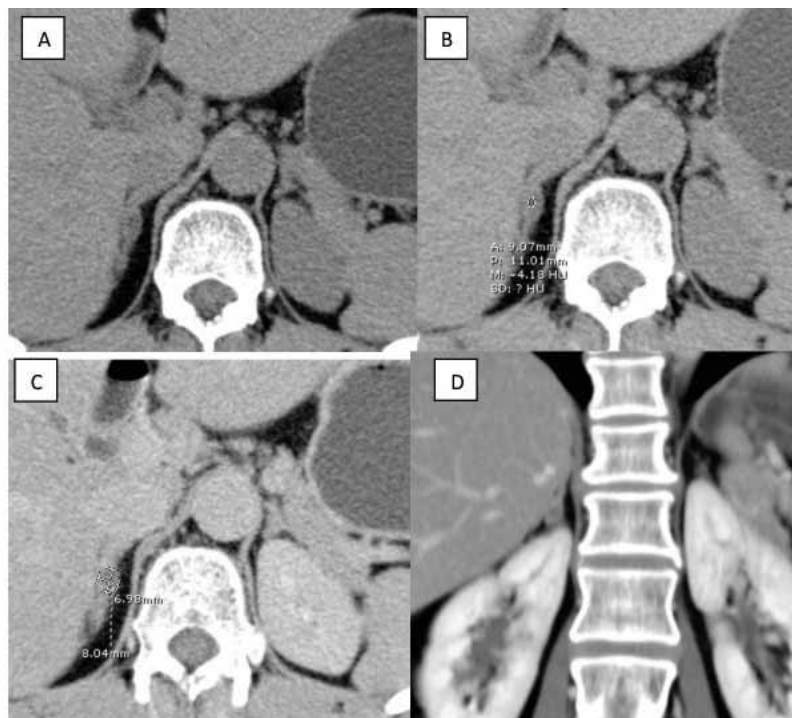


Fig.3 A 50-years-old female had unilateral adrenal nodule and finally proven bilateral adrenal hyperplasia (A-B). Axial non contrast CT of adrenal gland reveals a nodule at medial limb of right adrenal gland which attenuation is less than 10 HU, indicating lipid-rich adenoma (C) Axial post contrast 15-min delayed phase of adrenal gland shows hypo enhancement of the right adrenal nodule that size less than 10 mm. (D) Coronal reformat in portovenous phase confirmed right adrenal nodule.

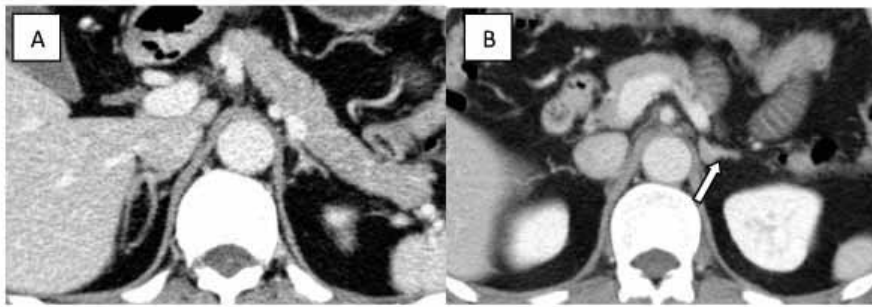


Fig.4 A 65-years-old male with left unilateral adrenal hyperplasia (UAH). (A-B) Post contrast axial CT of adrenal glands reveal normal appearance of right adrenal gland and pump (arrow) at left adrenal gland.

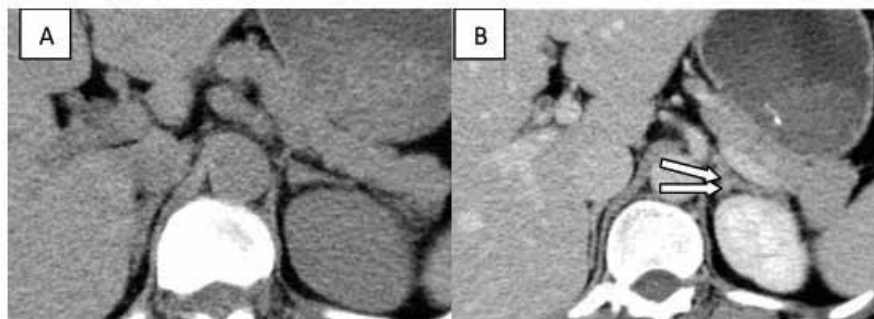


Fig.5 A 57-years-old male with BAH. (A) Pre contrast and (B) post contrast axial CT of adrenal gland reveal pumps (arrow) at left adrenal gland. He underwent left adrenalectomy due to lateralization from AVS ratio greater than 2 that is not cure after adrenalectomy.

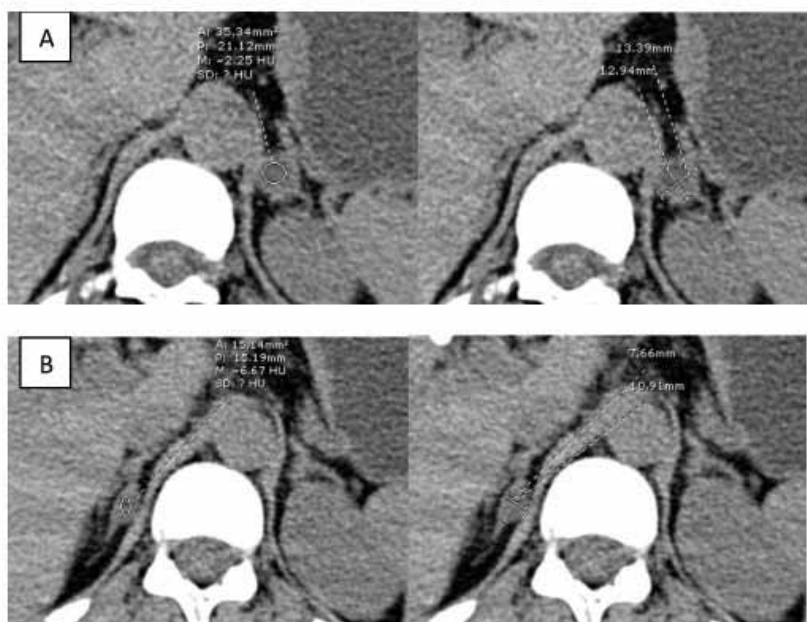


Fig.6 A 34-years-old female with BAH. Plain CT of adrenal glands reveals a 13x13-mm nodule at medial limb of left adrenal gland(A) and a 11x8-mm nodule at medial limb of right adrenal gland(B), which attenuation are less than 10 HU and AVS results indicated bilateral lesions.

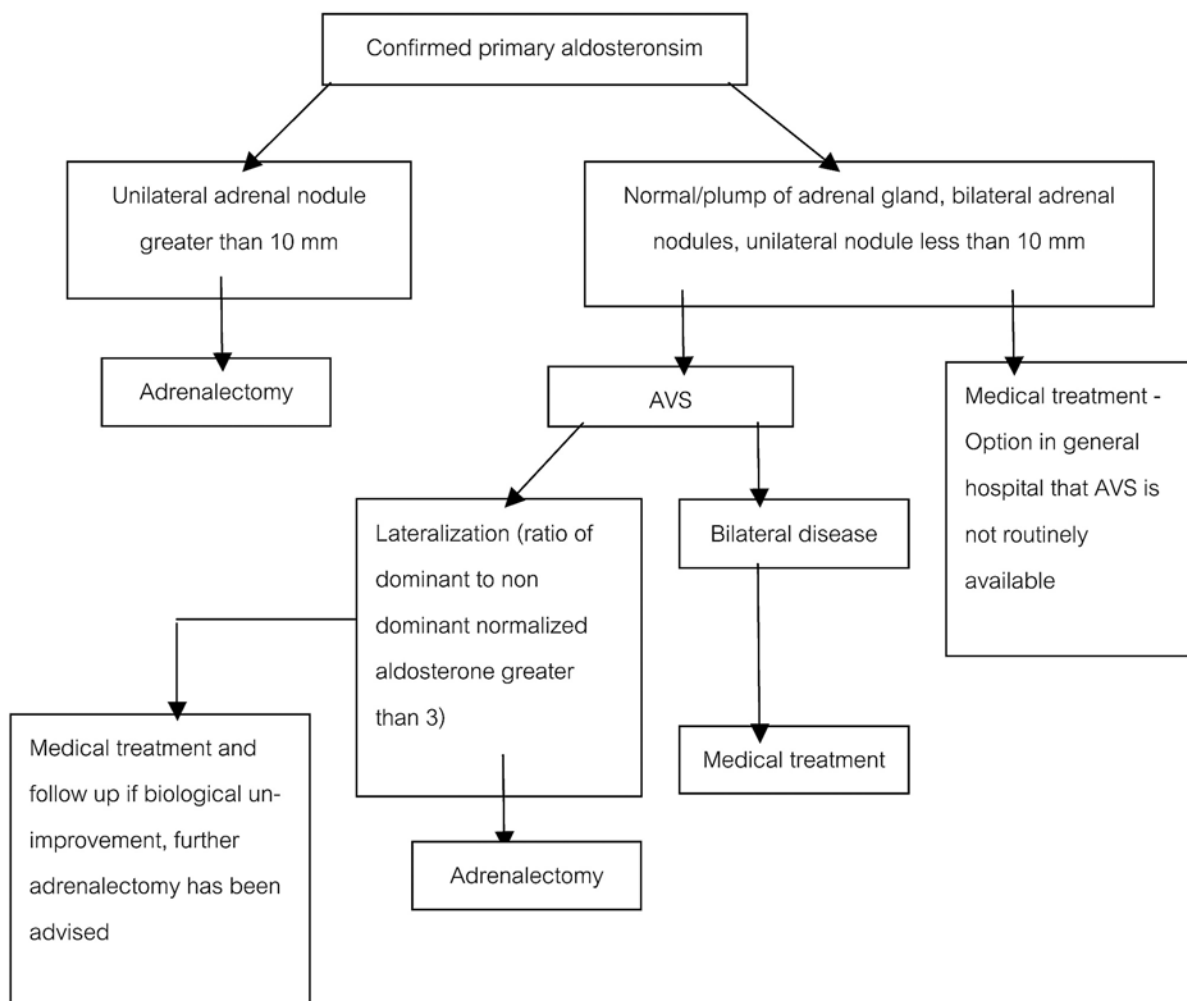


Fig.7 Flow chart for management of primary hyperaldosteronism.

Table.1 Sensitivity, specificity, accuracy, PPV and NPV to detect adrenal adenoma by AVS at cut point normalized aldosterone ratio (AVS ratio) at 2, 3 and 4.

| | AVS ratio ≥ 2 | AVS ratio ≥ 3 | AVS ratio ≥ 4 |
|-------------|--------------------|--------------------|--------------------|
| Sensitivity | 100% | 100% | 83.3% |
| Specificity | 50% | 75% | 87.5% |
| Accuracy | 71.43% | 85.7% | 85.7% |
| PPV | 60% | 75% | 83.3% |
| NPV | 100% | 100% | 87.5% |

such as Sarlon-Bartol G, et al⁽¹¹⁾ and Oh EM, et al⁽¹³⁾ reported that many of patients (37% and 22.09%, respectively) had received inappropriate surgery and/or management if decision making is based solely on CT findings alone. And both studies recommended that AVS should be performed before an adrenalectomy regardless of the nodule size found by CT. In other prior studies showed superiority of AVS over CT in differentiating subtype of PAL. Sensitivity of CT varies among previous literatures, approximately 53% in study of Happer R et al⁽³⁾ and 82% in study of Dunnick NR, et al⁽¹⁴⁾. Direct comparison between the two methods in study of Doppman JL, et al⁽¹⁵⁾ reported only 67% sensitivity for CT and 92% sensitivity for AVS.

Our study shows about 66.67% sensitivity and 77.78% NPV of CT/MRI to detect APA and 100% sensitivity and 100% NPV of AVS at cut point ratio = 2 to detect APA which similar to the study of Doppman JL, et al⁽¹⁵⁾ that the sensitivity and NPV of CT are lower than AVS. However, PPV of CT in our study is higher than PPV of AVS (80% vs 60%) and can reach 100% in case of macronodule. Similar results were also suggested by Happer R, et al⁽³⁾ who studies AVS and CT imaging in 34 patients. This study reported that PPV of CT scan is about 100% and also suggested that if CT imaging of patients with PAL showed a focal mass, ipsilateral adrenalectomy could be performed with the expectation of cure. However, if no mass was found on CT imaging, AVS could be used to detect an adenoma instead.

Some clinician recommended that for the patient aged below 40 years old, who has an adrenal macronodule and normal appearance of contralateral gland, no further imaging or evaluation is needed, and the patient should be referred for

adrenalectomy⁽¹⁶⁾. However, there is no patient under 40 years old with adrenal nodule had been included in our study.

AVS is a better alternative for detecting undemonstrable nodule because of its high NPV which sometimes reaches 100% compared to CT and MRI imaging which produce significantly lower NPV. If AVS showed no lateralization, patient should be treated medically. However, If AVS found lateralization; surgical treatment should be carefully considered. Due to low PPV of AVS, it may cause false positive in adrenal hyperplasia which cannot be cured by adrenalectomy. Cut point value for lateralization criteria vary between different institutions. Higher cut point raised specificity of AVS but decreased sensitivity. From our study, we can increase the cut point AVS ratio up to 3 without degrading sensitivity and NPV and also increase specificity to 75%. However, when the cut point AVS ratio is raised up to 4, the specificity can be as high as 87.5%, which equal to CT scan but decrease sensitivity and NPV.

Zarnegar et al⁽¹⁸⁾ concluded that a CT could be used to reliably diagnose adenomas larger than 10 mm and that AVS should be used when CT scan findings are normal or both adrenal glands are abnormal.

Our suggestion which similar to study of Zarnegar et al⁽¹⁸⁾ which suggested that if unilateral adrenal adenoma larger than 10 mm in case of suspected PAL is found, patient should be decided to adrenalectomy without performing AVS. AVS should be preserved when CT scan findings shows normal adrenal gland or both adrenal glands are abnormal. In case of unilateralization found on AVS and AVS ratio more than 3 should be decided to adrenalectomy and in case of bilateral disease, medical treatment is recommended which summa-

rized in diagram on Fig 7. However, our study is limited due to retrospective study with small number of cases. Further study with increase number of the patients should be considered.

Conclusion

The results of this study confirm that differentiation of subtype in patients with PAL is most reliably achieved with AVS. However, CT/MRI still has high PPV in case of detectable unilateral adrenal nodule, especially the nodule size is more than 10 mm. This patient groups should be referred to adrenalectomy without performing AVS. AVS is suitable for patient who had no adrenal nodule from CT/MRI imaging. If no lateralization is detected from AVS, medical treatment should be considered. And the cut point of AVS ratio at 3 is a proper value for differentiating APA from BAH due to increased PPV without degrading sensitivity and NPV.

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