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## Original article

## Adrenal computed tomography and NP-59 usefulness for diagnosing aldosterone-producing adenomas and idiopathic hyperaldosteronism in primary hyperaldosteronism

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## ABSTRACT

**Objectives:** Two major causes of primary aldosteronism are aldosterone-producing adenomas (APA) and idiopathic hyperaldosteronism (IHA). In this study, we attempted to determine the role of NP-59 in identifying APA prior to adrenalectomy, especially when diagnostic computer tomography (CT) is equivocal.

**Methods:** We performed a retrospective analysis in patients with a clinical diagnosis of primary aldosteronism. The medical records of 36 patients were reviewed, which included 25 patients who had received adrenalectomy. All patients underwent adrenal CT alone or a combination of adrenal CT and NP-59 prior to surgery for the subtyping of primary aldosteronism, based on the protocols established in our institution. The accuracy of the adrenal CT and NP-59 findings was determined by a comparison with the pathologic findings and postoperative outcomes.

**Results:** Twenty-three patients received unilateral adrenalectomy under the diagnosis of APA. The diagnoses were based on CT findings in 11 patients and on CT and NP-59 findings in 12 patients. The results of pathology were adrenal cortical adenoma in these 23 patients and the positive predictive value was 100%. Blood pressure and potassium levels significantly improved after surgery in these patients ( $p < 0.01$ ). Serum biochemistry and adrenal size of the limbs and bodies of patients with IHA were not significantly different from those of patients with APA.

**Conclusion:** For the subtyping of primary aldosteronism, the imaging modality of adrenal CT alone or the combination of adrenal CT and NP-59 adrenal scan has a high positive predictive value for APAs. We suggest that all patients undergo an adrenal CT as their initial study, after confirming the diagnosis of primary aldosteronism, and to use NP-59 when adrenal CT findings are atypical or inconclusive. Lateralization by this modality prior to adrenalectomy can reduce unnecessarily invasive examinations such as adrenal venous sampling and also provide excellent treatment outcomes.

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### 1. Introduction

Primary aldosteronism is a group of disorders in which aldosterone production is inappropriately high. The disorder results in hypertension and hypokalemia.<sup>1</sup> The incidence of primary

aldosteronism is much higher than previously thought.<sup>2</sup> There are two major causes of primary aldosteronism: aldosterone-producing adenomas (APAs) and idiopathic hyperaldosteronism (IHA). Differentiating between these two causes is important because an APA is treated surgically, whereas idiopathic hyperaldosteronism is generally managed medically.

Biochemical differentiation for the subtype classification of primary aldosteronism is usually imprecise.<sup>3</sup> Adrenal computer tomography (CT) is recommended as the initial study to determine the subtype and exclude adrenocortical carcinoma.<sup>1</sup> However, poor specificity limits its use in decision-making. [Iodine-131]6-beta-

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iodomethyl-19-norcholesterol is a cholesterol analog that is essentially captured by low-density lipoprotein (LDL) receptors in the adrenal glands.<sup>4</sup> NP-59 scintigraphy of the adrenal cortex can be used to correlate functional and anatomical abnormalities, but it is rarely used because of its poor sensitivity.<sup>5</sup> The NP-59 scan is not useful for evaluating small adrenal nodules because tracer uptake is poor in APAs <1.5 cm in diameter.<sup>6</sup> Bilateral adrenal venous sampling is considered the gold standard in lateralizing aldosterone hypersecretion; to avoid inappropriate operations, it should be performed prior to any surgical treatment.<sup>1</sup> However, adrenal venous sampling is invasive and operator-dependent. Success rates vary in part with local expertise.

In this study, we attempted to determine whether NP-59 scintigraphy in patients who had equivocal CT findings could provide a high positive predictive value for identifying APAs, especially in a subgroup of patients undergoing unilateral adrenalectomy.

## 2. Methods

We performed a retrospective analysis of patients who received a clinical diagnosis of primary aldosteronism from 2003 to 2013. Thirty-six patients were eligible for the study and were then reviewed. The research protocol was approved by the Institutional Review Board of Mackay Memorial Hospital (Taipei, Taiwan). Patient privacy and confidentiality were protected by the de-identification of all information. Clinical characteristics, laboratory studies, preoperative images, surgical treatment, pathology results, and postoperative outcomes were all recorded. Primary aldosteronism was diagnosed, based on the clinical findings of hypertension, increased aldosterone concentration, and suppressed plasma renin activity. All patients had a plasma aldosterone-to-renin ratio >50.

After confirming the diagnosis of primary aldosteronism, all patients underwent adrenal CT as the initial approach to localization. Images were reviewed by an experienced radiologist (P.S. Tsai) and patients were classified as having APA, IHA, or as inconclusive by radiologic characteristics. A CT diagnosis of adenoma was based on the presence of a single, well-defined, hypodense, and macronodular lesion with a normal appearance in the remaining ipsilateral and contralateral adrenal gland, whereas a diagnosis of hyperplasia was based on the presence of symmetric and enlarged adrenal glands. The results were inconclusive if the adrenal glands

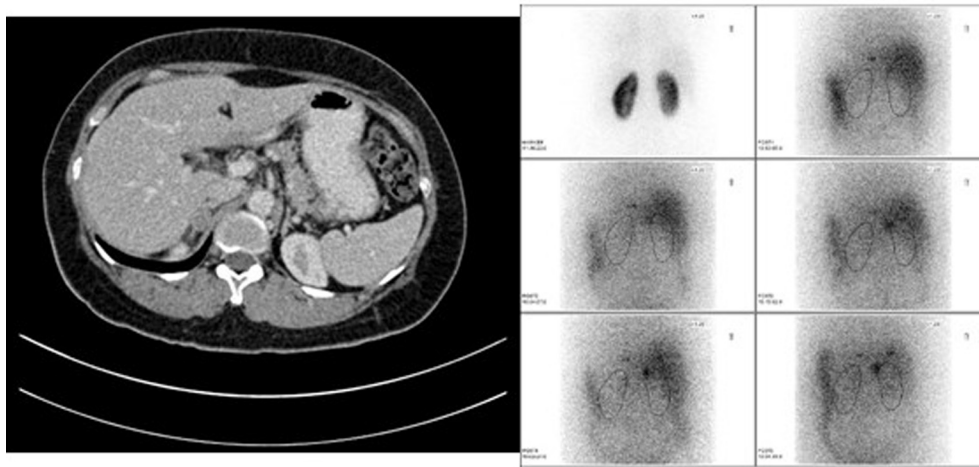
appeared normal or if CT imaging showed focal or unilateral adrenal limb thickening, unilateral adrenal micronodules, bilateral macronodules, or atypical nodular lesions. Based on the radiologist's experience, the inconclusive group was further subclassified into "suspected APA" and "suspected IHA." The size of the adrenal glands was also measured by the radiologist who measured the maximal adrenal gland body and limb widths for every gland.

If the adrenal CT findings were equivocal, NP-59 scintigraphy was performed to confirm the diagnosis. From 2 days prior to the NP-59 injection to 6 days after, 0.5 mg dexamethasone was administered orally four times daily to suppress nonautonomous adrenocortical activity. Patients then received an injection of 1 mCi of radiolabeled cholesterol. Planar imaging was started 3 days after the injection. Patients underwent final imaging 7 days after injection. Unilateral or highly asymmetric uptake on Days 3–5 was suggestive of an adenoma. The results of NP-59 were interpreted by experienced nuclear medicine physicians (M.Z. Wu, B.F. Shi, Q.H. Cao, and G.H. Lin).

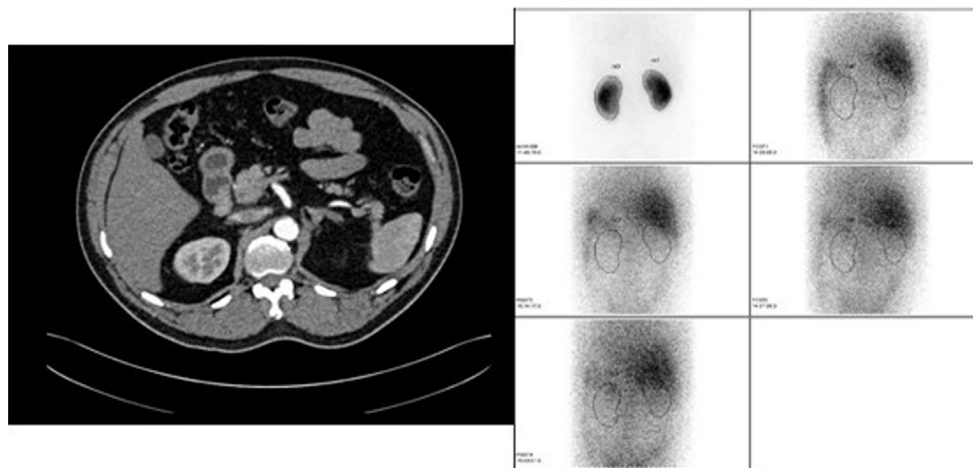
Patients with a definite diagnosis of APA (based on CT) or suspected APA (based on both CT and NP-59) underwent unilateral adrenalectomy (Fig. 1). The final diagnosis of APA was based on the histopathological examination of the specimen. By contrast, IHA was diagnosed by radiologic findings or suspected findings on both CT and NP-59. If findings of NP-59 scan and adrenal CT were inconsistent, further adrenal venous sampling or surgery was performed in accordance with the patient's choices (Fig. 2).

The primary aim of our study was to compare the adrenal CT and NP-59 findings with the pathologic diagnosis. Clinical outcomes included systolic blood pressure measurements and use of anti-hypertensive drugs. Biochemical outcome included serum potassium level and plasma aldosterone and renin levels. The patients' hypertension was categorized as "cured", "improved", or "not improved." Hypokalemia was considered cured if the serum potassium level returned to the normal range without any regular potassium supplementation. The follow-up period was defined from the operative date to the latest urologic or endocrinologic outpatient department visit.

In the statistical analysis, all data were expressed as mean  $\pm$  SD. The Student two-sample *t* test for normally distributed variables was performed on various data sets, and  $p < 0.05$  was considered statistically significant. The statistical analysis was performed using SPSS version 1.2 software (SPSS Inc., Chicago, IL, USA).



**Fig. 1.** Abdominal computer tomography of a 51-year-old female shows a 1.5 cm  $\times$  0.9 cm nodular lesion in the right adrenal gland with enhancement and low attenuation in the delayed films, which is more in favor of an adenoma. NP-59 was arranged; it showed early visualization of the right adrenal gland on Day 3. The patient received a right laparoscopic adrenalectomy. Pathology confirmed an adrenocortical adenoma.



**Fig. 2.** Abdominal computer tomography of a 55-year-old male shows a nodular lesion arising from the left adrenal gland. It measures approximately 1.4 cm in diameter. The dimensions of the left adrenal gland appears to be increased in size. On Day 4, the bilateral adrenal glands are faintly visible on NP-59 scintigraphy. We arranged for adrenal venous sampling of the patient. He was diagnosed as having idiopathic hyperaldosteronism.

### 3. Results

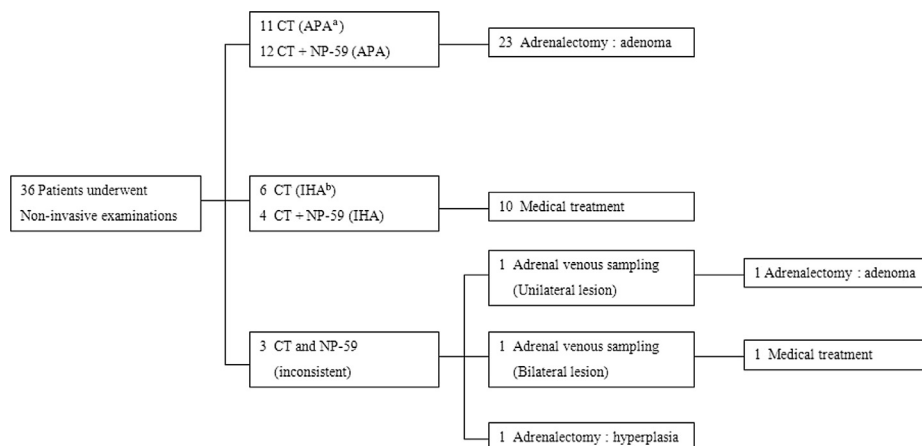
Twenty-three women and 13 men were evaluated in this study. The mean age was  $48.75 \pm 11.0$  years, the mean systolic blood pressure prior to treatment was  $170.0 \pm 18.0$  mmHg, and the mean serum potassium level was  $2.86 \pm 0.88$  mEq/L. The mean plasma aldosterone was  $507.7 \pm 313.7$  ng/dL, and the mean plasma renin activity was  $1.70 \pm 2.23$  ng/mL/h. All patients had their hypertension controlled with oral drugs. Only 27 (75%) patients presented with hypokalemia at the initial evaluation.

All 36 patients received an adrenal CT scan. Eleven patients were diagnosed with APA, and six patients were diagnosed with IHA. There were 19 patients that had an inconclusive diagnosis, which included 15 patients with suspected APA and four patients with suspected IHA, based on adrenal CT. These 19 patients then underwent NP-59 scan. Of these, 16 patients were definitively diagnosed on comparing the results of the adrenal CT and the NP-59 scan. The 12 patients with suspected APA on CT had unilateral uptake on NP-59, and the other four patients with suspected IHA had symmetric uptake. There were three patients with suspected APA on CT who had bilateral uptake. Adrenal venous sampling was

performed in two of the three patients with an inconclusive diagnosis after the adrenal CT and NP-59 study. In one patient, adrenal venous sampling showed unilateral disease; in another patient, it revealed bilateral disease. The third patient received an operation directly.

Twenty-three patients were diagnosed as having APA and received unilateral retroperitoneoscopic adrenalectomy. Final pathology confirmed cortical adenomas in all 23 patients. We also performed an adrenalectomy in two patients with an inconclusive diagnosis based on their adrenal CT and NP-59 study. One patient was proven to have unilateral disease by adrenal venous sampling and the pathology showed APA. The other patient underwent surgery directly upon the patient's request and pathology revealed IHA (Fig. 3).

Blood pressure and serum potassium levels significantly improved after adrenalectomy. In the APA group, the mean preoperative systolic blood pressure was  $174 \pm 12.0$  mmHg and the mean postoperative systolic blood pressure was  $124.7 \pm 12.6$  mmHg ( $p = 0.001$ ). The mean preoperative serum potassium was  $2.66 \pm 0.81$  mEq/L and the mean postoperative serum potassium was  $4.35 \pm 0.32$  mEq/L ( $p = 0.001$ ). Seventeen (74%)



**Fig. 3.** Noninvasive examinations for subclassification of primary aldosteronism. All participants underwent adrenal computer tomography (CT) as their initial evaluation. NP-59 was performed if the CT findings were equivocal. Adrenal venous sampling or surgery was performed for further diagnosis if CT and NP-59 reports were inconsistent. Patients with a definitive diagnosis of aldosterone-producing adenoma on CT or suspected aldosterone-producing adenoma on both CT and NP-59 underwent unilateral adrenalectomy. <sup>a</sup> aldosterone-producing adenoma. <sup>b</sup> idiopathic hyperaldosteronism. APA = aldosterone-producing adenoma; CT = computed tomography; IHA = idiopathic hyperaldosteronism.

patients were normotensive postoperatively and did not require any antihypertensive agents. The need for antihypertensive drugs was reduced in the other six patients. In the IHA group, all patients received long-term antihypertensive agents for hypertension control. One patient needed regular potassium supplementation at our outpatient clinic.

A comparison of biochemical parameters between APAs and IHAs showed that the aldosterone level was significantly higher in patients with APAs ( $581.8 \pm 312.2$  vs.  $378 \pm 153.5$ ,  $p = 0.014$ ), but there were no significant differences in blood pressure, potassium, renin, and aldosterone-to-renin ratio. Also, radiologically there were no significant differences in adrenal size between the two groups, except that the left body was larger in the IHA group ( $9.12$  mm vs.  $12.16$  mm;  $p = 0.03$ ).

#### 4. Discussion

Primary aldosteronism is a recognized important cause of secondary hypertension. The prevalence of primary aldosteronism has increased recently because of changes in the methods used to detect primary aldosteronism.<sup>7</sup> As a curative etiology, the diagnosing of APAs is crucial for the management of primary aldosteronism. Early intervention for APA can also prevent excess cardiovascular events.<sup>8</sup> Lateralizing evaluation is usually performed by adrenal CT and adrenal venous sampling; adrenal venous sampling is considered the gold standard test for lateralization.<sup>1</sup> Unilateral and bilateral adrenal disease should be distinguished by adrenal venous sampling when surgical treatment is feasible.<sup>1</sup> Authors from the Mayo Clinic also recommend adrenal venous sampling in older patients (> 40 years).<sup>5</sup> However, adrenal venous sampling is invasive and occasionally not possible. Therefore, we used NP-59 as a noninvasive functional test for lateralization, and demonstrated that the combination of adrenal CT and NP-59 was highly accurate with regards to APA diagnosis.

As an initial study in subtype testing, adrenal CT can be used to exclude adrenal malignancies and to locate macroadenomas.<sup>1</sup> However, CT findings are frequently misleading. False positive results may lead to unnecessary adrenalectomies. There are several reasons for these false positive results. First, nonfunctioning unilateral adrenal macroadenomas are common, especially in the elderly.<sup>9</sup> Second, apparent adrenal microadenomas may actually represent areas of hyperplasia.<sup>1</sup> Third, contralateral micronodular lesions may exist and result in surgical failure. False negative results are usually because of micronodular lesions that cannot be seen on CT scans. If CT alone were used to determine the subtype, 14.6% of such patients would inappropriately undergo unilateral adrenalectomy, which would not have been curative.<sup>10</sup> In NP-59 scintigraphy of the adrenal cortex, the LDL receptors in the adrenal cortex capture the cholesterol analog labeled with iodine-131.<sup>4</sup> Detection of hyperfunctional lesions requires that the normal adrenal cortex uptake be suppressed by dexamethasone. NP-59 can detect functional lesions in the adrenal cortex. Aldosterone-producing adenomas often show unilateral uptake, whereas symmetric uptake is typical in IHA.<sup>11</sup>

A major limitation of NP-59 is the resolution of planar imaging. Small lesions < 1.5 cm in diameter may not be visible.<sup>6</sup> This results in false negative results during APA detection. However, Yen et al<sup>12</sup> reported that as a lateralization modality after CT, it significantly improved the diagnostic accuracy in detecting APA. Based on our experience, adrenal CT and NP-59 provide a high degree of accuracy when diagnosing APA. The combination of these two exams could correlate functional with anatomical abnormalities. As a result, the positive predictive value of the imaging modalities in histologically detecting proven APA was 100% in this study. Both the clinical and

biochemical outcomes under the diagnosis protocol were also excellent.

As the gold standard diagnostic tool for primary aldosteronism, adrenal venous sampling has disadvantages that are worth noting. Two major problems with the procedure are its success rate and related complications. The right adrenal vein is difficult to identify and cannulate, and the success rate varies according to local expertise. The average success rate of right adrenal vein cannulation is reportedly 74%.<sup>13</sup> With experience, the success rate can be improved.<sup>5</sup> Complications related to adrenal venous sampling are also common. The complication rate varies from 1% to 10% and is dependent on operator experience.<sup>14–16</sup> The most frequent complications are groin hematoma and adrenal hemorrhage. Major complications such as adrenal vein dissection, adrenal vein thrombus, and adrenal infarction are relatively rare. Because of these possible complications, searching for a noninvasive alternative to adrenal venous sampling could be of benefit to clinicians and patients.

After the resection of the adenomas, there were six (26.0%) patients whose blood pressure did not normalize and they still required antihypertensive drugs. Stone et al report that the length of hypertension history may affect the time to normalization of blood pressure after an adrenalectomy in primary aldosteronism patients.<sup>17</sup> Therefore, a longer follow-up period is necessary in such patients. Concurrent essential hypertension or adrenal CT misdiagnosis may also explain this high blood pressure after surgery.

Biochemical and radiological findings are also helpful in distinguishing APA and IHA in some reports. In general, patients with APAs have more severe hypertension and hypokalemia; and these patients are also younger than patients with IHA.<sup>5</sup> Lingam et al<sup>18</sup> report that the adrenal glands, especially the adrenal limbs, were larger in patients with IHA. In our study, a comparison of the biochemical and radiological findings between the two subtypes showed a trend towards younger patients, higher blood pressure, more severe hypokalemia, and larger adrenal glands in the APA group. However, these differences were not statistically significant.

There were some limitations regarding this study that should be highlighted. First, patients with characteristics highly suggestive of IHA did not undergo surgery; therefore, we did not have histopathologic proof of the diagnosis. Thus, we could not evaluate the false negative rate of NP-59. However, as part of the preoperative evaluation, the imaging modalities (i.e., CT and NP-59) still had a high positive predictive value for APAs, which could reduce unnecessary surgeries and improve operative outcomes. Second, adrenal venous sampling was not performed in every patient to confirm the diagnosis. Third, the small sample size restricted the statistical power of our study.

In conclusion, the utilization of adrenal CT alone or the combination of adrenal CT and NP-59 provided good diagnostic accuracy for diagnosing APAs when subtyping primary aldosteronism. We suggest that adrenal CT should be used as the first lateralization tool. NP-59 could be used when adrenal CT has atypical lesions or is inconclusive. Adrenal venous sampling should only be considered if the findings of both noninvasive imaging studies are inconsistent or inconclusive. Biochemical and radiological features are not specific enough to distinguish APAs from IHA.

#### Conflicts of interest

The authors have no conflicts of interest to declare in relation to this study.

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