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Diagnostic value of adrenal iodine-131 6-beta-iodomethyl-19-norcholesterol scintigraphy for primary aldosteronism: a retrospective study at a medical center in North Taiwan

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Background Primary aldosteronism (PA) is a common cause of secondary hypertension. Among the many leading causes of PA, the two most frequent are, bilateral adrenal hyperplasia (BAH) and aldosterone-producing adenomas (APA). Since a solitary APA may be cured surgically, but BAH needs lifelong pharmacologic therapy, confirmation is mandatory before surgery. We herein sought to determine the diagnostic value of iodine-131 6-beta-iodomethyl-19-norcholesterol (NP-59) adrenal scintigraphy to distinguish BAH from APA.

Patients and methods Patients clinically suspected of PA from March 2000 to October 2016 were retrospectively analyzed. A total of 145 patients, including 74 postunilateral adrenalectomy and seven postradiofrequency ablation for adrenal mass, were reviewed. All patients received NP-59 adrenal scintigraphy prior to surgery. The accuracy of the NP-59 adrenal scintigraphy was confirmed by the pathologic findings and postoperative outcomes.

Results Among 81 patients receiving interventional procedures for adrenal mass, adenoma was eventually diagnosed in 72 patients according to their pathologic results, with 60 unilaterally and seven bilaterally localized lesions by NP-59 scintigraphy; nevertheless, there were five negative findings initially. The sensitivity, specificity, and positive predictive value of NP-59 scintigraphy for APA detection were therefore 83.3, 44.4, and 92.3%, respectively. Moreover, single-photon emission computed tomography/computed tomography scan increased the sensitivity and specificity, but not the positive predictive value (85.0, 60.0, and 89.5%) of NP-59 scintigraphy in this study.

Conclusion NP-59 adrenal scintigraphy is a useful imaging test to detect APA. Lateralization by this modality prior to surgical intervention may reduce the need for such invasive procedures as adrenal venous sampling. *Nucl Med Commun* 40:568–575 Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc.

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Keywords: aldosterone-producing adenomas, NP-59 adrenal scintigraphy, primary aldosteronism, single-photon emission computed tomography/computed tomography scan

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Introduction

Primary aldosteronism (PA) is a common cause of secondary hypertension. The prevalence of PA among hypertensive patients is reported to range from 1 to 20% [1]. Identifying PA is important because it is associated with higher risks of cardiovascular and metabolic dysfunction such as metabolic syndrome and diabetes mellitus [2–4]. Treatment of mineralocorticoid excess in patients presenting with PA can improve not only hypertension but also cardiovascular and metabolic sequels [5,6]. Two major forms of PA – bilateral adrenal hyperplasia (BAH) and aldosterone-producing adenomas (APA) – account for more than 90% of clinical cases [5]. While APA can be surgically cured by unilateral adrenectomy, BAH presents the dilemma that bilateral adrenalectomy inevitably leads to subsequent adrenal insufficiency and recurrent disease is not infrequently encountered in subtotal or unilateral adrenalectomy [7]. Therefore, differentiation between a unilateral adrenal hormone-producing lesion and BAH is mandatory.

Usually but not always, clinical manifestations of hypertension and hypokalemia raise the suspicion of PA, which will then screened by the aldosterone to renin ratio and confirmed by either captopril or saline infusion tests [8]. Abdominal computed tomography (CT) or MRI will be performed to explore the adrenal tumor. Functional localization tests such as iodine-131 (^{131}I) labeled 6-beta-iodomethyl-19-norcholesterol (NP-59) adrenal scintigraphy or adrenal venous sampling (AVS) will be arranged for adrenal mass confirmation in CT/MRI inconclusive cases. Although AVS is the gold standard for APA lateralization, this highly technically-dependent procedure has limited clinical application [9]. NP-59 is a radioiodine-labeled cholesterol analog with radioisotopic activity. Similar to those of un-labeled cholesterol, NP-59 is transported, and accumulated in cells via LDL receptors [10]. ^{131}I is an appropriate radiotracer in clinical practice for adrenal cortical imaging due to its greater avidity for adrenal cortex. The iodocholesterol is esterified and stored intracellularly without further metabolism or incorporation into adrenocortical steroid hormones [11]. For better differentiation of PA, dexamethasone is given before the study to suppress ACTH in order to enhance the functional difference between zonae glomerulosa and fasciculata. Normally, no focal tracer uptake will be produced prior to the fifth day of tracer injection. Early visualization (before day 5) indicates APA or BAH [12]. Since most of the cases suspected of PA will receive NP-59 adrenal scintigraphy, the aim of this study was to determine the accuracy of NP-59 adrenal scintigraphy to identify APA in patients in a medical center at Northern Taiwan.

Patients and methods

Patient preparation and scintigraphy technique

Patients referred for NP-59 adrenal scintigraphy for PA screening in a tertiary hospital in Taiwan were retrospectively analyzed from March 2000 to October 2016. The scintigraphic as well as CT/MRI reports and medical records were reviewed from the Picture Archiving and Communication System and electronic patient records from the Hospital Research Databank. The result of NP-59 adrenal scintigraphy, CT/MRI, laboratory tests, subsequent treatment plans, histopathology findings, and clinical outcomes were evaluated. The study protocol was reviewed and approved by the Ethics Committee on Research of the hospital Institutional Review Board (approval number 201701833B0).

After 3 days of dexamethasone suppression, 37 MBq (1 mCi) of ^{131}I labeled NP-59 was intravenously injected. Both anterior and posterior planar images were taken in third, fourth, and fifth days after injection of the tracer. Combined single-photon emission computed tomography (SPECT) with CT has been available since June 2012 at this institute. Scintigraphic images were interpreted by fully qualified nuclear medicine radiologists. Successful lateralization was defined as early visualization of tracer uptake on either side and asymmetrical uptake in subsequent delayed imaging.

A total of 145 consecutive patients receiving dexamethasone suppression NP-59 adrenal scintigraphy were retrospectively retrieved. All of the patients presented at least one of the following clinical manifestations: hypertension and hypokalemia; refractory hypertension; hypertension and adrenal incidentaloma. Eventually, 81 patients received either unilateral adrenalectomy (74) or radiofrequency ablation (7) of the adrenal mass under the impression of APA (Fig. 1). On retrospective inspection, the NP-59 adrenal scintigraphies of these patients were categorized into unilateral lateralization (group A), bilateral lateralization (group B), and negative uptake (group C). All of the 65 patients in group A received operation; 10 of those in group B and six of those in group C also received operation due to unilateral visible adrenal mass on CT/MRI. All of the surgically dissected specimens were reviewed by experienced pathologists.

Laboratory tests

Laboratory tests, including plasma aldosterone concentration (PAC) and direct renin concentration (DRC), were performed in the central laboratory of the hospital. PAC was measured by a radioimmunoassay kit with a quantitative measurement (Beckman Colter, Pasadena, California, USA). The analytical sensitivity was 0.764 ng/dl. The reference value was 4.93–17.5 ng/dl in the supine position and 3.4–27.5 ng/dl in the upright position. DRC was measured by immunoradiometric assay equipment (Renin III Generation; Cisbio Bioassays International, Codolet, France). The reference value at rest in the supine position in patients aged 20–40 years was 3.6–20.1 and 1.1–20.2 ng/l in those aged 41–60 years. In the upright position in patients aged 20–40 years, the reference value was 5.1–38.7 and 1.8–59.4 ng/l for those aged 41–60 years.

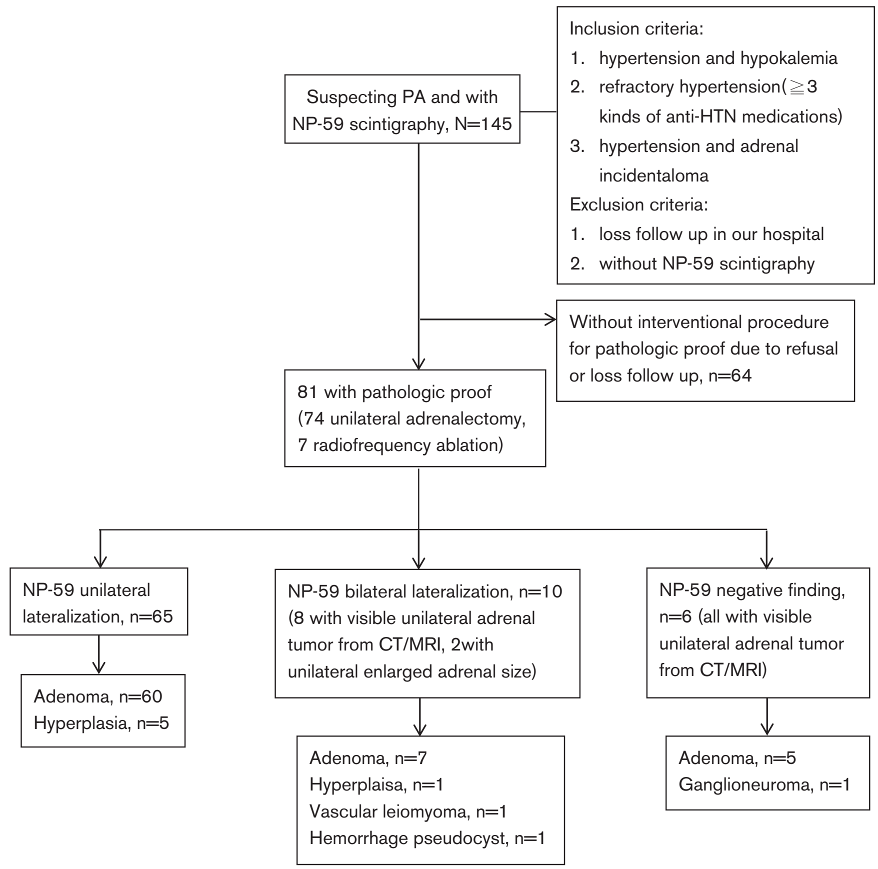
Statistical analysis

Continuous variables were presented as mean ± SD and range, categorical variables were presented as number and percentage. The comparison of the characteristics in these three group patients was calculated by one-way analysis of variance for continuous variables with normal distribution, Kruskal–Wallis analysis of variance was used for continuous variables without normal distribution and χ^2-test for categorical variables. The sensitivity and specificity of APA detected by ^{131}I NP-59 scintigraphy were determined via 2 by 2 χ^2-test. Paired-Sample *t*-test was used to compare blood pressure and serum potassium level before and after surgical intervention in APA patients. The receiver operating characteristic curve and Youden Index were carried out to identify the most predictive tumor size which can be visible on NP-59 planar scintigraphy. The increase in APA size related to successful detection by NP-59 adrenal scintigraphy was determined by univariate binary logistic regression. Analysis was performed using SPSS statistical software (version 19.0; SPSS Inc., Chicago, Illinois, USA). A *P*-value less than 0.05 was considered statistically significant.

Results

Table 1 summarizes the demographic characteristics of the 81 patients suspected of having APA. Typically, the

Fig. 1



Flow chart of the case selection and the result of I-131 NP-59 scintigraphy. Despite the atypical NP-59 scintigraphy findings, patients in groups B and C received unilateral adrenectomy or ablation due to classical primary aldosteronism features and unilateral localization of adrenal mass by CT/MRI. CT, computed tomography; HTN, hypertension; ^{131}I, iodine-131; NP-59, iodine-131 6-beta-iodomethyl-19-norcholesterol; PA, primary aldosteronism.

diagnosis of APA should be supported by unilateral lateralization of a functioning tumor by NP-59 adrenal scintigraphy (Fig. 2). We divided the 81 patients into three groups according to their NP-59 scintigraphy results, unilateral (group A, $n=65$), bilateral (group B, $n=10$) and negative (group C, $n=6$) radioactive uptake of the adrenal glands. The mean age was 42.8 ± 8.9, 44.1 ± 12.8, and 50.5 ± 8.2 years, respectively, in the three groups ($P=0.166$). No sex difference ($P=0.598$) was observed between groups (the proportion of male patients was 44.6% in group A, 60% in group B, and 66.7% in group C). Among the three groups, the number of patients presenting with hypertension and hypokalemia was 47 (72.3%), 6 (60.0%), and 5 (83.3%) ($P=0.646$); the number of cases of refractory or uncontrolled hypertension was 25 (38.5%), 5 (50.0%), and 4 (66.7%) ($P=0.344$); and the number of those with hypertension and adrenal incidentaloma was 17 (26.2%), 2 (20.0%), and 1 (16.7%) ($P=0.807$), respectively, for groups A, B, and C. The size of the adrenal mass measured by CT/MRI was 1.9 ± 0.6, 1.4 ± 0.3, and 1.4 ± 0.5 cm, respectively, for groups A, B, and C ($P=0.010$).

The preoperative mean PAC were 43.9 ± 31.8, 61.7 ± 47.7, and 32.2 ± 11.2 ng/dl ($P=0.336$); DRC were 8.1 ± 6.8, 10.5 ± 7.5, and 5.3 ± 1.7 ng/l ($P=0.507$) in groups A, B, and C, respectively. The preoperative serum potassium levels were 2.9 ± 0.8, 3.1 ± 0.8, and 2.5 ± 0.9 mmol/l ($P=0.232$), and systolic blood pressure (SBP) was 161.8 ± 23.3, 157.0 ± 34.7, and 170.8 ± 13.6 mmHg ($P=0.549$), respectively, in groups A, B, and C. The serum potassium levels and blood pressure improved significantly after adrenalectomy or ablation with the serum potassium level returned to 4.3 ± 0.5, 4.1 ± 0.6, and 4.2 ± 0.3 mmol/l ($P=0.662$) and the postoperative SBP becoming 130.9 ± 13.1, 133.6 ± 18.9, and 130.5 ± 9.4 mmHg ($P=0.841$), respectively.

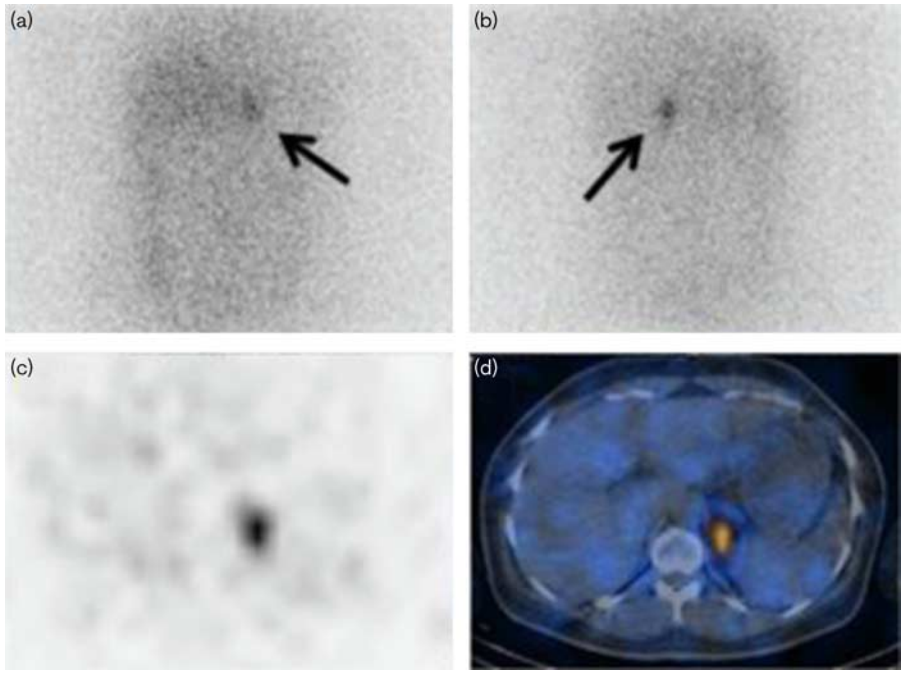
To analyze the individual response to the intervention, we defined a responder as one who either stopped or reduced antihypertensive medications after the interventional procedure. The number (percentage) of responders in each group was 58 (89.2%), 10 (100%), and 6 (100%), in groups A, B, and C ($P=0.762$), respectively. Similarly, a serum potassium responder was defined as a subject with preoperative hypokalemia who returned to

Table 1 **Characteristics of 81 patients with interventional pathologic proof of aldosterone-producing adenomas**

Variables	Group A (unilateral lateralization) ($N=65$)	Group B (bilateral lateralization) ($N=10$)	Group C (negative finding) ($N=6$)	P value
Age (years)	42.8 ± 8.9 (27.0–65.0)	44.1 ± 12.8 (29.0–66.0)	50.5 ± 8.2 (35.0–56.0)	0.166
Sex				
Male	29 (44.6)	4 (40.0)	4 (66.7)	0.598
Female	36 (55.4)	6 (60.0)	2 (33.3)	
Clinical manifestations				
Hypertension and hypokalemia	47 (72.3)	6 (60.0)	5 (83.3)	0.646
Refractory or uncontrolled hypertension	25 (38.5)	5 (50.0)	4 (66.7)	0.344
Hypertension and adrenal incidentaloma	17 (26.2)	2 (20.0)	1 (16.7)	0.807
Adrenal mass size from CT/MRI (cm)[a]	1.9 ± 0.6 (1.0–4.1)	1.4 ± 0.3 (1.0–1.8)	1.4 ± 0.5 (1.0–2.4)	0.010*
APA pathologic gross size (cm)[a]	2.1 ± 0.7 (0.8–3.9)	1.8 ± 0.8 (0.5–3.8)	1.1 ± 0.2 (0.9–1.3)	0.008*
Adenomas	60 (92.3)	7 (70.0)	5 (83.3)	0.077
Preoperative serum potassium (mmol/l)[a]	2.9 ± 0.8 (1.7–4.6)	3.1 ± 0.8 (2.0–4.6)	2.5 ± 0.9 (1.8–4.1)	0.232
Postoperative serum potassium (mmol/l)[a]	4.3 ± 0.5 (4.1–4.4)	4.1 ± 0.6 (3.6–4.6)	4.2 ± 0.3 (4.1–4.4)	0.662
Serum potassium response numbers	45/49 (91.8)	7/8 (87.5)	5/5 (100.0)	0.705
Plasma aldosterone (ng/dl)[a]	43.9 ± 31.8 (7.9–219.6)	61.7 ± 47.7 (18.5–166.0)	32.2 ± 11.2 (21.9–52.4)	0.336
Direct renin concentration (ng/l)[a]	8.1 ± 6.8 (1.6–30.1)	10.5 ± 7.5 (4.4–22.4)	5.3 ± 1.7 (3.7–7.0)	0.507
Preoperative systolic blood pressure (mmHg)	161.8 ± 23.3 (108.0–216.0)	157.0 ± 34.7 (106.0–229.0)	170.8 ± 13.6 (159.0–194.0)	0.549
Preoperative diastolic blood pressure (mmHg)	97.5 ± 15.6 (64.0–139.0)	89.6 ± 18.2 (67.0–123.0)	92.0 ± 13.6 (67.0–105.0)	0.275
Postoperative systolic blood pressure (mmHg)	130.9 ± 13.1 (104.0–167.0)	133.6 ± 18.9 (101.0–164.0)	130.5 ± 9.4 (120.0–146.0)	0.841
Postoperative diastolic blood pressure (mmHg)	82.6 ± 9.3 (61.0–107.0)	81.7 ± 13.4 (67.0–107.0)	83.5 ± 12.5 (71.0–105.0)	0.938
Number of antihypertensive medication before operation	2.2 ± 1.2 (0.0–5.0)	2.3 ± 1.3 (1.0–4.0)	2.8 ± 0.8 (0.0–5.0)	0.511
Number of antihypertensive medication after operation	0.7 ± 1.0 (0.0–4.0)	0.4 ± 0.8 (0.0–2.0)	1.0 ± 0.9 (0.0–2.0)	0.458
Blood pressure response numbers	58 (89.2)	10 (100.0)	6 (100.0)	0.762

Continuous variables presented as mean ± SD (range) or n (%).
One-way ANOVA was used for continuous variables with normal distribution.
Definition of blood pressure response: decreased numbers of antihypertensive medications after operation; serum potassium response: preoperative hypokalemia and postoperative serum potassium in normal range (3.5–5.0 mmol/l).
χ^2-Test was used for categorical variables.
ANOVA, analysis of variance; APA, aldosterone-producing adenoma; CT, computed tomography.
[a]Kruskal–Wallis ANOVA was used for continuous variables with non-normal distribution.
*$P < 0.05$.

Fig. 2



Images of a 45-year-old female patient who presented with hypertension and hypokalemia. Planar anterior (a) and posterior (b) iodine-131 6-beta-iodomethyl-19-norcholesterol imaging indicated radiotracer uptake within the left adrenal (a, b, arrow). Single-photon emission computed tomography (c) and single-photon emission computed tomography-computed tomography (d) images also show intense uptake and a 3.5 cm tumor of the left adrenal gland, consistent with left adrenal adenoma.

eukalemia postoperatively. Thus, the number (percentage) of serum potassium responder was 45/49 (91.8%), 7/8 (87.5%), and 5/5 (100.0%) ($P=0.705$), respectively, in groups A, B, and C. In general, regardless of the NP-59 finding, most of the patients with adrenal adenoma proven by pathology show significantly improved blood pressure and serum potassium levels after adrenalectomy or ablation (preoperative SBP 161.1 ± 23.4 mmHg vs. postoperative SBP 129.9 ± 12.6 mmHg, $P<0.001$; preoperative diastolic blood pressure 96.9 ± 15.8 mmHg vs. postoperative diastolic blood pressure 81.6 ± 8.6 mmHg, $P<0.001$; preoperative potassium 2.9 ± 0.8 mmol/l vs. postoperative potassium 4.3 ± 0.5 mmol/l, $P<0.001$, Fig. 3).

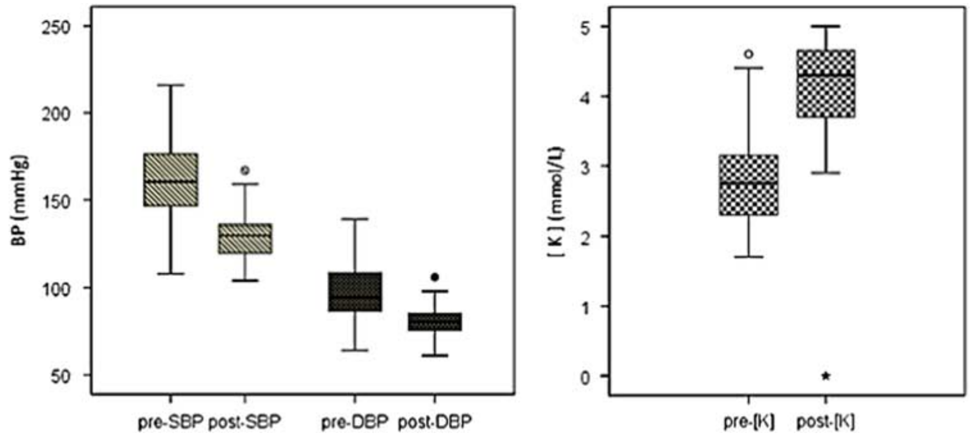
Pathologic reports confirmed the existence of adrenal adenoma in 60 (92.3%), 7 (70.0%), and 5 (83.3%) patients of groups A, B, and C ($P=0.077$), with gross tumor size ranging 2.1 ± 0.7, 1.8 ± 0.8, and 1.1 ± 0.2 cm ($P=0.008$), respectively. Therefore, were able to analyze the sensitivity and accuracy of NP-59 adrenal scintigraphy to detect APA in this cohort. Our result showed that the sensitivity of NP-59 scintigraphy was 83.3%; specificity was 44.4%; and positive predictive value was 92.3% (Table 2). A total of 25 cases received NP-59 adrenal scintigraphy in combination with SPECT/CT before surgical intervention after SPECT/CT was available in this institute in 2012. The sensitivity, specificity, and positive predictive value of APA detection by NP-59 scintigraphy in combination with SPECT/CT scan was 85.0, 60.0, and 89.5%, respectively (Table 2).

Discussion

The estimated prevalence of PA in hypertensive populations has increased from less than 1% to about 10% in western countries [6,13,14]. Surgery is a potential curative treatment for unilateral disease, such as APA and less frequently for carcinomas or selected unilateral nodular idiopathic adrenal hyperplasia. However, medical therapy remains the standard treatment for BAH [15], unless it has become medically intractable [16]. The establishment of a precise lateralizing imaging system is thus a critical step towards improved management of PA.

NP-59 adrenal scintigraphy is applied for PA lateralization in many Asian and European countries, but not currently in the USA [17]. The Asian experience and other isolated reports show that NP-59 adrenal scintigraphy can identify unilateral uptake of the tracer and help distinguish an APA from a BAH with the aid of dexamethasone suppression [17,18]. Nevertheless, different series report variable degrees of accuracy, ranging 47–94%, in differentiating the two conditions by NP-59 scintigraphy [19–25]. With the simultaneous use of integrated SPECT/CT to provide both functional and anatomical information, the accuracy of the NP-59 scintigraphy is reportedly remarkably improved [12,24]. In

Fig. 3



The comparison of systolic blood pressure (SBP), diastolic blood pressure (DBP) and serum potassium (K) before (pre-) and after (post-) unilateral adrenalectomy or ablation in aldosterone-producing adenoma patients ($n = 72$) proven by pathologic result. BP, blood pressure.

Table 2 Sensitivity and specificity of aldosterone-producing adenomas detected by iodine-131 6-beta-iodomethyl-19-norcholesterol scintigraphy only and combined single-photon emission computed tomography/computed tomography scan

	Sensitivity [n/N (%)]	Specificity [n/N (%)]	Diagnostic accuracy [n/N (%)]	PPV [*n*/*N* (%)]	NPV [*n*/*N* (%)]	*P* value
NP-59 scintigraphy	83.3 (60/72)	44.4 (4/9)	79.0 (64/81)	92.3 (60/65)	25.0 (4/16)	0.048
NP-59 scintigraphy with SPECT/CT scan	85.0 (17/20)	60.0 (3/5)	80.0 (20/25)	89.5 (17/19)	50.0 (3/6)	0.035

CT, computed tomography; NP-59, iodine-131 6-beta-iodomethyl-19-norcholesterol; NPV, negative predictive value; PPV, positive predictive value; SPECT, single-photon emission computed tomography.

agreement, a sensitivity of 83.3% in our series suggests that NP-59 adrenal scintigraphy can be used as an alternative imaging study for APA lateralization. Furthermore, SPECT/CT improved the specificity of planar APA detection (from 44.4 to 60.0%) but did not significantly improve its sensitivity (from 83.3 to 85.0%).

Typically, bilateral symmetrical adrenal uptake of radioactive tracer suggests BAH according to the interpretation of NP-59 results [26,27]. In certain conditions, bilateral asymmetric uptake of NP-59 provides limited ability to distinguish adenoma from partially suppressed normal contralateral adrenal gland or asymmetrically expanded adrenal glands in bilateral hyperplasia [27]. This was the case in our series, with two of the 10 patients in the bilateral visualization group presenting asymmetric uptake, which was eventually proven adenomas postoperatively. The other eight patients showed bilateral symmetric visualization at day 3–5 after injection of the tracer; these proved to be five adenomas, one hyperplasia, one vascular leiomyoma, and one hemorrhagic pseudocyst.

Because of the resolution limit of NP-59 planar imaging, lesions smaller than 1.5 cm in diameter may not be visible on planar scintigraphy [14]. In agreement, we also found poorer NP-59 scintigraphy uptake in lesions smaller than 1.5 cm (the number of patients with tumors sized less than 1.5 cm were 9 of 65, 6 of 10, and 5 of 6 in groups A, B, and C, respectively). Thus, the diagnostic odds ratio (95% confidence interval) of APA detection by NP-59 adrenal scintigraphy was 1.93 (1.15–3.24) fold for each millimeter increase in tumor size ($P = 0.013$).

We tried to find out the correlation between aldosterone/renin levels in patients with different NP-59 scintigraphy findings, since a higher PAC and a lower DRC has been reported in patients with APA relative to those with BAH [28]. Our results showed no significant differences in PAC ($P = 0.221$) or DRC ($P = 0.552$) in APA patients with different (unilateral, bilateral, and negative) radioactive tracer uptake.

According to the American Endocrine Society guidelines [14], lateralization by cross-sectional imaging such as CT is usually recommended for patients with biochemically confirmed PA. Reconfirmation with AVS or NP-59 adrenal scintigraphy may be considered if the CT result is equivocal [29]. Although AVS is the gold standard for subtype diagnosis [8,9,30], the availability in many hospitals is limited because it usually requires an experienced doctor and the complications of the invasive procedure are potentially hazardous [31]. Based on these considerations, the Taiwan Society of Aldosteronism suggests NP-59 adrenal scintigraphy for functioning tumor lateralization for lesions larger than 1 cm [8]. Our findings also suggest that NP-59 adrenal scintigraphy can be a clinically useful tool to confirm the nature of PA with a 92.3% positive predictive value.

Williams *et al.* [32] reported a 37% complete success rate and a 47% partial success rate with a 94% biochemically successful correction of hypokalemia and normalization of aldosterone to renin ratio at 6–12 months after unilateral adrenectomy. The recurrence rate of APA after adequate surgery or radiofrequency ablation was exceptional in the only case reports in the literature [33,34]. Similarly, the clinical and biochemical improvement of the 81 patients were followed up in our series for 1 month to 1 year post-operatively, and although the proportion of remissions after intervention was high, there still existed failure (6.2%), partial success (50.6%), and no recurrence event.

Our study had some limitations. First, our PA patients were retrospectively collected from the patient lists of those who had ever had NP-59 adrenal scintigraphy performed and their condition pathologically proven. Second, the nature of retrospective analysis resulted in inevitable missing data. Furthermore, some of the blood tests were done while patients were taking medications such as calcium channel blockers, angiotensin-receptor blockers, and spirolactone. Lastly, bias may exist in the specificity and false negative rate of NP-59 adrenal scintigraphy because of the small number of patients in this study.

Conclusion

^{131}I NP-59 adrenal scintigraphy with SPECT/CT scan is a useful functional imaging tool to detect APA. Lateralization by this modality prior to surgical intervention can reduce unnecessary invasive procedures such as adrenal venous sampling and may also provide an excellent treatment outcome.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest.

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