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Diagnostic Dilemma of Small Incidentally Discovered Adrenal Masses: Role for ^{131}I-6β-Iodomethyl-norcholesterol Scintigraphy

Richard T. Kloos, M.D.,[1] Milton D. Gross, M.D.,[1,2] Brahm Shapiro, M.B., Ch.B., Ph.D.,[1,2] Isaac R. Francis, M.D.,[3] Melvyn Korobkin, M.D.,[3] Norman W. Thompson, M.D.[4]

[1]Division of Nuclear Medicine, Department of Internal Medicine, University of Michigan Medical Center, 1500 E. Medical Center Drive, B1G412, Box 28, Ann Arbor, Michigan 48109, U.S.A.
[2]Nuclear Medicine Service (115), Department of Veterans Affairs Medical Centers, 2215 Fuller Road, Ann Arbor, Michigan 48105, U.S.A.
[3]Department of Radiology, University of Michigan Medical Center, 1500 E. Medical Center Drive, B1D520, Box 30, Ann Arbor, Michigan 48109, U.S.A.
[4]Department of Surgery, University of Michigan Medical Center, 2920D Taubman Center, 1500 E. Medical Center Drive, Ann Arbor, Michigan 48109-0331, U.S.A.

Abstract. Incidentally discovered adrenal masses are detected in 0.35% to 5.00% of patients imaged with computed tomography (CT) for reasons other than suspected adrenal pathology. Most small adrenal masses are benign, although malignant tumors ≤ 3 cm in diameter are well described. In the setting of normal adrenal hormonal secretion, the preferential accumulation of ^{131}I-6β-iodomethyl-norcholesterol (NP59) by adrenocortical tissues allows the distinction of adenomas from other space-occupying or destructive lesions, with diagnostic images being obtained in 100% of lesions > 2 cm. Although some lesions ≤ 2 cm have yielded nondiagnostic images, the frequency of this phenomenon and thus the utility of NP59 scintigraphy for the evaluation of small adrenal lesions has remained incompletely characterized. Between January 1976 and December 1994 a total of 166 patients with nonhypersecretory unilateral adrenal masses ≤ 3 cm in maximal diameter, discovered incidentally during CT examinations of the abdomen or chest for reasons other than clinically suspected adrenal disease, were studied with NP59 scintigraphy. Nonhypersecretory masses ≤ 1 cm, > 1 to ≤ 2 cm, and > 2 to ≤ 3 cm yielded diagnostic images in 52%, 89%, and 100% of patients, respectively. Lesions other than adenomas, including malignancies, > 1 to ≤ 2 cm and > 2 to ≤ 3 cm were present in 9% and 10% of patients, respectively. These findings emphasize the need to determine the nature of small incidentally discovered adrenal masses whose management may alter patient care and confirm the utility of NP59 scintigraphy to evaluate nonhypersecretory adrenal masses regardless of size.

The likelihood of malignant incidentally discovered adrenal masses (incidentalomas) rises with increasing diameter [1]. However, in the absence of known extraadrenal primary malignancy, benign adrenal masses outnumber malignant masses regardless of size [1]. Furthermore, malignant neoplasms must be small at some time in their development, and some benign masses may become large. Adrenal malignancies < 3 cm are well described [1]. The large incidentally discovered adrenal mass (> 3 cm in diameter) poses little difficulty for anatomic characterization with computed tomography (CT) or magnetic resonance imaging (MRI), functional characterization with adrenocortical scintigraphy or positron emission tomography (PET), or tissue characterization by CT-guided adrenal biopsy [1, 2]. Smaller masses (≤ 3 cm in diameter) may pose greater difficulty. Yet determination of their etiology remains no less important, as subsequent critical clinical and diagnostic decisions may be based on the presence or absence of primary adrenal malignancy, metastatic disease in the adrenal(s), or the presence of some adrenal lesions other than simple nonhypersecretory adenomas.

We have previously noted that the frequency of diagnostically useful imaging patterns is reduced when lesions ≤ 2 cm are studied scintigraphically, but the regularity of this occurrence and thus the relation of lesion diameter to sensitivity of ^{131}I-6β-iodomethyl-norcholesterol (NP59) imaging have not been documented in detail. Thus when faced with the problem of a small nonhypersecretory adrenal mass, the utility of adrenal scintigraphy has remained incompletely characterized. In this paper we report our experience with the scintigraphic characterization of small (≤ 3 cm in diameter) incidentally discovered euadrenal masses.

Materials and Methods

Between January 1976 and December 1994 a total of 166 patients with unilateral adrenal masses discovered incidentally during CT examination of the abdomen or chest performed for reasons other than clinically suspected adrenal disease were studied with NP59 scintigraphy. CT was initially performed with an EMI-5005 and later with a Picker 1200SX at the VA Medical Center, Ann Arbor, and with a GE-8800 or GE-9800 scanner at the University of Michigan Medical Center. Contiguous 5- to 10-mm sections were obtained on the newer scanners after intravenous or oral radiographic contrast administration.

All patients referred for NP59 scintigraphy gave written in-

Correspondence to: R.T. Kloos, M.D., University of Alabama at Birmingham, 1808 Seventh Avenue South, BDB 756, Birmingham, AL 35294-0012, U.S.A.

Table 1. Nomenclature of adrenal scintigraphy for the characterization of nonhypersecretory incidentalomas.

Image pattern	Description of pattern	Lesion responsible
Concordant	Increased radiotracer uptake by the adrenal mass	Benign adrenal cortical adenoma or nodular hyperplasia
Discordant	Absent, decreased, or distorted adrenal radiotracer uptake by the adrenal mass	Destructive or space-occupying nonadenomatous lesion including primary and metastatic malignancy
Nonlateralizing	Normal symmetric adrenal radiotracer uptake despite "adrenal" mass lesion	Consider periadrenal or pseudoadrenal mass; some adenomas and nonadenomas show this pattern when ≤ 2 cm in greatest diameter

Table 2. Indications for the computed tomography that revealed small adrenal masses.

Indication for CT	No. of cases
Staging of known or suspected malignancy	86
Abdominal pain	56
Pneumonia/chronic obstructive pulmonary disease	4
Weight loss	4
Renal cyst(s)	3
Hypertension	2
Pleural effusion	2
Renal failure	2
Venous thrombosis	2
Aortic aneurysm	1
Bronchopleural fistula	1
Fever	1
Hematuria	1
Retroperitoneal fibrosis	1
Total	166

formed consent for the study that was approved by each hospital's Institutional Review Board for Human Experimentation. NP59 (1 mCi) was injected intravenously followed by posterior, usually lateral and occasionally anterior, abdominal scans (at least 50,000 counts per image) performed one or more times between days 5 and 10 after injection. Saturated potassium iodide solution (SSKI) was begun 24 to 48 hours prior to radiopharmaceutical administration and continued for 14 days to suppress thyroid uptake of free ^{131}I. A mild laxative (bisacodyl 10 mg once or twice daily by mouth) was also given to most patients, beginning 2 days before the first day of imaging, to reduce potentially interfering colonic ^{131}I radioactivity [3].

For each patient various combinations of blood and urine biochemical measurements were obtained to exclude the presence of adrenal cortical and medullary hypersecretion. They included normal plasma levels of cortisol; urinary free cortisol excretion; plasma renin activity; serum or urine (or both) aldosterone, potassium, epinephrine, norepinephrine, metanephrine, and normetanephrine; urinary 17-hydroxycorticosteroids and 17-ketosteroids; serum dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), or both; urinary vanillylmandelic acid (VMA); normal cortisol response to dexamethasone; and in some cases normal serum cortisol response to intravenous adrenocorticotropic hormone (ACTH) administration. Medications that might interfere with the scintigraphic or biochemical studies were discontinued prior to investigation [1, 2]. Certain features of some cases (138 patients) have been included (in a different context) in reports of adrenal masses in patients with preexisting malignancy [4] and in large series on the use of NP59 for evaluation of adrenal masses of all sizes [5, 6]. Following NP59 scintigraphy and reevaluation of the CT scan, those cases that proved to have pseudoadrenal or periadrenal masses, rather than true adrenal mass lesions, have been excluded from consideration.

The correlation of relative NP59 uptake between the two adrenals was assessed qualitatively based on previously established criteria for normal adrenal NP59 uptake [7] and an interpretative algorithm for incidentally discovered adrenal masses (Table 1) [1].

Statistical analyses were performed using Student's *t*-test and the chi-square test.

Results

The indications for study with CT that initially demonstrated the presence of an adrenal mass are listed in Table 2. There were 82 men and 84 women with a mean (± SD) age of 59.0 ± 11.5 years (range 24–88 years). There were 76 right-sided and 90 left-sided masses (chi-square not significant). The distribution of adrenal masses as a function of their largest diameter estimated by CT is shown in Table 3.

A final diagnosis of adenoma was made by adrenalectomy in 18 patients, CT-guided adrenal biopsy in 10, and no change in adrenal appearance on repeat CT scans and clinical follow-up 6 months or more from the initial CT examination in the remaining 104 patients.

Fourteen intraadrenal space-occupying or destructive lesions other than adenomas were detected and confirmed by CT-guided adrenal biopsy or adrenalectomy. Metastatic lung carcinoma was responsible for the masses in seven patients and adrenal cysts in two patients; in the remaining five patients adrenal masses were due to leukemia, metastatic colon adenocarcinoma, metastatic renal carcinoma, pheochromocytoma, and an adrenal hematoma, respectively. The results of NP59 scintigraphy are shown in Table 3.

Discussion

Scintigraphy with NP59 was diagnostic in 149 of 166 (90%) cases (Figs. 1, 2). Normal (nonlateralizing) imaging patterns were observed in 17 patients (10%) of whom 3 had adrenal metastases (1.5, 1.8, and 2.0 cm in maximal diameter) and 14 had adenomas (≤ 1 cm in 10 patients and > 1 to ≤ 2 cm in maximal diameter in 4 patients).

Stratification of adrenal masses by size demonstrated a diagnostic pattern in all masses > 2 cm in maximal diameter. However, an increasing number of nonlateralizing imaging patterns was seen in progressively smaller masses: 7 of 64 (11%) masses > 1 to ≤ 2 cm and 10 of 21 (48%) masses ≤ 1 cm in diameter (Table 3).

Malignancy rates of adrenal masses in the setting of a known extraadrenal primary malignancy have ranged from 32% to 73%, and benign masses have been reported in 27% to 68% of cases [1].

Table 3. Utility of ^{131}I-6β-iodomethyl-norcholesterol (NP59) scintigraphy for the adrenal incidentaloma.

Mass size (cm)	Total cases (no.)	Concordant pattern (no.)	Discordant pattern (no.)	Nonlateralizing pattern (no.)	Sensitivity (%) TP[a]/(TP + FN[b])	Specificity (%) TN[c]/(TN + FP[d]	Diagnostic image (accuracy) (%) (TN + TP)/(TN + TP + FN + FP)	Negative predictive value (%) TN/(TN + FN)	Positive predictive value (%) TP/(TP + FP)
≤ 1	21	11	0	10[e]	—	100 (84–100)[f]	52 (30–74)	52 (30–74)	—
> 1 to ≤ 2	64	54	3	7[g]	30 (18–42)	100 (95–100)	89 (82–96)	89 (82–96)	100 (95–100)
> 2 to ≤ 3	81	73	8	0	100 (95–100)	100 (95–100)	100 (95–100)	100 (95–100)	100 (95–100)
Total	166	138	11	17	39 (31–47)	100 (97–100)	90 (85–95)	89 (84–94)	100 (97–100)

[a]TP = True positive: discordant pattern for lesion other than an adenoma.
[b]FN = False negative: nonlateralizing pattern with a known intraadrenal lesion.
[c]TN = True negative: concordant pattern for an adenoma.
[d]FP = False positive: discordant pattern for an adenoma.
[e]All adenomas.
[f]Ninety-five percent confidence limits.
[g]Three lesions other than adenomas and four adenomas.

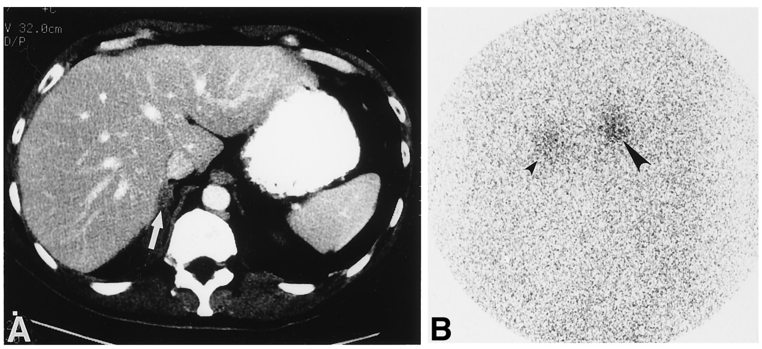

Fig. 1. CT examination performed to stage squamous cell lung carcinoma disclosed a 1 cm diameter right adrenal mass that yielded a concordant NP59 image pattern. **A**. CT scan with oral and intravenous contrast demonstrates the right adrenal mass (white arrow). **B**. Posterior abdominal NP59 scintiscan 5 days after radiotracer injection demonstrates intense uptake in the right adrenal gland (large arrowhead) and normal NP59 uptake in the left adrenal gland (small arrowhead). The lesion remained stable on follow-up CT examinations despite progression of the primary tumor and development of distant nonadrenal metastases.

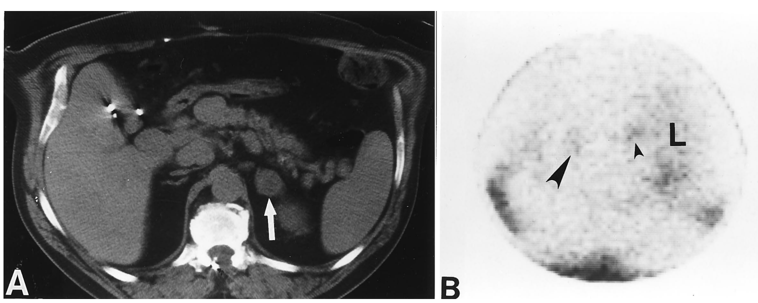

Fig. 2. CT examination performed for abdominal pain disclosed a 2 cm in diameter left adrenal mass that yielded a discordant NP59 image pattern. **A**. CT scan without contrast demonstrates the left adrenal mass (white arrow). **B**. Posterior abdominal NP59 scintiscan at 5 days after radiotracer injection demonstrates normal uptake in the liver (L) and decreased uptake in the left adrenal gland (large arrowhead) compared to that of the normal right adrenal gland (small arrowhead). The remaining peripheral foci depict normal gastrointestinal radiotracer activity. Subsequent CT-guided fine-needle biopsy demonstrated leukemic infiltration of the left adrenal gland.

In this setting, malignancy rates among those with adrenal masses ≤ 3 cm have ranged from 0% to 50%, whereas among those with adrenal masses > 3 cm malignancy rates have ranged from 43% to 100% [1]. Thus diagnostic algorithms based on size alone miss a small but significant number of potentially clinically important adrenal neoplasms.

Many authors advocate serial CT follow-up examinations and suggest that a lesion stable in size is benign whereas those that enlarge are malignant. This strategy is impractical for patients with known extraadrenal malignancy who are being considered for potentially curable resection of their primary tumors. The opportunity for cure may be lost in those primary adrenal malignancies (cortical or medullary) diagnosed only after demonstration of tumor growth, local invasion, or the appearance of local or distant metastases. Serial CT examinations subject a large number of patients with benign adenomas to unnecessary and expensive follow-up imaging. Finally, the optimal interval and duration of serial imaging protocols is unknown, during which time many patients are lost to follow-up [1].

Thin-section (5 mm or less) unenhanced CT allows analysis of tissue x-ray attenuation characteristics that appear to distinguish benign from metastatic neoplasms better than size criteria alone [1, 2]. An unenhanced CT attenuation coefficient of 0 Hounsfield units (HU) or less has been reported as being 100% specific for benign adenomas versus metastasis; but given the high percentage of adrenal adenomas with attenuation values > 0 HU, low sensitivities of 33% and 47% have been reported [1]. Similarly, a threshold of 10 HU results in a sensitivity of approximately 73% and a specificity of 96% [2]. There appears, however, to be a progressive decrease in the ability to accurately determine attenuation coefficients in decreasingly smaller masses, and thus efficacy would be expected to diminish [8, 9].

A growing body of evidence supports the use of MRI for characterizing adrenal incidentalomas [1, 2]. Intensity ratios of normal tissue (usually liver or spleen) to adrenal lesions [1, 10] and novel pulse sequences that provide some insight into the lipid content of adrenal tissues can be shown to differentiate benign from malignant masses with a sensitivity for detecting adenomas of around 81% to 84% and a specificity near 100% [1, 2]. However, smaller adrenal masses may present problems, with partial volume averaging with MRI leading to spurious tissue signal results [11, 12]. Although most series include masses that are as small as 10 mm, few report results stratified with respect to mass diameter.

Positron emission tomography (PET) with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) has been used to characterize adrenal masses [1.5–10.0 cm in diameter (mean 2.8 cm)] in 20 patients with cancer [13]. PET tumor/background ratios [standardized uptake value (SUV)] correctly differentiated benign from malignant lesions in all patients. However, patients with adrenal masses < 1.5 cm in diameter were not included, and it is estimated that the spatial resolution of PET is approximately 1 cm (although possibly less for lesions with intense FDG uptake). This remarkable separation of benign from malignant tumors has not been duplicated by others.

Percutaneous adrenal biopsy under ultrasound or CT guidance offers both high accuracy (80–100%) and specificity toward differentiating benign lesions from metastases to the adrenal glands [1]. In some series, however, all false-negative biopsies (7%) were from lesions < 3 cm in greatest diameter [14]. Significant complications occur in 3% to 13% of cases [1, 14]. Percutaneous adrenal biopsy is considered relatively contraindicated to differentiate benign adenomas from adrenocortical carcinomas given the low sensitivity (54–86%) and the low, but possible, risk of seeding malignant cells along the needle tract in an otherwise potentially curable patient [1, 2]. Because most small adrenal masses are benign, biopsy or adrenalectomy of those masses that exhibit characteristics compatible with malignancy (i.e., a discordant imaging pattern on NP59 scintigraphy) would optimize the selection of masses for these more invasive procedures [1].

Adrenal scintigraphy has been used to distinguish benign from malignant or space-occupying adrenal masses in euadrenal patients [1]. Although NP59 remains an investigational new drug (IND) in the United States, it is available for investigative use from the Nuclear Pharmacy at the University of Michigan Medical Center after filing an abbreviated IND with the U. S. Food and Drug Administration. Unilateral and bilateral adrenal masses can be characterized according to function in the sense that the mass(es) can or cannot accumulate the radiopharmaceutical (e.g., NP59) sufficient for in vivo scintigraphic imaging [1]. For unilateral, nonhypersecretory adrenal masses, NP59 uptake that exceeds the anatomically normal contralateral adrenal gland (as demonstrated by CT or MRI) would be considered benign (Fig. 1), whereas decreased or absent NP59 uptake in a mass seen on CT or MRI would be compatible with some other space-occupying or destructive lesion (Fig. 2) [1]. Thus iodocholesterol scintigraphy can be used to select which adrenal masses would be the best candidates for further (and likely invasive) diagnostic evaluation.

The overall efficacy of adrenal scintigraphy for the evaluation of euadrenal masses is high and exceeds that of both CT and MRI [1, 5, 6]. Previous studies have illustrated that the number of false-negative NP59 studies increases with decreasing mass diameter [5, 6]. It is not surprising that for a mass to deform or destroy sufficient adrenal cortex to be detected as a discordant imaging pattern scintigraphically ("cold spot imaging") size is an important factor [5, 15]. The importance of size in relation to NP59 imaging may be somewhat less critical for functioning masses, as their iodocholesterol accumulation compared to that in the contralateral anatomically normal adrenal gland more easily allows scintigraphic visualization (concordant imaging pattern; "hot spot imaging"). This point is evidently true, as 54 of 58 (93%) adrenal adenomas > 1 to ≤ 2 cm in diameter demonstrated diagnostic concordant patterns of imaging, whereas only 3 of 6 (50%) lesions that were not adenomas in this same size range demonstrated the characteristic discordant imaging pattern. The continued relative importance of mass size for adrenal adenomas is demonstrated by the fact that for masses ≤ 1 cm in diameter the number of false-negative studies is greater (10 of 21, 48%) than that seen in masses > 1 to ≤ 2 cm in diameter (4 of 58, 7%) (Table 3).

It is not surprising that sensitivity falls to 39% in the current study for lesions ≤ 3 cm; as the proportion of false-negative studies increases, however, other parameters of efficacy remain high. The "false-negative" group contained few malignant lesions (3 of 17, 18%), and so the better measure of clinical utility is the accuracy (90%), which denotes the probability of obtaining a diagnostic image that has been 100% specific. Thus even with masses ≤ 1 cm, 52% of patients had diagnostic images. No malignancies were present that were ≤ 1 cm in diameter. It is not surprising that this series contains no primary adrenocortical carcinomas. Statistically, one would expect to find approximately one primary adrenocortical carcinoma among each 10,000 to 500,000 adrenal incidentalomas ≤ 5 cm in diameter [1, 16]. Although the prevalence of metastases for masses > 1 to ≤ 2 cm in diameter is low (6 of 64, 9%), it is not trivial. Thus regardless of size, it remains possible to determine with high efficacy the nature of many adrenal masses by the presence or absence of NP59 uptake.

Lacking direct comparison, the decision as to which, if any, modality should be used routinely to determine the nature of small adrenal masses cannot be answered by the present study. Preliminary data using formal decision analysis based on available estimates of diagnostic performance and reimbursement costs, suggests that NP59 scintigraphy is the most cost-effective diagnostic tool to evaluate the adrenal incidentaloma [17].

Résumé

Les «incidentalomes» surrénaliens sont découverts chez 0.35 à 5% des patients ayant eu une tomodensitométrie pour une pathologie non surrénalienne. Alors que la plupart des masses de la surrénale sont bénignes, on a décrit des tumeurs malignes de trois cm ou moins. Lorsque l'hormonologie surrénalienne est normale, l'accumulation préférentielle de 131-I-6β-iodométhyl-nor-cholésterol (NP59) par la cortico-surrénale en scintigraphie permet de distinguer les adénomes des autres lésions, les images étant obtenues dans 100% des cas de lésions < 2 cm de diamètre. Parfois cependant, des lésions de 2 cm ou moins ne s'accompagnent d'aucune image. L'utilité de la scintigraphie NP59 dans l'évaluation des lésions de la surrénale reste donc incomplètement élucidée. Méthodes: Entre Janvier 1976 et Décembre 1994, 166 patients porteurs d'une masse surrénalienne unilatérale non-hypersécrétoire de trois cm ou moins, découverte de façon fortuite sur une tomodensitométrie de l'abdomen ou du thorax, ont été évalués par la scintigraphie NP59. Résultats: Les masses non-hypersécrétoires de diamètre ≤ 1 cm, de > 1-≤ 2 cm, et de > 2-≤ 3 cm ont fourni des images chez respectivement 52%, 89%, et 100% des patients. Les lésions autres que les adénomes, y compris les lésions malignes > 1-≤ 2 cm et de > 2-≤ 3 cm, ont été retrouvées, chez respectivement 9% et 10% des patients. Conclusions: Ces données confirment le besoin de déterminer la nature des masses surrénaliennes de découverte fortuite. Leur traitement pourrait changer la prise en charge du patient. Une scintigraphie NP59 permettrait d'évaluer la masse indépendamment de sa taille.

Resumen

Antecedentes: Las masas suprarrenales que se descubren en forma incidental ocurren en 0.35%–5% de los pacientes que son sometidos a TAC por razones diferentes a la sospecha de patologia adrenal. A unque la mayorìa de las masas adrenales pequeñas son de caràcter benigno, tambièn ocurren tumores malignos de A3 3 cm de diàmetro. En el contexto de secreciòn normal de las hormonas adrenales, la concentraciòn preferencial del 131-I-yodometil-norcolesterol (NP59) por los tejidos adrenocorticales permite la diferenciaciòn entre adenomas y otras lesiones que ocupan espacio que causan destrucciòn local, logràndose una imagen adecuada en el 100% de las lesiones > 2 cm. A pesar de que algunas lesiones A3 2 cm no resultan en una imagen diagnòstica, la frecuencia de tal fenòmeno y, por consiguiente, la utilidad de la escintigrafia con NP59 en la valoraciòn de lesiones adrenales de tamaño pequeño no ha sido completamente definida. Mètodos: En el perìodo comprendido entre enero de 1976 y diciembre de 1994, se estudiaron 177 pacientes con masas adrenales, con diàmetro màximo A3 3 cm, unilaterales, no hipersecretoras, descubiertas incidentalmente en el curso de exàmenes por TAC del abdomen o del tòrax, practicados por razones diferentes de sospecha clìnica de enfermedad adrenal. Resultados: Las masas no hipersecretoras de A3 1 cm, 1- A3 2 cm y > 2 - A3 3 cm produjeron imagen diagnòstica en 52%, 89% y 100% de los pacientes, respectivamente. Se encontraron otras lesiones diferentes de adenomas, incluso tumores malignos de > 1 - A3 2 cm, 0 > 2 - A33 cm en 9% y 10% de los pacientes, respectivamente. Conclusiones: Nuestros hallazgos resaltan la necesidad de determinar la naturaleza de las pequeñas masas adrenales que sean descubiertas incidentalmente, cuyo tratamiento puede implicar una modificaciòn en el manejo del paciente y confirmar la utilidad de la escintigrafia con NP59 en la valoraciòn de las masas adrenales no hipersecretoras, no importa cual sea su tamaño.

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