Scintigraphic Evaluation of Clinically Silent Adrenal Masses

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We studied 229 patients with abnormal adrenal anatomy depicted by CT who were without biochemical evidence of endocrine dysfunction using the presence of ^{131}I-6β-iodomethyl-norcholesterol (NP-59) adrenal gland uptake as an index of differential adrenal function in the evaluation of the clinically "silent" adrenal mass lesion. **Methods:** NP-59 (1 mCi) was injected intravenously with posterior and lateral abdominal images obtained 5–7 days postinjection. **Results:** One-hundred and fifty-nine of 185 patients with unilateral adrenal enlargement on CT had scintigraphic evidence that the mass represented a functioning (NP-59 avid) but not hypersecretory, (biochemically normal) adrenal cortical adenoma (concordant imaging pattern). Forty-one of 44 patients with intra-adrenal neoplasms were depicted on scintigraphy as decreased or absent NP-59 accumulation on the side of the adrenal mass (discordant imaging pattern). In this study, sensitivity was 71% (41 of 58 patients; 95% confidence interval (CI), 58% to 88%); specificity was 100% (171 of 171 patients; 95% CI, 95% to 100%) and accuracy was 93% (212 of 229 patients; 95% CI, 88% to 96%). **Conclusions:** These data confirm our earlier observations that the functional information depicted by scintigraphy complements the morphological evaluation by CT and in the absence of hormonal dysfunction, the presence of concordant CT and ^{131}I-NP-59 scans are characteristic of functioning, but not hypersecretory, benign adrenocortical adenomas. Conversely, discordant CT and ^{131}I-NP-59 scans are suggestive of nonfunctioning, space-occupying, adrenal lesions.

Key Words: adrenal masses; iodine-131-6β-iodomethylnorcholesterol; incidentaloma

J Nucl Med 1994; 35:1145–1152

Clinically silent adrenal mass lesions are identified by computed tomography (CT) in patients without symptoms or signs of adrenal disease. These lesions most frequently represent benign, nonhypersecretory, nonautonomous, adrenal adenomas (*1*). Incidentally discovered masses of this type have been seen in 2%–9% of cases in autopsy series (*2*). Prior to the introduction of CT, adrenal neoplasms went undetected until massively enlarged or until the development of clinical signs and symptoms due to excessive hormone production. Tissue characteristics seen on CT or MRI have been used to separate benign from malignant lesions, but almost 30% cannot be distinguished using anatomic criteria exclusively (*3,4*). Fine needle aspiration of adrenal masses is useful in diagnosis and plays an important role, but because of difficulties encountered in differentiating adrenal adenoma from carcinoma by cytologic criteria and demonstrable morbidity, an improved process for the selection of patients who would benefit from this invasive procedure would be welcome (*5–7*).

Adrenal cortical scintigraphy has demonstrated clinical utility in the diagnosis of functional abnormalities involving all three histologic zones of the adrenal cortex (*8,9*). We have found ^{131}I6β-iodomethyl-norcholesterol (NP-59) scintigraphy to be useful in the differentiation of hypersecreting adrenocortical adenomas from bilateral hyperplasia and carcinoma, and for the pre-surgical lateralization of hyperfunctioning adrenocortical adenomas (*10*). More recently, NP-59 has demonstrated increased relative tracer accumulation in nonhypersecreting, benign adrenocortical adenomas, while decreased or absent adrenocortical NP-59 uptake is compatible with adrenal metastases, primary adrenocortical malignant neoplasms and other nonfunctioning space-occupying, adrenal lesions (*11,12*). In this report, we will update and extend our experience with adrenal scintigraphy in the evaluation of patients with abnormal adrenal anatomy discovered incidentally during CT examinations of the abdomen. A management plan which includes NP-59 scintigraphy is proposed as a complimentary, noninvasive approach to anatomic imaging to depict the presence of functioning adrenal tissues in the evaluation of the incidentally discovered adrenal mass, and reduce the need for biopsy or adrenalectomy in many of these patients.

MATERIALS AND METHODS

Between January 1976 and December 1992, 229 patients with adrenal masses discovered incidentally during CT examinations of

Received Jul. 12, 1993; revision accepted Jan. 20, 1994.

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the abdomen or chest performed for reasons other than clinically suspect adrenal disease were studied with NP-59 scintigraphy. CT imaging was performed initially on an EMI-5005, and later on a Picker 1200SX at the VA Medical Center, Ann Arbor and on GE-8800 or GE-9800 scanners at the University of Michigan Medical Center. Contiguous 5–10-mm sections on the newer scanners were obtained after intravenous and, in many patients, oral radiographic contrast administration.

All patients referred for NP-59 studies gave their written informed consent for the study which was approved by the Institutional Review Board for Human Experimentation. NP-59 (1 mCi) was injected intravenously followed by posterior, anterior and lateral abdominal scans (50,000 counts/image) performed on days 5 through 7 after injection (*13*). Saturated potassium iodide solution (2–3 drops) was administered twice daily, 24 hr prior to and throughout the imaging sequence to suppress thyroidal uptake of free ^{131}I. A mild laxative (bisacodyl) was also given (10 mg) twice daily in most patients, beginning 2 days before the first day of planned imaging to reduce potentially interfering colonic ^{131}I radioactivity (*14*).

In each patient, combinations of blood and urine biochemical measurements were obtained to exclude the presence of adrenal cortical or medulla dysfunction. This included, in most cases, normal plasma levels of cortisol, renin activity, aldosterone, epinephrine, norepinephrine, urinary cortisol, 17-hydroxycorticosteroids, 17-ketosteroids and vanillymandelic acid; normal cortisol responses to dexamethasone, and, in some cases, adrenocorticotrophin (ACTH) administration. All medications that might interfere with either the scintigraphic or biochemical studies were stopped prior to study. A total of 119 of the 229 cases have been the subject of three previous reports initially examining the significance of NP-59 uptake in a selected group of 9 patients (*11*); evaluation of NP-59 imaging in 28 patients with known extra-adrenal malignancies (*15*); and the efficacy of NP-59 scintigraphy in patients with unilateral adrenal masses (*12*).

Scan interpretation was based on previously established criteria in which either the presence or absence of significant asymmetry of NP-59 uptake either favoring the side of the abnormal adrenal on CT; (a concordant imaging pattern), or decreased, distorted, or absent NP-59 uptake seen on the side of the abnormal adrenal on CT (a discordant imaging pattern) (*12*). Bilaterally symmetrical NP-59 uptake (within the limits of normal and previously established adrenal asymmetry) was considered normal (*16*).

Statistical analyses were performed using Students' t-test and the confidence interval estimation for the binomial parameter (*17*). Confirmation of diagnoses were obtained from surgical exploration and adrenalectomy or needle biopsy in 99 patients and serial follow-up with clinical, biochemical and CT evaluations in 130 patients.

RESULTS

Computed tomography was performed in 101 patients for staging or evaluation of a previously known or suspected nonadrenal malignancy and in 102 patients for unexplained abdominal pain. The remaining 26 had CT for pleural or abdominal effusions, or both (4 patients); renal insufficiency (5 patients); hematoma (3 patients); back pain (4 patients); esophageal stricture (1 patient); weight loss (4 patients); pneumonia (2 patients); fever of unknown origin (1 patient); retroperitoneal fibrosis (1 patient); and intraperitoneal hemorrhage (1 patient). Mean age was 63 yr (range 18–90 yr) and there were 114 females and 115 males. There were 100 right adrenal masses and 129 left adrenal masses. Mean lesion diameter (±s.d.) was 3.2 ± 1.6 cm (range, 1–16 cm).

TABLE 1
Discordant Patterns of ^{131}I-6-β-Iodomethyl-Norcholesterol (NP-59) and CT in Nonhypersecretory Unilateral Adrenal Masses*

Adrenal lesions	No. of cases
Metastatic lung carcinoma	
Bronchogenic	10
Small-cell	4
Squamous-cell	3
Metastatic colon carcinoma	2
Lymphoma or leukemia	3
Adrenal cortical carcinoma	7
Fibrous histocytoma	2
Ganglioneuroma	1
Neuroendocrine tumor	3
Adrenal cyst	7
Myelolipoma†	1

*Accumulation of NP-59 on the side opposite to the abnormal adrenal lesion on CT.
†Displacement of adrenal from normal position.

A final diagnosis of adenoma was made in 185 patients from cytologic findings obtained by CT-guided biopsy of the mass in 19, adrenalectomy in 26 or no change in the appearance of the mass on CT scans performed over a follow-up interval of at least 6 mo (range, 6 mo to 3 yr) after the initial CT scan. Forty-four intra-adrenal neoplasms were identified and the diagnosis was made by CT-guided needle biopsy or adrenalectomy in each case (Table 1). Non-neoplastic, space-occupying, adrenal lesions were identified in 7 cases (adrenal cysts). Symmetrical NP-59 uptake was observed in 29 patients. Peri-adrenal masses adjacent to but not actually in the adrenal gland were present in 6 patients, while pseudoadrenal masses (nonadrenal masses initially believed to arise from the adrenal, but in fact derived from other structures) were identified in 6 patients that included a gastric varix, retroperitoneal hematoma, myelolipoma, renal cyst and a gastric leiomyoma (Table 2).

Iodine-131-6β-iodomethylnorcholesterol (NP-59) scintigraphy demonstrated 159 of 171 unilateral, benign masses (e.g., adenoma) as asymmetric, increased or lateralizing accumulations of ^{131}I-NP-59 activity to the side of the adrenal mass on CT (concordant imaging) (Fig. 1). Mean lesion diameter in this group was 3.0 ± 1.2 cm (range, 1–7 cm). Bilaterally symmetric patterns of NP-59 uptake were present in 12 patients, and all of these were 2 cm or less in diameter (Table 2). Of this group, two adrenal adenomas were proved by CT-guided biopsy and in 12 patients, adrenal masses were unchanged after a 6–36-mo interval of follow-up.

TABLE 2
Normal (symmetrical) Patterns of NP-59 Imaging in Patients With Unilateral Adrenal Masses on CT*

Diagnosis	No. of Cases
Adenoma†	2
Lung carcinoma†	1
Renal cell carcinoma†	2
Periadrenal masses	6
malignant histiocytoma (1)†‡	
lung carcinoma (1)†	
hypernephroma (3)§	
teratoma (1)	
Gastric varix¶	1
Gastric leiomyoma**	1
Hematoma§	2
Myelolipoma§	1
Renal cyst†	1
Adrenal mass unchanged§§	12

*Normal patterns of NP-59 uptake in patients with abnormal CT.
†Proved by CT-guided needle biopsy.
‡Numbers in parentheses refer to the number of patients and type of periadrenal metastases.
§Proved by laparotomy.
¶Proved by angiography.
**Mass associated with stomach on repeat CT, no change in diameter at a 6 and 30-m follow-up.
§§By repeat CT at a 6–36-mo interval.

Asymmetric NP-59 uptake lateralizing to the side opposite of the abnormal adrenal in patients with unilateral masses on CT (discordant imaging) was seen in 41 patients with destructive, malignant or space-occupying, intra-adrenal lesions (Fig. 2 and Table 1). The mean lesion diameter in this group was 4.3 ± 2.1 cm (range, 1.5–16 cm). In three patients with metastatic intra-adrenal neoplasms proven by biopsy, the NP-59 scan was normal without significant lateralization of iodocholesterol to the side opposite of the mass on CT (Table 2). These lesions, a metastatic lung carcinoma and two renal cell carcinomas, were 1.5, 1.8 and 2 cm in diameter, respectively.

The efficacy of scintigraphy in nonhypersecretory, unilateral adrenal masses is presented in Table 3, where true-positive is defined as a discordant pattern of imaging in destructive or space-occupying lesions. True-negative is defined as a concordant pattern of imaging in a patient with a benign mass (adenoma) and a normal pattern of NP-59 imaging when the "adrenal" lesion seen on CT did not truely involve the adrenal (periadrenal or pseudoadrenal mass). Sensitivity was 71% (95% confidence interval (CI); 58%–88%); specificity was 100% (95% CI; 95%–100%); and accuracy was 93% (95% CI; 88%–96%). The predictive value of a positive test was 100% (95% CI; 95%–100%) and the predictive value of a negative test was 91% (95% CI; 86%–96%).

DISCUSSION

The nonhypersecreting adrenal mass is a commonly encountered clinical problem. The extent to which these masses should be subject to further investigation remains controversial, but most would agree that the clinical status of the patient harboring the lesion and the size of the lesion are primary concerns (*2, 18, 19*). The notion, however, that once identified, small lesions (<3 cm in diameter) can be

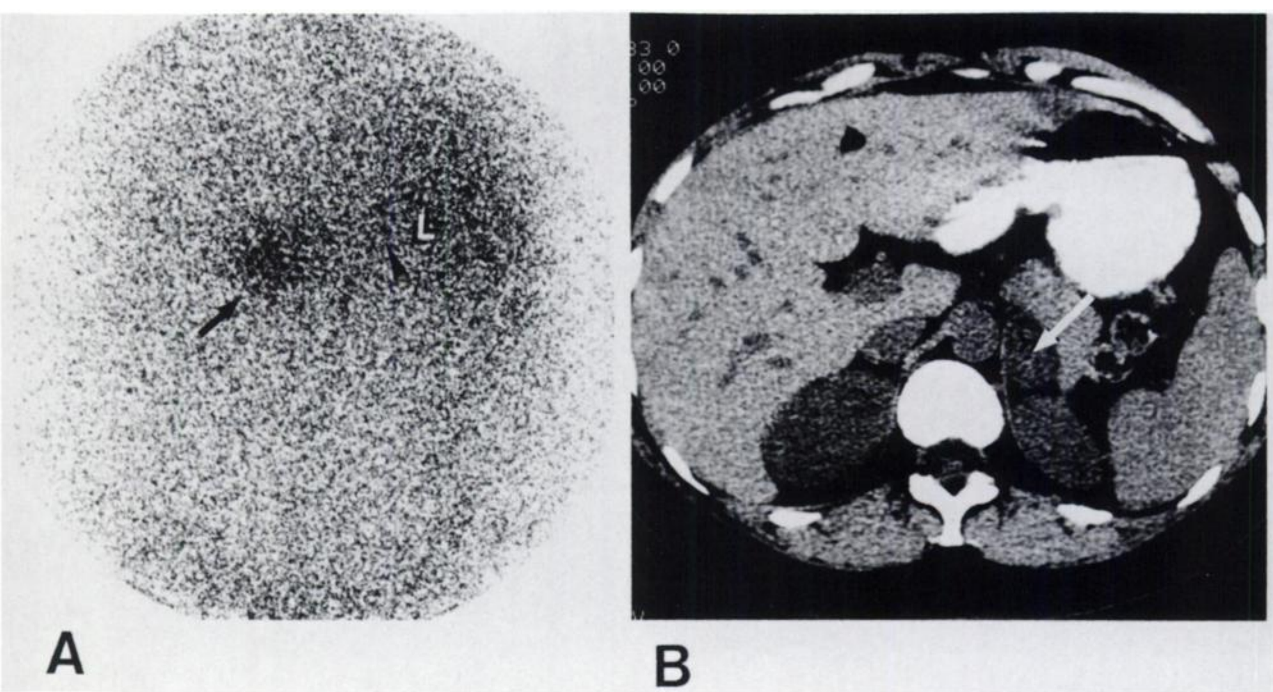

FIGURE 1. Incidentally discovered adrenal mass in a 25-yr-old female with normal adrenal biochemistry. (A) NP-59, 7 days postinjection showing tracer uptake (concordant imaging pattern) in enlarged left adrenal (arrow). Faint normal uptake is seen in the normal sized right adrenal (arrow head). L = normal liver uptake. (B) Left sided adrenal mass 2 × 3 cm (white arrow) on CT performed for abdominal pain.

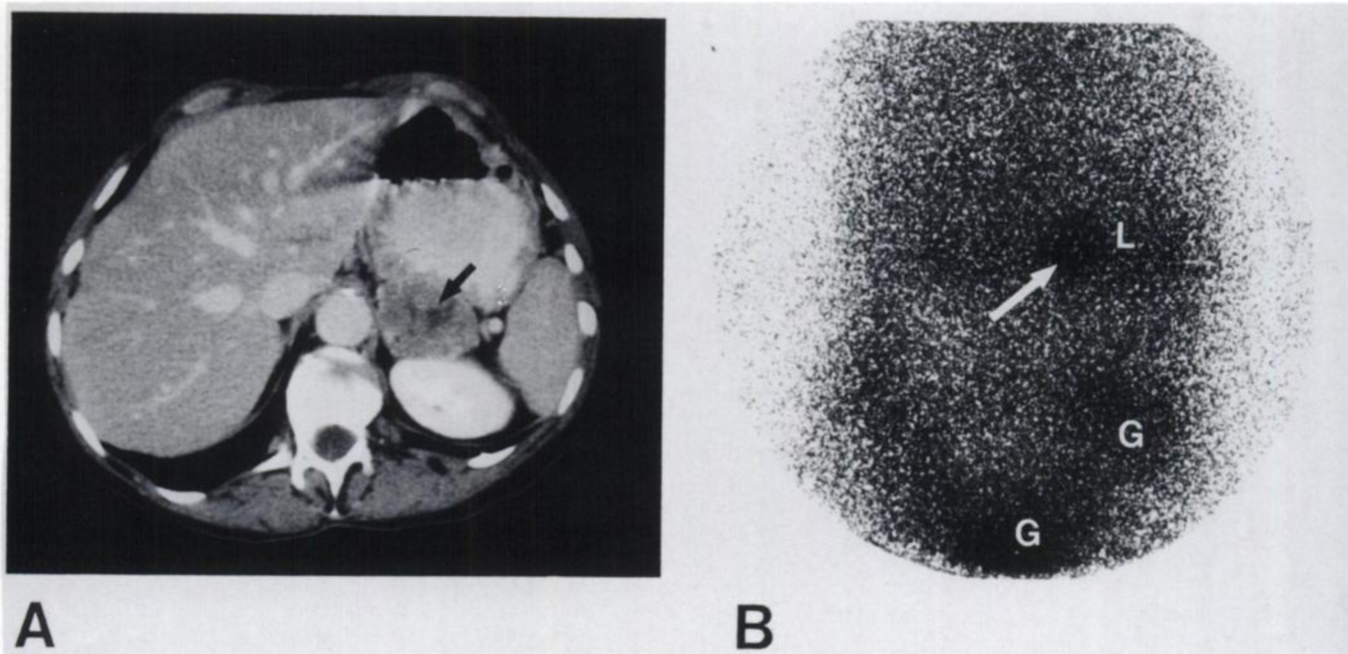

FIGURE 2. Incidentally discovered adrenal mass in a 54-yr-old female with normal adrenal biochemistry. (A) Left-sided adrenal mass 4 × 4 cm (arrow) on CT performed for abdominal pain. (B) NP-59, 7 days postinjection showing normal tracer uptake in the normal right adrenal, normal liver (L) and gut (G), distribution of tracer and absent uptake in the enlarged left adrenal (discordant imaging pattern). Left adrenalectomy revealed an anaplastic metastatic neuroendocrine tumor.

ignored and all large lesions (>5 cm in diameter) represent a malignancy is too simplistic an approach (*12*). Large series document that many metastatic and primary malignant lesions in otherwise asymptomatic and biochemically euadrenal patients are at some time during their development small, while many large lesions (>5 cm in diameter) may be benign (*18–21*). As the majority of adrenal masses will be benign regardless of their size, an accurate noninvasive diagnostic approach would be useful to distinguish malignant from nonmalignant masses and preclude unnecessary invasive evaluations (*12,20*). Numerous tests, both anatomic and functional, have been suggested as a means to distinguish adenomas from malignant or metastatic adrenal masses (*22–24*). Biochemical measurements of adrenal cortical function and a test of glucocorticoid suppressibility (and in the proper clinical context, tests of medulla function) are indicated at a minimum to exclude adrenal hypersecretion and autonomy (*25*). With the finding of normal biochemistry, a nonhypersecreting adrenal mass (an incidentaloma) may be diagnosed. In clinical practice the most important issues posed by the incidentally discovered adrenal mass once it's state of function (or dysfunction) is established is whether the mass is a metastasis or, less commonly, a primary adrenal malignancy. Further-

TABLE 3
Efficacy of NP-59 Scintigraphy in Distinguishing Space-Occupying Unilateral Adrenal Masses

Sensitivity		
TP/TP+FN	41/41+17	71% (58–89)*
Specificity		
TN/TN+FP	171/171+0	100% (95–100)*
Accuracy		
TN+TP / TN+TP+FP+FN	171+41 / 171+41+0+17	93% (88–96)*
Predictive value of a negative test		
TN/TN+FN	171/171+17	91% (86–96)*
Predictive value of a positive test		
TP/TP+FP	41/41+0	100% (95–100)*

TP = true-positive; FN = false-negative (3 metastatic adrenal tumors and 14 adenomas; see Table 2); TN = true-negative (159 concordant CT/NP-59 scans and 12 normal NP-59 scans; see Table 2); FP = false-positive.
*95% confidence limits.

more, in a patient with a known malignancy, the finding of an adrenal metastasis (if there is no other evidence of dissemination) might greatly influence tumor staging and the direction of subsequent therapy.

Clinically inapparent primary adrenal cortical carcinoma is very rare (prevalence 1 per 250,000 persons) (*1*). Because adrenal carcinoma is uncommonly encountered, studies have recommended follow-up CT scanning at 6-mo intervals to identify rapid growth of such lesions (*1,18*). Several series have attempted to define specific imaging characteristics on CT scans which may be used to increase the diagnostic likelihood that a lesion is malignant, and to select those lesions which should be surgically removed early on (*26,27*). The likelihood of an adrenal mass being malignant increases with lesions 5 cm or more in diameter (*1*), and thus it has been suggested that all lesions >3–3.5 cm in diameter, regardless of their radiologic or cytologic characteristics be removed (*18,19*). This approach would however, ignore or delay direct study of smaller adrenal lesions (2–3 cm in diameter). Furthermore, CT has been shown to underestimate adrenal size especially in masses <6 cm in diameter (*28*). If adrenal mass diameter is thus used to direct further action, underestimation of actual size may play a significant role in confounding subsequent care. Because of the relatively low incidence of both primary and metastatic neoplasms to the adrenals when compared with benign adrenal adenomas, many more benign than malignant masses would be biopsied, and/or surgically removed (*12,20*).

MRI has been used to distinguish benign from malignant adrenal masses on the basis of tissue characteristics, but their separation is by no means complete (*3,4,29–31*). Recent MR pulse sequences that allow estimation of intra-adrenal lipid content have been shown to provide discrimination of benign (lipid-rich) from malignant or metastatic (lipid-poor) lesions (*30*). Needle aspiration of adrenal masses under CT guidance can assist in diagnosis (*31–35*). The cytologic features of adrenal cells are frequently not sufficient to discern diagnostic differences between benign adenoma and adrenocortical carcinoma (*5*). Further, needle aspiration has significant morbidity (*33–35*). By relying solely upon specific CT characteristics and changes in serial CT studies obtained over several months, it would be possible to prevent some unnecessary operations to confirm clinically insignificant lesions. The complementary information provided by NP-59 scintigraphy for the noninvasive determination of relative adrenal cortical function permits the differentiation of benign from malignant disease in the vast majority of cases as demonstrated in this series.

Adrenal scintigraphy provides not only anatomic localization of the adrenal glands, but also their functional characterization due to specific accumulation of NP-59 by functioning adrenal cortical tissues (*36*). The degree of adrenocortical NP-59 uptake correlates with the level of hormonal dysfunction in Cushing's syndrome, primary aldosteronism and adrenal hyperandrogenism (*37–39*). Conversely, nonfunctioning adrenocortical carcinomas and other space-occupying or destructive lesions are depicted as areas of diminished or absent adrenal radiocholesterol uptake (*3,10,40,41*).

Iodocholesterol has previously been used to characterize nonhypersecreting adrenal masses (*42*). These masses have been referred to as nonhyperfunctioning (*43,44*). A more appropriate description is nonhypersecreting because in nonhypersecreting, there is no excessive hormone secretion but these adenomas do function in the sense of their ability to accumulate NP-59. In a selected group of patients with incidentally discovered, nonhypersecretory masses and concordant CT and NP-59 scans, the functional asymmetry of NP-59 uptake was confirmed by a parallel asymmetry of effluent adrenocortical hormone levels (*11*). The fact that, in addition to cortisol, aldosterone and androgens were also measurable in the adrenal vein effluent from the gland containing the mass, confirms that these lesions produce a full complement of adrenocortical hormones (*11*). The asymmetry of NP-59 uptake further suggests relative, but not complete, suppression of hormone output from the normal, contralateral adrenal cortex (*11*). In some cases, there is scintigraphic nonvisualization of the anatomically normal contralateral adrenal gland suggesting partial functional autonomy of the adrenal mass despite overall normal adrenal function as defined by biochemical parameters in the normal range. That a small number of these patients may evolve to secretary autonomy and hyperfunction is possible and there are recent reports that suggest functional transformation occurs, but the frequency and time course of this process remains poorly characterized (*45–48*).

In our study, concordant NP-59 and CT scans were present in 159 of the 185 patients with benign, unilateral, adrenal masses. Although many of these lacked direct pathologic confirmation, their biological behavior was characteristic of an adenoma and have been classified in this and other reports as adenomas. There were no false-positive studies; however, there were 14 false-negative scans in patients with benign masses in which there was no apparent lateralization of NP-59 uptake. These scans were considered to be normal by previous interpretative criteria, and in all of these cases, the adrenal mass was less than 2 cm in diameter (*12*). Overall, for unilateral masses having concordant imaging patterns, the specificity and predictive value of a positive scan were 100%, respectively, confirming the efficacy of scintigraphy in identifying functioning (in the sense of NP-59 uptake), but not hypersecretory (in the endocrinologic sense; e.g., an absence of elevated peripheral or urinary hormones or metabolite levels), benign adrenal masses which most likely represent adrenal adenomas (Table 3). Although biopsy and adrenalectomy confirmation was available in only a few cases, the results were uniformly benign.

The decrease or absence of discernible NP-59 uptake into an adrenal mass seen on CT (discordant imaging pattern) suggests a hypofunctional, destructive or space-oc-

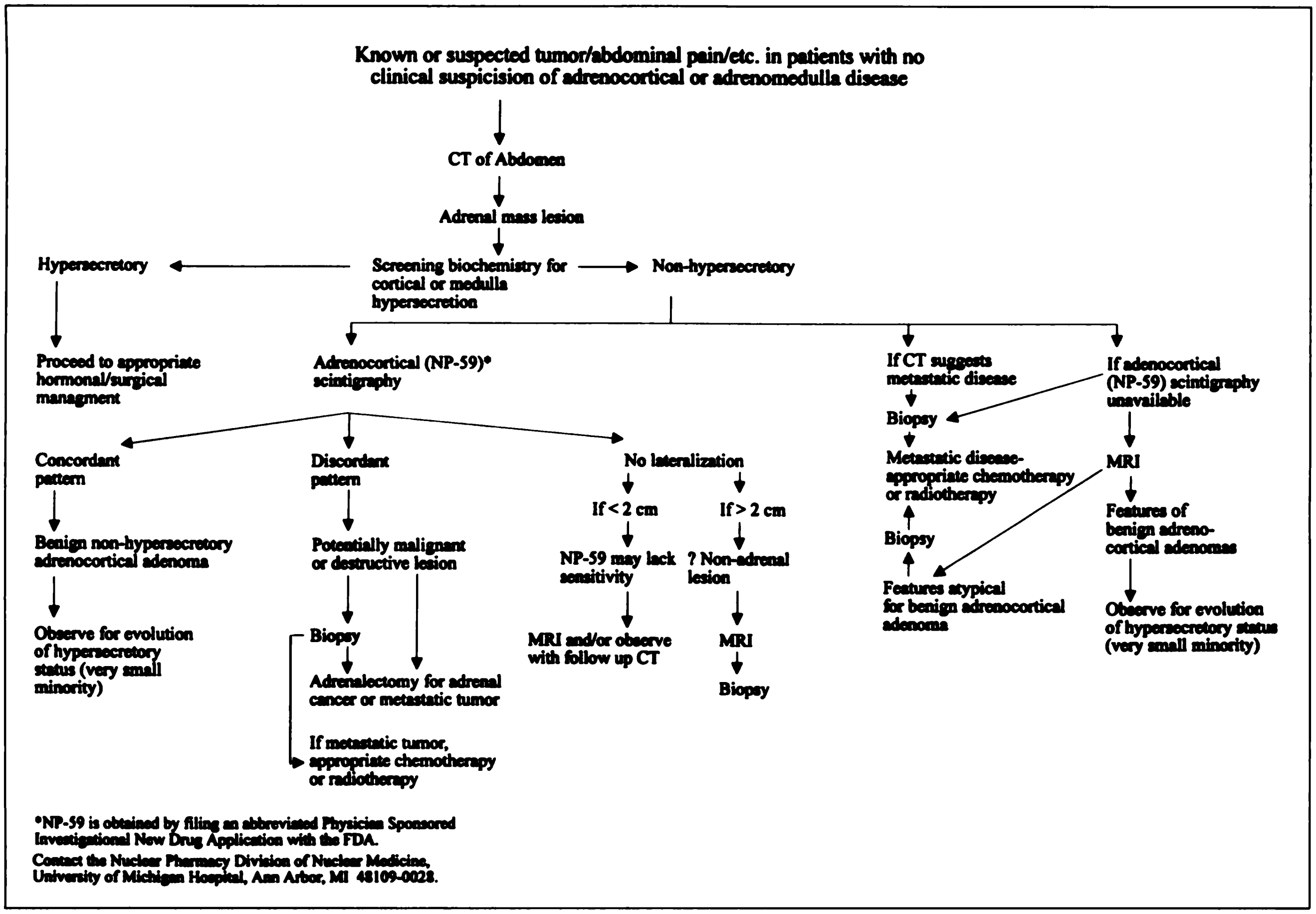

FIGURE 3. Suggested approach to the diagnostic evaluation of incidentally discovered adrenal masses.

cupying lesion (*12,15*). In the present series, 44 malignancies were identified and in 41, discordant CT and NP-59 scans were noted. In three patients with adrenal metastases, normal patterns of imaging were seen and in each instance, lesion diameters were 2.0 cm or less.

The remaining normal NP-59 scans were seen in 12 patients in whom the lesion had no direct adrenocortical involvement (Table 2). These masses were initially considered to be intra-adrenal, but because the normal NP-59 scans suggested otherwise, repeat CT or other diagnostic studies (including MRI and angiography) were used to establish their true locations. A normal NP-59 scan (nonlateralizing) should prompt reevaluation of the abdominal CT scan to confirm that a mass is truly intra-adrenal, especially if the mass is <2 cm in diameter (49,50, Nakajo M, *personal communication*). Thus, size appears to be important because some lesions <2.0 cm in diameter may not be depicted as asymmetric tracer accumulation on NP-59 scintigraphy. A mass must have sufficient size to deform or replace the adrenal cortex to result in a discordant imaging pattern, or a sufficient amount of functioning tissues to produce enough asymmetry to result in a concordant pattern of imaging in the case of benign adenomas. Although there was a difference in mean lesion diameter between the concordant and discordant groups, (2.9 ± 1.3 cm and 4.2 ± 2.1 cm, respectively; $p < 0.01$), there was considerable overlap of lesion diameter with large (>5 cm in diameter) benign (concordant) masses and small (<3 cm in diameter) malignant or space-occupying (discordant) masses. Thus, in the 2–4-cm diameter range size was a particularly poor discriminator between benign and malignant adrenal masses.

Using this approach, a nonlateralizing scintiscan in a patient with an adrenal mass represents a suspicious clinical circumstance requiring additional diagnostic study (e.g., a biopsy) (Fig. 3). Despite a small number of nonlateralizing scintiscans, a concordant CT and NP-59 study predicted a benign process, whereas a discordant CT and NP-59 study predicted a space-occupying or potentially malignant adrenal mass. Further diagnostic evaluation to include adrenal biopsy would be best directed toward the discordant and normal (symmetrical) scan groups and not to the concordant group; this approach would limit the number of patients sent for more invasive diagnostic procedures to those in whom noninvasive tests suggested a potentially malignant adrenal mass (Fig. 3). Similar observations have been made with NP-59, ^{131}I-19-iodocholesterol and ^{75}Se-selenomethylnorcholesterol *(40,41,48,50,* Nakajo M, *personal communication*). This is analogous to the use of thyroid scintigraphy in the evaluation of thyroid nodules (*36*). The scintigraphic evaluation of bilateral adrenal masses represents a more difficult problem as the present interpretative algorithm depends upon the presence of an anatomically normal adrenal gland (by CT criteria) for comparison and were omitted from this study.

Our findings have important clinical implications as they suggest that in the absence of abnormal hormone production, concordant CT and NP-59 imaging is predictive of benign, euadrenal masses, while discordant CT and NP-59 imaging is suggestive of nonfunctioning, space-occupying, destructive adrenal lesions. We conclude that NP-59 adrenal scintigraphy, as a noninvasive means to depict differential adrenal function, has demonstrable utility in complementing the anatomic imaging parameters defined by high-resolution CT (and perhaps MRI) in incidentally discovered, clinically silent, unilateral adrenal masses.

ACKNOWLEDGMENTS

The authors thank Thomas Mangner, PhD, and Clarke Hogen for the synthesis of NP-59; the Phoenix Memorial Laboratories for the use of their radiochemistry facilities; and Mary Beth Linn for secretarial assistance. Partial support for this study was provided by grants RO1-CA-43300-01, NCI CA09015, NIAMDD RO1-AM2147702 RAD and GCRC-HEW 3 M01RR-0042-21SI CLR from the National Institutes of Health; and the Department of Veterans Affairs Research Service and the Nuclear Medicine Research Fund of The Division of Nuclear Medicine, The University of Michigan.

REFERENCES

1. Copeland PM. The incidentally discovered adrenal mass. *Ann Intern Med* 1983;98:940–945.
2. Neville AM. The nodular adrenal. *Invest Clin Pathol* 1978;1:99–111.
3. Francis IR, Gross MD, Shapiro B, Korobkin M, Quint LE. Integration imaging of adrenal disease. *Radiology* 1992;184:1–13.
4. Dunnick NR. Adrenal imaging: current status. *Am J Roentgenol* 1990;154: 927–936.
5. Weiss LM. Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. *Am J Surg Pathol* 1984;8:163–169.
6. Bernardino ME, Walther MM, Phillips VM, et al. CT-guided adrenal biopsy: accuracy, safety, and indications. *Am J Roentgenol* 1985;144:67–68.
7. Yankaskas BC, Staab EV, Craven MB, et al. Delayed complications from fine-needle biopsies of solid masses of the abdomen. *Invest Radiol* 1986;21: 325–328.
8. Shapiro B, Gross MD, Sandler MD. The adrenal scan revisited: a current status report on radiotracers, clinical utility and correlative imaging. In: LM Freeman, HS Weissman, eds. *Nuclear medicine annual*. Raven Press: New York; 1967:193–232.
9. Britton KE. Imaging the adrenal cortex: why and wherefore? *Nucl Med Comm* 1992;13:485–487.
10. Fig L, Ehrman D, Gross MD, Shapiro B, Schteingart D, Glazer G. The localization of abnormal adrenal function in ACTH-independent Cushing's syndrome. *Ann Int Med* 1988;109:547–553.
11. Gross MD, Wilton G, Shapiro B, et al. Functional and scintigraphic evaluation of the silent adrenal mass. *J Nucl Med* 1987;28:1401–1407.
12. Gross MD, Shapiro B, Bouffard AJ, et al. Distinguishing benign from malignant euadrenal masses. *Ann Intern Med* 1988;109:613–618.
13. Gross MD, Valk TW, Swanson DP, Thrall JH, Grekin RJ, Beierwaltes WH. The role of pharmacologic manipulation in adrenal cortical scintigraphy. *Semin Nucl Med* 1981;9:128–148.
14. Shapiro B, Nakajo M, Gross MD, et al. Value of bowel preparation in adrenocortical scintigraphy with NP-59. *J Nucl Med* 1983;24:732–734.
15. Francis IR, Smid A, Gross MD, Shapiro B. Adrenal masses in oncologic patients. Functional and morphologic evaluation. *Radiology* 1988;166:353–356.
16. Freitas JE, Thrall JH, Swanson DP, Rifai A, Beierwaltes WH. Normal adrenal asymmetry: explanation and interpretation. *J Nucl Med* 1978;19: 149–154.
17. Remington RD, Schork MA. *Statistics with applications to biological health sciences*. Englewood Cliffs, New Jersey: Prentice-Hall; 1970;19:149–154.
18. Abecassis M, McLoughlin M, Langer B, Kudlow JE. Serendipitous adrenal masses: prevalence, significance, and management. *Am J Surg* 1985;149: 783–788.
19. Belldegrun A, Hussain S, Seltzer SE, Loughlin KR, Gittes RF, Richie JP. Incidentally discovered mass of the adrenal gland. *Surg Gynecol Obstet* 1986;163:203–208.
20. Prinz RA, Brooks MG, Churchill R, et al. Incidental asymptomatic adrenal masses detected by computed tomographic scanning: is operation required? *JAMA* 1982;248:701–704.
21. Khafagi F, Gross MD, Shapiro B, et al. Clinical significance of the large adrenal mass. *Br J Surg* 1991;78:828–833.
22. Glazer HS, Weyman PJ, Sagel SS, Levitt RG, McClennan BL. Nonfunctioning adrenal masses: incidental discovery on computed tomography. *Am J Roentogenol* 1982;139:81–85.
23. Mitnick JS, Bosniak MA, Megibow AJ, Naidich DP. Nonfunctioning adrenal adenomas discovered incidentally on computed tomography. *Radiology* 1983;148:495–499.
24. Guerrero LA. Diagnostic and therapeutic approach to the incidental adrenal mass. *Urology* 1985;26:435–440.
25. Ross NA, Aron DC. Hormonal examination of the patient with an incidentally discovered adrenal mass. *N Engl J Med* 1990;323:1401–1405.
26. Hussain S, Belldegrun A, Seltzer S, Ritchie JP, Gittes RF, Abrams HL. Differentiation of malignant from benign adrenal masses: predictive indices on computed tomography. *Am J Roentgenol* 1985;144:61–65.
27. Beland LL, Koslin DB, Kenney PJ, Stanley RJ, Lee JY. Differentiation between small benign and malignant adrenal masses with dynamic incremented CT. *Am J Roent* 1988;151:95–101.
28. Remer EM, Weinfield RM, Glazer GM, et al. MRI characterization and comparison on hyperfunctioning and nonhyperfunctioning benign adrenal cortical lesions. *Radiology* 1989;171:681–685.
29. Cufolio RJ, Vaughan ED, Brennan TG, Hirvela ER. Accuracy of computed tomography in predicting adrenal size. *Surg Gynecol Obstet* 1993;176:307–309.
30. Mitchell DG, Corvello M, Matteucci T, Petersen RO, Miettinen MM. Benign adrenocortical masses: diagnosis with chemical shift MR imaging. *Radiology* 1992;185:345–351.
31. Katz RL, Shirkhoda A. Diagnostic approach to incidental adrenal nodules in the cancer patient: results of a clinical, radiologic and fine-needle aspiration study. *Cancer* 1985;55:1995–2000.
32. Hussain S, Belldegrun A, Seltzer SE, Richie JP, Abrams HL. CT diagnosis of adrenal abnormalities in patients with primary nonadrenal malignancies. *Eur J Radiol* 1986;6:127–131.
33. Heaston CK, Handel DB, Ashton PR, Korobkin M. Narrow-gauge needle aspiration of solid adrenal masses. *Am J Roentogenol* 1982;138:1143–1148.
34. Bernardino ME, Walther MM, Phillips VM, et al. CT-guided adrenal biopsy: accuracy, safety, and indications. *Am J Roentogenol* 1985;144:67–69.
35. Berkman WA, Bernardino ME, Sewell CW, Price RB, Sones PJ Jr. The computed tomography-guided adrenal biopsy: an alternative to surgery in adrenal mass diagnosis. *Cancer* 1981;53:2098–2103.
36. Gross MD, Shapiro B, Thrall JH, Freitas JE, Beierwaltes WH. The scintigraphic imaging of endocrine organs. *Endocr Rev* 1984;5:221–325.
37. Gross MD, Shapiro B, Freitas JE, Grekin RJ, Meyers LS, Beierwaltes WH. The relationship of iodomethylnorcholesterol adrenal gland uptake to indices of adrenal zona glomerulosa function in primary aldosteronism. *J Clin Endocrinol Metab* 1983;54:477–481.
38. Gross MD, Valk TW, Freitas JE, Swanson DD, Schteingert DE, Beierwaltes WH. The relationship of adrenal iodomethylnorcholesterol uptake to NP-59 indices of adrenal cortical function in Cushing's syndrome. *J Clin Endocrinol Metab* 1981;52:1062–1066.
39. Gross MD, Shapiro B, Freitas JE, et al. The relationship of 131-6β-iodomethyl-norcholesterol (NP-59) adrenal cortical uptake to indices of androgen secretion in women with hyperandrogenism. *Clin Nucl Med* 1984;5:262–270.
40. Reschini E, Catania A. Clinical experience with the adrenal scanning agents iodine 131-19-iodocholesterol and selenium 75-6-selenomethylcholesterol. *Eur J Nucl Med* 1991;18:817–823.
41. Quraishi MA, Costanzi JJ, Balachandran S. Iodocholesterol adrenal scanning for the detection of adrenal metastases in lung cancer and its clinical significance. *Cancer* 1981;48:714–716.
42. Beierwaltes WH, Sturman MF, Ryo U, Ice RD. Imaging functional nodules

of the adrenal glands with ^{131}I-19-iodocholesterol. *J Nucl Med* 1974;15:246–257.
43. Rizza RA, Wahner WH, Spelsberg TC, Northcutt RC, Moses HL. Visualization of nonfunctioning adrenal adenomas with iodocholesterol: possible relationship to subcellular distribution of tracer. *J Nucl Med* 1978;19:458–463.
44. Guerin CK, Wahner HW, Gorman CA, Carpenter PL, Sheedy PF II. Computed tomographic scanning versus radioisotope imaging in adrenocortical diagnosis. *Am J Med* 1983;75:653–657.
45. Virkkala A, Valimaki M, Pelkonen R, et al. Endocrine abnormalities in patients with adrenal tumors incidentally discovered on computed tomography. *Acta Endocrinol (Copenh)* 1989;121:67–72.
46. McLeod M, Thompson N, Gross M, Bondeson A, Bondeson L. Subclinical Cushing's syndrome in patients with adrenal gland incidentalomas. Pitfalls in diagnosis and management. *Am Surgeon* 1990;56:398–403.
47. Jockenhovel F, Kuck W, Benker G, Lederbogen S, Olbricht TA, Reinwein D. Prognosis of untreated incidentally discovered adrenal tumors (incidentalomas) [Abstract]. *Clin Res* 1991;39:26A.
48. Reincke M, Nieke J, Krestin GP, Saeger W, Allolio B, Winkelmann W. Preclinical Cushing's syndrome in adrenal "incidentalomas": comparison with adrenal Cushing's syndrome. *J Clin Endocrinol Metab* 1992;75:826–832.
49. Troncone L, Rufini V, Daidone MS, Valentini AL. Adrenal imaging in the evaluation of incidentally discovered adrenal masses [Abstract]. *Eur J Nucl Med* 1990;160:4.
50. Tsukamoto K, Itoh K, Nakada K, Furudate M. Adreno-cortical scintigraphy to evaluate adrenal mass incidentally discovered on computed tomography [Abstract]. *Eur J Nucl Med* 1990;161:41.

EDITORIAL

Classification of Silent Adrenal Masses: Time to Get Practical

Establishing the nature of incidentally discovered adrenal masses has been a major concern in the imaging literature for more than a decade (*1–4*). Interest arises from the fact that the adrenal glands are frequently involved by metastatic disease. Benign adrenal masses are also common and are usually detected as an incidental finding on an imaging procedure performed for an unrelated diagnostic problem. The number of such masses has increased substantially because of serendipitous detection of much smaller lesions by the new generation CT systems.

Silent adrenal masses are problematic because, once they are discovered, their nature must be defined in order to exclude a metastatic lesion and, to a lesser degree, a pheochromocytoma or a primary adrenal carcinoma. As in the excellent study by Gross et al., distinction of silent adrenal masses in the imaging literature is focused on the positive identification of benign adrenocortical adenomas, which represent the most frequent incidental finding in the adrenal gland above the age of 50 (*5*).

The size of an adrenal mass has been suggested as a cost-effective prognostic criterion to separate benign from malignant disease but, as the authors indicate, fails as a single discriminator in individual patients if long-term follow-up studies are not performed. More recent criteria used on CT and MR to separate adenomas from other masses include density or intensity measurements on enhanced and non-enhanced studies and the signal intensity indexes of adrenal masses on fast low-angle shot chemical shift MR images (*6–12*). On nuclear medicine studies, discrimination is based on the accumulation of NP-59 in the adenoma productive of a concordant imaging pattern with the anatomical study (*2,13,14*). Due to the limited resolution of scintigraphy, these patterns may not be demonstrable in lesions less than 2 cm in diameter. Overall, the sensitivity of the various techniques to identify adenomas approximates 70%–80%, with a specificity of nearly 100%.

Discriminating parameters on CT, MRI and NP-59 scintigraphy for adrenal adenomas exploit the functional ability of the adrenal cortex to accumulate cholesterol esters. Adrenal scintigraphy, although not providing anatomic detail, does provide unique metabolic information in the form of the specific uptake of a radiopharmaceutical mimicking an adrenal substrate. These radiopharmaceuticals are transported in the circulation like native cholesterol bound to low-density lipoproteins (LDL), which, in turn, binds to specific LDL receptors on adrenocortical cells—following which, the cholesterol and NP-59 are internalized (*3*). In the normal adrenal cortex, both cholesterol and NP-59 are esterified and form a pool of cholesterol ester substrate from which adrenal steroid hormones are synthesized in acute situations through ACTH-mediated deesterification. An adrenal adenoma is thought to represent nontumorous overgrowth of adrenocortical cells usually from the zona fasciculata. They consist of cholesterol ester laden clear cells and are often seen at autopsy when the adjacent nonnodular cortex has become lipid-depleted as a result of the stress of dying. The composition of the lipid droplets, which no longer form a "stand-by" pool of cholesterol, probably consists of cholesterol esters in a quasi-crystalline phase, similar to cholesterol in atherosclerotic plaques (*1,3,15*).

Because of the high fat content, these lesions have a characteristic low density on CT and are easily identifiable as adrenal adenoma by this criterion alone. On MRI, the short T2 relaxation time of the quasi-crystalline phase of cholesterol esters makes these lipids generally invisible on T2-weighted spin echo sequences with long echo times. As a result, adenomas are isointense to liver on T2-weighted spin echo images and demonstrate a high fat content on chemical shift images with a short echo time. When an adenoma has a low attenuation on CT, it will have a low intensity

Received Mar. 23, 1994; accepted Mar. 28, 1994.
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