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ORIGINAL RESEARCH & CONTRIBUTIONS

Evaluation of Small Adrenal Incidental Nodules: Is Imaging Follow-Up Necessary?

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ABSTRACT

Introduction: Low incidence of adrenal cortical carcinoma in the general adult population has prompted a reevaluation of current protocol for the assessment of adrenal incidentalomas.

Objective: To determine whether follow-up imaging for small (≤ 4 cm) incidental adrenal nodules is necessary for patients without known cancer.

Methods: We performed a retrospective analysis of all patients found to have an incidental adrenal nodule on abdominal computed tomography (CT) scan during a 27-month period. The electronic medical record was reviewed to determine clinical outcomes in all patients with a minimum of 3 years of follow-up (mean follow-up = 6.7 years). Patients with a known primary cancer were excluded from the analysis unless they had a prior CT scan that documented an incidental adrenal nodule. Unenhanced CT attenuation was measured for all nodules, if available.

Results: A total of 392 patients with an incidental adrenal nodule had a mean (standard deviation [SD]) clinical follow-up of 6.7 (2.7) years. There were 200 men and 192 women with a mean (SD) age of 66.0 (13.2) years. None of these patients developed primary adrenocortical carcinoma during the follow-up period.

Two hundred forty of these patients also had a minimum 3 years of imaging follow-up (mean [SD], 6.4 [2.4] years; range, 3.1-13.6 years). There were 173 left-sided and 91 right-sided nodules on index CT scan. There was no significant difference in the mean (SD) rate of growth between left- and right-sided nodules (0.1 [0.8] mm/year vs 0.1 [0.8] mm/year, p = 0.58). Mean unenhanced CT attenuation of adrenal nodules did not affect the likelihood of adrenal malignancy during follow-up.

Conclusion: Patients with small incidental adrenal nodules do not require additional imaging to exclude the possibility of adrenocortical carcinoma.

INTRODUCTION

An adrenal incidentaloma is defined as an adrenal mass of 1 cm or larger that is incidentally discovered on cross-sectional imaging performed for reasons other than suspected adrenal disease. The incidence of adrenal incidentalomas is approximately 4% in abdominal computed tomography (CT) scans.[1] The vast majority of adrenal incidentalomas are benign, found in patients with no known malignancy.[2] However, the adrenal gland may be a site for metastases as well as hyperfunctioning adrenal lesions, such as pheochromocytomas, aldosteronomas, and Cushing syndrome, which may require intervention. The prevalence of adrenal cortical carcinoma is very low, with 1 study reporting a prevalence of only 1 case per 1.3 million people per year.[3] Furthermore, small (≤ 4 cm) adrenal incidentalomas are almost never malignant.[3]

Current American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons guidelines recommend that all patients with adrenal incidentalomas undergo hormonal evaluation, and repeat CT scan is recommended in 3 to 6 months and annually for 1 to 2 years for nonhyperfunctioning adrenal incidentalomas less than 4 cm with benign characteristics.[4]

Similarly, the American College of Radiology recommends that nondiagnostic 1 cm to 4 cm lesions in patients with no history of cancer and no prior imaging undergo 12-month follow-up with CT scan or magnetic resonance imaging (MRI).[5]

Given the relatively high and rising incidence of adrenal incidentalomas on cross-sectional imaging, and low incidence of adrenal cortical carcinoma in the general adult population, a reevaluation of current guidelines should be considered. We hypothesized that imaging follow-up of small (≤ 4 cm) adrenal incidental nodules in patients who do not have cancer at the time of imaging is not necessary.

METHODS

Our institutional review board approved this study with waiver of consent. This retrospective analysis was performed on patients all of whom belonged to a geographically isolated health maintenance organization in which all imaging is provided within the organization and in which all inpatient and outpatient information is available on an electronic medical record. We reviewed all CT scans of the abdomen performed in the first 3 months of 2008 and all 12 months of 2009 and 2010 to find every patient with an adrenal nodule. We call these CT studies the index CT scans. For each index CT scan, we reviewed the

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images of the CT scan to determine whether there was an adrenal nodule larger than 1 cm. The longest diameter of each nodule was recorded as well as the laterality of the nodule—that is, right or left. Patients with diffuse thickening of the gland without a discrete nodule were not included in this study. Our picture archiving and communication system contains all cross-sectional imaging studies obtained by the health maintenance organization since July 2001. For each patient with an adrenal nodule identified on the index CT scan, we then reviewed our picture archiving and communication system to look for the first cross-sectional imaging study of the adrenal glands. These included CT scans or MRI scans of the chest or abdomen as well as CT scans or MRI scans of the thoracic or lumbar spine if they included the adrenal glands. We call these imaging studies the initial scan. For each of these studies, we measured the longest diameter of the adrenal nodule. If there was no adrenal nodule on the initial study, the measurement was recorded as 0 mm.

None of the patients in our study developed an adrenal carcinoma at a mean of 6.7 years.

Finally, we reviewed our picture archiving and communication system to look for the most recent cross-sectional imaging study of the adrenal glands. Again, these included CT scans or MRI scans of the chest or abdomen as well as CT scans or MRI scans of the thoracic or lumbar spine if they included the adrenal glands. We call these studies the final scan. For each of these studies, we also measured the longest diameter of the adrenal nodule.

The CT studies of the first 3 months of 2008 were included in this study so that we could compare the rates of detection of adrenal nodules using multislice and single-slice CT scanners. Throughout 2008, all patients were imaged on 1 of 3 CT scanners, 2 of which were single-slice CT scanners and 1 a 4-slice scanner. At the start of 2009, 1 of the single-slice CT scanners was replaced with a 64-slice CT scanner.

For every patient with an adrenal nodule, we reviewed his/her electronic medical record to determine whether there were any relevant comorbidities related to the adrenal gland. These included any history of cancer for which the patient was undergoing regular imaging surveillance. We looked for any laboratory values related to the adrenal gland, including serum or urinary aldosterone, cortisol, metanephrines, vanillylmandelic acid, or catecholamines. We looked for any surgical pathology from an adrenal biopsy or resection. Finally, we recorded the date of their last clinical encounter and whether there was a mention of an adrenal cortical carcinoma.

All patients who did not have at least three years of clinical follow-up from the date of the initial scan were excluded from the final analysis. We also excluded all patients who carried a diagnosis of cancer unless they had a cross-sectional imaging study that demonstrated the incidental adrenal nodule that predated the patient's cancer diagnosis by at least six months.

For all patients who had at least three years of clinical follow-up, we also looked through all of their CT scans to determine whether any were performed without intravenous contrast. If one was found, we measured the mean attenuation of the nodule to determine whether the mean attenuation was less than ten Hounsfield units (HU). We also looked for any abdominal MRI studies that included in-phase and out-of-phase imaging of the adrenal glands. If such a study was found, we recorded whether there was signal drop-off on the out-of-phase images to suggest a benign adenoma. For each patient with a minimum of three years of imaging follow-up, we also measured the change in size from the time of the initial scan to that of the final scan. This value was then normalized to an annual rate of growth.

RESULTS

Figure 1 provides a flow diagram of the different patient cohorts in this study. Table 1 provides patient and nodule characteristics for each patient cohort.

There were 653 patients found to have an adrenal nodule on all index CT scans. There were 346 men and 307 women with an average age of 66.0 ± 13.2 years (range 18-101 years of age). There was no statistical difference between the mean (standard deviation [SD]) ages of the men and women (men: 65.9 [13.0] vs women: 66.1 [13.4], p = 0.86). These 653 patients had a total of 731 nodules; 412 patients had a left adrenal nodule, 163 patients had a right adrenal nodule, and 78 patients had bilateral adrenal nodules. The mean (SD) size of the left-sided nodules was 1.8 (1.1) cm. The mean (SD) size of the right-sided nodules was 2.0 (1.0) cm, which was statistically larger than the left-sided nodules (p = 0.036). Only 35 (4.8%) of the 731 nodules were larger than 4 cm on the index CT scan.

There were 155 patients who did not have at least 3 years of clinical follow-up. An additional 83 patients had a diagnosis of cancer at the time of their initial scan demonstrating an adrenal nodule or developed a diagnosis of cancer within 6 months of their initial scan and were excluded from further analysis. Fifteen patients with known cancer developed a new adrenal mass during follow-up and were excluded from the analysis. There was one 69-year-old woman who was found to have a 4.8-cm solid heterogeneous right adrenal mass with irregular enhancement on her index CT scan who had no prior imaging studies of the adrenal glands. The mass was surgically removed because it was both large and solid. This proved to be an adrenocortical carcinoma. Finally, 7 patients were excluded because they had an adrenal nodule greater than 4 cm on their index CT scan.

The remaining 392 patients had a minimum of 3 years of clinical follow-up and did not have a cancer diagnosis for at least 6 months after their adrenal incidentaloma was first seen on cross-sectional imaging. These included 200 men and 192 women. Again there was no significant difference in mean (SD) age between men and women (66.1 [12.4] vs 65.1 [13.7] years, p = 0.44). There were 44 patients with bilateral adrenal nodules whereas 250 patients had only left-sided nodules and 98 patients had only right-sided nodules.

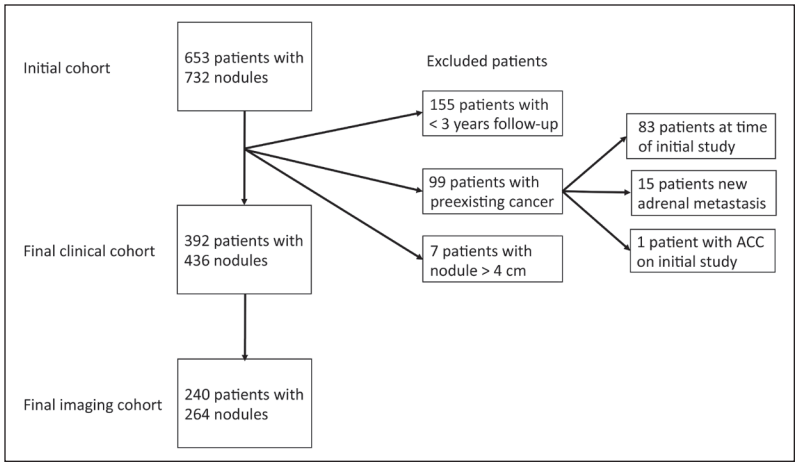

Figure 1. Flow diagram of the different patient cohorts discussed in this study.

ACC = adrenocortical carcinoma.

There was no significant difference in the mean (SD) size of the 294 left-sided nodules (1.6 [0.6] cm) compared with that of the 143 right-sided nodules (1.8 [0.6] cm) (p = 0.06).

The mean (SD) duration of clinical follow-up between the patients' initial cross-sectional imaging study demonstrating the incidental adrenal mass and the last physician office visit was 6.8 (2.7) years (range, 3.1-15.0 years). Three hundred patients did not have or develop cancer during their follow-up period. Ninety-two patients developed cancer during the study period but at least 6 months after their initial imaging study documented an incidental adrenal nodule. For these 92 patients, the mean (SD) time between their initial cross-sectional imaging study and initial cancer diagnosis was 3.6 (2.4) years (range, 0.6-12.1 years).

Of the 392 patients, 286 did not have any laboratory analysis for cortisol, metanephrines, catecholamines, or aldosterone. Eighty-eight patients underwent serum cortisol testing, of whom 13 had elevated cortisol. Seventy-three patients had urinary metanephrines and/or catecholamine evaluation, of whom 5 patients had elevated metanephrines, 1 patient had elevated catecholamines, and 1 patient had both elevated metanephrines and catecholamines. Sixty-seven patients had serum aldosterone levels checked, of whom 6 patients had elevated aldosterone but only 1 of these patients also had a low serum renin level. None of these patients with elevated levels of the various endocrine compounds had an adrenal biopsy or resection.

Only 1 patient who had laboratory evaluation underwent adrenal biopsy or resection. A percutaneous biopsy was performed in a 55-year-old man with a 4-cm left adrenal nodule and normal levels of aldosterone and catecholamines and was reported as adrenal hyperplasia or possibly an adenoma. Among the 286 patients who did not have any laboratory evaluation that could be related to the adrenal nodule, none underwent adrenal biopsy or resection during the follow-up period.

There were no patients who developed adrenocortical carcinoma during their follow-up period. None of the 92 patients who developed cancer during their follow-up period were reported to have an adrenal metastasis.

Of the 392 patients in the final clinical cohort, 255 had an unenhanced CT scan of their incidental adrenal nodule. In 138 of these patients, the nodule had a mean attenuation greater than 10 HU. Seventy-two patients had an abdominal MRI, which included in-phase and out-of-phase imaging of the adrenal nodule. In 11 of these patients, the MRI did not show the usual signal dropout on the out-of-phase images consistent with a benign adenoma. However, irrespective of the mean attenuation of the nodule on unenhanced CT scan or if the adrenal did not show intranodular fat signal on MRI, the incidental nodules in these patients were not adrenocortical carcinomas on the basis of imaging or

Table 1. Patient and nodule characteristics for each patient cohort

Description	Initial cohort: all patients	Patients with ≥ 3 years of clinical follow-up	Patients with ≥ 3 years of clinical and imaging follow-up
Number	653	392	240
Men	346	200	132
Women	307	192	108
Age, years			
Mean (SD)	66.0 (13.2)	65.6 (13.1)	67.2 (12.9)
Range	18-101	32-96	35-96
Nodules			
Total	731	436	264
Left only	412	250	149
Right only	163	98	67
Bilateral	78	44	24
Size, mean cm (SD)	1.8 (1.1)	1.7 (0.6)	1.7 (0.6)
Nodules by size			
1.0-1.9 cm	520	322	193
2.0-4.0 cm	176	114	71
> 4 cm	35	—	—

SD = standard deviation.

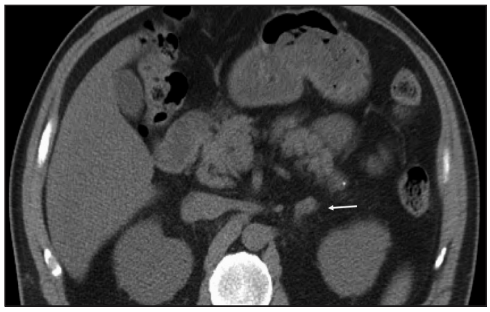

Figure 2A. Evaluation of a 55-year-old Asian man with 1.8-cm left adrenal nodule (white arrow) seen on an unenhanced index computed tomography scan in April 2011. Mean (SD) attenuation of the nodule was 20 (15) Hounsfield units.

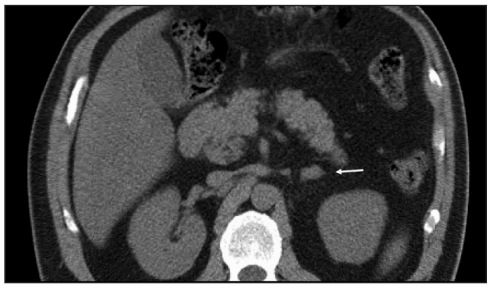

Figure 2B. Unenhanced initial computed tomography scan dated January 2007 demonstrates the same size left adrenal nodule (white arrow). Mean (SD) attenuation of the nodule on this study was 34 (19) Hounsfield units.

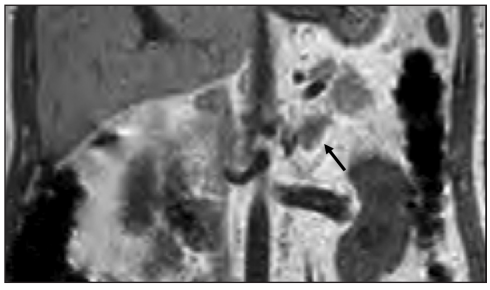

Figure 2C. In-phase coronal 1.5T magnetic resonance image (Echo time (TE) 4.6 msec) obtained in June 2009 demonstrates the same left adrenal nodule (black arrow).

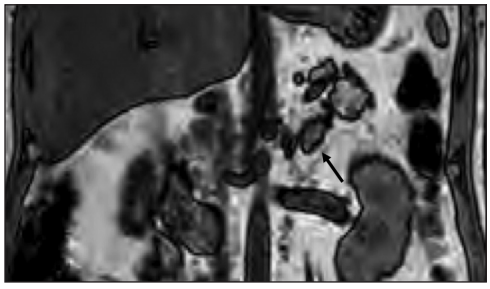

Figure 2D. Out-of-phase coronal magnetic resonance image (TE 2.3 msec) demonstrates no significant signal loss (black arrow) from intralesional fat.

SD = standard deviation; TE = time delay between excitation and echo maximum.

clinical assessment by the time of their latest clinical encounter. Figures 2A-2D demonstrate a left adrenal nodule in a 55-year-old man who was stable for more than 4 years with mean attenuation at least 20 HU on both unenhanced CT studies and that did not show fat signal on the dual-echo MRI images.

Of the 392 patients with a minimum 3 years of clinical follow-up (ie, the final clinical cohort), 240 patients with 264 nodules had at least 3 years of cross-sectional imaging follow-up (mean [SD], 6.4 [2.4] years; range, 3.1-13.6 years). These included 24 patients with bilateral adrenal nodules, 149 patients with left-sided nodules, and 67 patients with right-sided nodules. There was no significant difference in the mean (SD) size of the 173 left and 91 right adrenal nodules on the index CT studies (1.7 [0.6] cm vs 1.7 [0.6] cm, p = 0.61). There was also no significant difference in the mean (SD) annual rate of growth between the left- and right-sided nodules (0.1 [0.8] mm/year vs 0.1 [0.8] mm/year, p = 0.58). Figure 3 shows the annual growth rate of the incidental adrenal nodules. Although 131 nodules (49.6%) demonstrated slow interval growth, 133 (50.4%) remained either stable or demonstrated a slight decrease in size during follow-up.

Finally, there were 61 patients who were found to have an adrenal nodule during the first 3 months of 2008, whereas 72 and 84 patients were noted to have adrenal nodules during the first 3 months of 2009 and 2010, respectively.

DISCUSSION

The prevalence of incidental adrenal nodules is reported to be 1% to 4% approximately,[2] but the prevalence of primary adrenocortical carcinoma is very low (between 1:1,000,000 and 1:2,000,000 per patient year).[3] Therefore, the vast majority of adrenal incidentalomas will be benign. In the current era of appropriate resource utilization and assessment of clinical outcomes, there are few data that form the basis of current imaging guidelines for incidental adrenal nodules. In this study, we retrospectively reviewed the clinical outcomes of a large group of patients who were found to have incidental adrenal nodules and who had a minimum of 3 years of clinical follow-up. Our data show that these patients do not need imaging follow-up.

In a recent study of 973 patients without known cancer and adrenal incidentalomas, 782 patients were imaged using unenhanced CT scan, and their lesions were assumed to be benign because of their low attenuation (< 10 HU), but clinical follow-up was not reported.[2] For another 128 patients, a 1- to 2-year follow-up was used to document lesion stability, and these lesions were also assumed to be benign.[2] In a prospective study, Muth et al investigated the natural history of adrenal incidentalomas in 226 patients with mean follow-up of 19.0 months.[6] In this latter study, none of the 226 patients developed an adrenal carcinoma.

In our study, 392 patients with an incidental adrenal nodule had a minimum of 3 years of clinical follow-up. Of those patients who also had a minimum of 3 years of imaging follow-up, we found that 131 of their adrenal nodules demonstrated slow interval growth (0.01 mm/year to 0.5 mm/year) whereas 133 remained stable or demonstrated a slight decrease in size during follow-up. None of the patients in our study developed an adrenal carcinoma at a mean of 6.7 years. Given the large size of this cohort and the long duration of clinical follow-up, it seems relatively safe to assume that small, incidental adrenal nodules do not require imaging follow-up to ensure their benign nature.

Furthermore, our results suggest that neither the mean CT attenuation of small adrenal incidentalomas nor their MRI characteristics affect their clinical outcome. Among patients who had an unenhanced CT scan or MRI, 54% of the incidental nodules had mean attenuation greater than 10 HU on unenhanced CT scan, and 15% of the adrenal nodules did not contain fat on the basis of MRI. Yet, none of these nodules proved to be adrenal carcinomas on clinical follow-up. Previous studies have also found that adrenal nodules with attenuation greater than 10 HU are not at increased risk for malignancy.

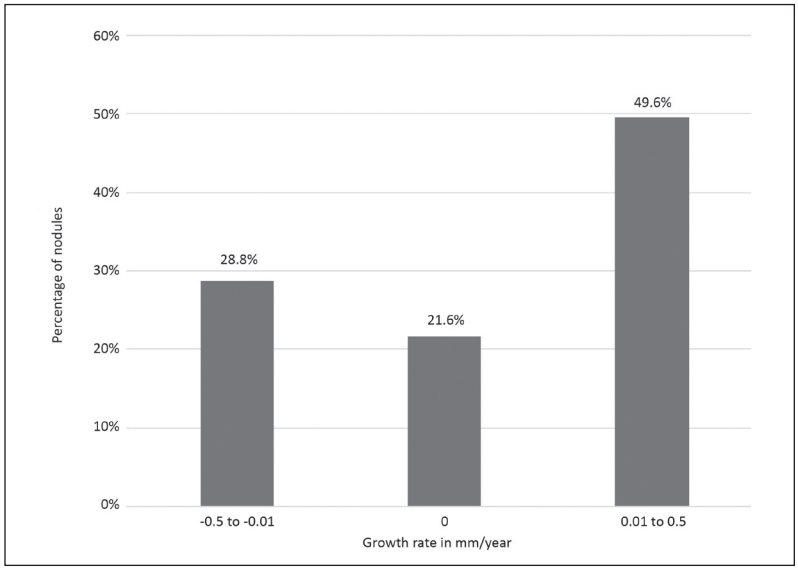

Figure 3. Growth rates of all small adrenal nodules with a minimum of three years of imaging follow-up.

For example, in the study by Song et al[2] of 1049 incidental adrenal lesions in low-risk patients, none proved to have adrenal cortical carcinoma irrespective of their Hounsfield attenuation. Similarly, in the prospective longitudinal study by Muth et al[6] of adrenal incidentalomas, no adrenal malignancy developed irrespective of imaging characteristics. Therefore, although MRI and multiphasic contrast-enhanced CT scan may be useful to assess for malignancy in patients undergoing surveillance for known cancer, their utility for adrenal incidentalomas in asymptomatic patients is not proven. CT attenuation may need to be taken into the context of other morphologic features, such as nodule contour and homogeneity.

There was only 1 patient in our study found to have adrenocortical carcinoma. A 4.8-cm mass was seen on the woman's index CT scan, which was also her first cross-sectional imaging study. The lesion did not present a diagnostic dilemma given both its large size and solid heterogeneous appearance. In a retrospective study of 15 adrenal cortical carcinomas resected over a period of 5 years, Terzolo et al[3] found that all but 1 were greater than 5 cm in size and all were irregular in appearance. Incidental adrenal nodules greater than or equal to 4 cm may benefit from surgical resection, unless they have obvious benign imaging characteristics indicative of cysts or macroscopic fat. In this study, only 35 (4.8%) of the total 731 adrenal nodules were larger than 4 cm.

We found a disproportionate number of patients with left adrenal nodules (412 patients, 63%) compared with the number of patients with right adrenal nodules (163 patients, 25%) or bilateral nodules (78 patients, 12%). Two prior studies have also reported some degree of disparity in the distribution of adrenal nodules. In a study of 268 patients with adrenal incidentalomas, Kim et al[7] found a distribution of adrenal incidentalomas between left, right, and bilateral lesions of 44.9%, 42.6%, and 12.5%, respectively. In a different Korean study of 348 patients with adrenal nodules, the distribution of left, right, and bilateral nodules was 62.0%, 30.2%, and 7.8%, respectively.[8] One possible explanation may be that the presence of the liver immediately adjacent to the right adrenal gland may decrease the conspicuity of small right-sided nodules. Whatever the reason, this discrepancy is unlikely of any clinical significance relative to malignant potential.

In this study, we noted an increase in the number of adrenal nodules detected by CT scan in the first 3 months of years 2009 and 2010 compared with 2008. This may have been caused by the replacement of a single-slice CT scanner with a new 64-slice CT scanner at the start of 2009. We expect that the number of adrenal incidentalomas will increase as CT technology continues to improve imaging resolution.

One of the limitations of this study was that 155 patients did not have at least 3 years of clinical follow-up. For most of those patients, this was caused by the loss or change of their health insurance. There were a few patients who died before 3 years of clinical follow-up. None of these patients died of adrenocortical carcinoma, according to their death notes.

Another limitation of this retrospective study is the variability of the evaluation of the incidental adrenal lesions. We were limited to the endocrine tests and additional imaging studies ordered by the patients' attending physicians, which proved to be quite variable. It was not within the scope of this study to determine the appropriateness of additional endocrine or imaging studies. However, the fact that only 27% of patients with an adrenal incidentaloma had any biochemical evaluation suggests that there is probably a need for better education of the referring physicians on the importance of functional evaluation as recommended by existing guidelines.[4,5]

Various medical groups have made recommendations on the appropriate management of incidental adrenal nodules. All of them recommend a thorough history and physical examination with appropriate endocrine laboratory tests based on clinical findings. Most guidelines also recommend additional imaging to determine whether adrenal incidentalomas should be considered benign using unenhanced or multiphasic CT scan or MRI scan. On the basis of the results of this study, we would recommend that additional imaging evaluation for small (≤ 4 cm) adrenal nodules incidentally found on cross-sectional imaging is not necessary in patients without known malignancy because the risk of malignancy is very low. Naturally, if the patient has a prior imaging study of the adrenal nodule,

comparison should be made to document lesion stability. Patients in whom a pheochromocytoma or other functional tumor is suspected should have biochemical evaluation and may benefit from additional imaging characterization if biopsy or surgery is being considered. In patients with known cancer and a previously documented adrenal incidentaloma, routine surveillance should be continued, but additional imaging just for the incidentaloma is unnecessary. New adrenal lesions should be evaluated as a possible metastatic focus.

CONCLUSION

In patients without preexisting cancer, additional imaging for small incidental adrenal nodules is unnecessary. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Some Important Office

The functions of the supra-renal capsules … are almost or altogether unknown. The large supply of blood which they receive from three separate sources; their numerous nerves, derived immediately from the semilunar ganglia and solar plexus; their early development in the foetus; their unimpaired integrity to the latest period of life; and their peculiar gland-like structure; all point to the performance of some important office.

— *On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules,*
Thomas Addison, 1793-1860, renowned English physician and scientist