ORIGINAL RESEARCH & CONTRIBUTIONS

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

Kara M Young; Michael K Wong; Myles M Mitsunaga, MD; Hyo-Chun Yoon, MD, PhD

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

³Current 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).³ 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

Kara M Young is a Senior at Bryn Mawr College and was a Summer Research Associate in Diagnostic Imaging at the Moanalua Medical Center in HI. E-mail: tokmyoung@dccglobal.net. Michael K Wong is a Freshman at Yale College at Yale University and was a Summer Research Associate in Diagnostic Imaging at the Moanalua Medical Center in HI. E-mail: mwong15@punahou.edu. Myles M Mitsunaga, MD, is a Resident in Radiology at the University of California, Davis Medical Center in CA. E-mail: mylesm@hawaii.edu. Hyo-Chun Yoon, MD, PhD, is the Associate Chief of Diagnostic Imaging at the Moanalua Medical Center in HI. E-mail: hyo-chun.yoon@kp.org.
None of the patients in our study developed an adrenal carcinoma at a mean of 6.7 years.
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
The prevalence of incidental adrenal nodules is reported to be 1% to 4% approximately, but the prevalence of primary adrenocortical carcinoma is very low (between 1:1,000,000 and 1:2,000,000 per patient year). 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 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.

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. 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. 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. In this latter study, none of the 226 patients developed an adrenal carcinoma.

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, but the prevalence of primary adrenocortical carcinoma is very low (between 1:1,000,000 and 1:2,000,000 per patient year). 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.

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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.
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\(^3\) 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\(^4\) 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\(^5\) 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.\(^6\) 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.\(^6\)\(^5\)

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,
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