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Original research

The impact of an adrenal incidentaloma algorithm on the evaluation of adrenal nodules

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ABSTRACT

Objective: To determine the impact of the use of an electronic medical record tool on the evaluation of adrenal incidentalomas.

Methods: Retrospective chart review was used to compare rates of hormone testing and follow up imaging for adrenal incidentalomas. Patients whose radiology reports contained an algorithm with recommendations, based on our 2013 clinical guideline for the workup of these nodules, were compared to those whose imaging reports did not contain the algorithm.

Results: For patients whose Radiology reports contained the algorithm, 69% had hormonal testing versus 43% of controls ($p < 0.0001$). By contrast, 57% of study group patients had a follow up imaging study, compared to 51% of controls ($p = 0.1000$). However, when the 18% of controls that were given guidance by the radiologist to perform follow-up imaging were excluded from those who received no guidance, there was a statistically significant difference in the rate of follow up imaging (57% vs 48%, $p < 0.0001$).

Conclusion: Implementation of a clinical algorithm for the evaluation of adrenal incidentalomas in radiology reports and on the intranet site of a major clinical center led to improved rates of hormone testing. There was also a significant increase in the rate of follow up imaging, compared to when no guidance was given. Additional efforts to further improve performance are needed to increase the detection of clinically significant lesions, particularly hormone secreting tumors that should be removed.

Introduction

The aim of this study was to determine the impact of the use of an electronic medical record tool on the evaluation of incidentally discovered adrenal nodules (adrenal incidentalomas).

The 2002 National Institutes of Health (NIH) guidelines defined an incidentaloma as a 'clinically inapparent adrenal mass discovered inadvertently in the course of diagnostic testing or treatment for other clinical conditions that are not related to suspicion of adrenal disease.' Further, the definition excluded patients undergoing imaging procedures as part of the staging and workup of cancer [1]. Consistent recommendations for the follow up of these lesions have been lacking, due to the absence of large evidence-based trial data outlining an effective long term approach [2], and guidelines for management of adrenal incidentalomas continue to evolve.

In 2009, the American Association of Clinical Endocrinologists (AACE) and American Association of Endocrine Surgeons (AAES) published guidelines that reinforced recommendations for biochemical evaluation, both at the time of diagnosis and annually up to 5 years. The AACE/AAES guidelines also recommend additional imaging for lesions that do not fulfill criteria for surgical resection, namely those that are not pheochromocytomas, aldosteronomas, or cause Cushing's syndrome and have imaging characteristics of benign adrenal nodules, every 3–6 months for 1–2 years [3].

At the end of our study period, the 2016 European Society of Endocrinology (ESE) and European Network for the Study of Adrenal Tumors (ENSAT) clinical practice guideline emerged, recommending in patients with no known extra-adrenal malignancy, no further imaging for < 4 cm adrenal masses with clearly benign imaging features, due to virtually no risk of malignant transformation. For patients with an indeterminate lesion who do not undergo adrenalectomy, a 6–12 month repeat imaging study to assess for growth is recommended [4].

Subsequently, a 2017 American College of Radiology (ACR) white paper, which is a revision of the 2010 publication recommending

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biochemical testing of adrenal hormones only when "clinical signs and symptoms of adrenal hyperfunction are present" [5], was published, advising "routine biochemical testing for most incidentally discovered adrenal masses," based on AACE/AAES guidelines [6].

In 2008, we examined the laboratory and imaging evaluation of incidentally discovered adrenal nodules at a large metropolitan health care center [7]. We found that although most adrenal incidentalomas are benign, nonfunctional tumors that don't often change significantly in size, the adherence to existing guidelines for the clinical evaluation of these nodules, published in 2002 by the NIH [1], was poor. In our study, only 30% of patients with incidentalomas had documented laboratory evaluation for hormone secretory status, while 76% of patients had at least one follow-up CT scan. When patients were seen by an endocrinologist, the nodules were routinely evaluated for hormone secretion. We concluded that more education was needed for primary care clinicians about the appropriate evaluation and follow-up of these nodules. Other studies, both within the USA and in other countries, performed in community hospitals and university centers, have also confirmed low rates of hormone testing and imaging follow up for adrenal incidentalomas [8–10]. This study is a follow up to our 2008 study.

Patients and methods

We retrospectively reviewed imaging studies performed at Harvard Vanguard Medical Associates/Atrius Health, a multispecialty group comprised of primary care clinicians including family practitioners and internists, as well as staff radiologists and endocrinologists, that provides care to over 700,000 patients in and around the Boston area. We included all chest or abdominal CT scans or MRI studies done at multiple sites within our health system during the study period between April 2013 and October 2016. The scans were read either by a radiologist who incorporated the clinical algorithm in the Impression section of the report, and/or a link to the intranet site where the algorithm is posted, or a radiologist who did not have access to or utilize the algorithm or link. The clinical algorithm contains specific recommendations for the ordering clinician about laboratory evaluation and follow up imaging ([11], and Appendix Fig. 1).

Using a key word search for "adrenal nodule", "adrenal mass/masses" and "adrenal lesion(s)", 1020 patients with 1210 adrenal nodules were identified on imaging done during the 3.5 year study period. Radiology reports and medical records were manually reviewed by two individuals. Patients whose imaging study was performed as part of the workup of a known extraadrenal malignancy, or who had a subcentimeter, poorly defined nodule, or adrenal gland thickening were excluded from the study group. Patient groups were separated into those that had the clinical algorithm and/or link to the intranet site in their radiology reports, versus those that did not. For scans that did not contain the algorithm or link, the presence of a clinical recommendation by the radiologist was recorded. We separately analyzed those who had an adrenal nodule detected prior to the study period and compared them to those that were identified during the study period. Laboratory evaluation, including at least one of the following measurements: 24 h urine collection for catecholamines, metanephrines, VMA (vanillylmandelic acid), overnight dexamethasone suppression testing for serum cortisol or 24 h urine free cortisol, and when indicated for those with either hypokalemia or hypertension, determination of serum aldosterone to plasma renin activity ratio, was documented. When reported, lesion size, density, characteristics (including those based on CT washout studies), follow-up size, a clinical diagnosis or treatment associated with the adrenal nodule, and whether the patients were seen by an endocrinologist, were recorded. Statistical analysis was performed with chi-square testing.

This study was approved by the Institutional Review Board (IRB) of Harvard Pilgrim Health Care. Individual patient authorization was waived by the IRB, according to the HIPAA Waiver of Authorization criteria.

Table 1
Reported Size and Imaging Characteristics of All Adrenal Nodules.

Extraadrenal Malignancy (number of patients)	Size < 4 cm	Size ≥4cm	Low density, HU ≤ 10 or loss of signal intensity on MRI	High density, HU > 10, heterogeneous, or no loss of signal intensity on MRI
No (n = 893)	813	28	313	104
Yes (n = 127)	102	8	15	12
Total (n = 1020)	915	36	328	116

Results

During the study period, 1020 patients with one or more adrenal nodules were identified. 127 patients were known to have extraadrenal malignancy and their imaging was done for staging purposes. A total of 1210 adrenal nodules were found (see Table 1 for imaging characteristics). The average size for the 951 nodules that were measured was 17.6 mm. Of those, 915 measured less than 4 cm, and 36 nodules measured greater than or equal to 4 cm. Eight of the nodules that were > 4 cm in size were in patients who were known to have an extraadrenal malignancy. Hounsfield unit density (HU) or MRI signal intensity was reported for 444 nodules: 328 were described as low density, had HU ≤ 10, or loss of signal intensity on out-of-phase (OOP) MRI and 116 nodules were reported as either high density, heterogeneous, HU > 10, or had no loss of signal intensity on OOP MRI. Of the 328 with low density nodules, 313 were in patients without a known extraadrenal malignancy, and of the 116 high density nodules, 104 nodules were in patients without a known malignancy (Table 1).

Table 2
Use of Clinical Algorithm.

	Algorithm and/or link (183 scans)	Control (710 scans)	P-value
Follow up scan	105 (57%)	359 (51%)	0.1000
Prior scan	44 (24%)	247 (35%)	0.0057
No prior or post scan	34 (19%)	104 (15%)	0.1895
Hormonal Testing	126 (69%)	308 (43%)	< 0.0001
Seen by Endocrinologist	79 (43%)	291 (41%)	0.5929

Table 3
Rate of Follow Up Imaging With Algorithm-link vs No Algorithm-link or Radiology Guidance.

	Follow up scan	No scan	P Value
Algorithm-link	105/183 (57%)	34/183 (19%)	< 0.0001*
Control with no guidance	280/584 (48%)	304/584 (52%)	

* p value represents the rate of follow up scans in the study group vs control group with no guidance

Guidance for reimaging varied from within 12 months for low risk lesions to 3–6 months for high risk lesions. During the study period, 23 nodules increased significantly in size, defined as growth > 5 mm. None of the patients without a prior history of malignancy proved to have adrenal metastases.

127 patients who had a known extraadrenal malignancy were excluded from the study group, leaving 893 patients who had adrenal incidentalomas. 183 of the study group patients had the adrenal nodule management algorithm in their Radiology reports, or a link to the algorithm embedded in the report. The remaining 710 patients did not have the algorithm or link in the Radiology report. 18% of Radiology reports in this subgroup had guidance about imaging follow up.

Imaging Follow-up

Within the study group, namely those that had the algorithm and/or link, 57% had a follow up imaging study, 24% had an imaging study that identified the nodule prior to the study period, and 19% had neither a preceding scan nor a follow up scan. The rate of follow up imaging was not significantly different between the study group and the control group (Table 2). However, when the control group reports were further analyzed for presence or absence of Radiology guidance, we found significant improvement in the rate of follow-up imaging for patients whose reports contained a radiologist recommendation (63% vs 48%, p = 0.0027) (Appendix Table 1). Additionally, there was a significant difference between the rate of follow-up imaging in patients whose reports contained the algorithm/link versus those whose reports contained neither the algorithm/link, nor guidance from a radiologist (57% vs 48%, p < 0.0001) (Table 3). A total of 370 patients from both study and control groups saw an endocrinologist during the study period. Of those, 58% had a follow up imaging study for the adrenal nodule vs 47% of patients who did not see an endocrinologist (p < 0.0001, Appendix Table 2).

Biochemical testing

For patients whose Radiology reports contained the algorithm and/or link, 69% had hormonal testing versus 43% of patients in the control group (p < 0.0001). There was no significant difference in the number of patients who saw an endocrinologist between the study group and the control group (Table 2). 77% of the 370 patients who saw an endocrinologist had hormone testing for the adrenal nodule, while only 29% of the patients who did not see an endocrinologist had hormone testing (p < 0.0001, Appendix Table 2).

Outcomes

A definitive diagnosis was made in 78 cases. Of the 42 cases that proved to be hormonally active tumors, 14 patients had abnormal cortisol levels on biochemical testing: 4 patients had Cushing's syndrome, 4 had subclinical Cushing's, and 6 were not further characterized. 20 patients were found to have primary hyperaldosteronism and 8 had pheochromocytomas. Eleven patients had adrenalectomy, 7 for pheochromocytoma, 2 for aldosteronoma, one for a nonsecretory adenoma and one for myelolipoma. One patient had radiofrequency ablation of 2 unilateral adenomas producing both aldosterone and cortisol. The remaining patients had diagnostic radiologic imaging characteristics of nonadenomatous disease, including cysts, adrenal hemorrhage, myelolipomas, and schwannoma. No cases of adrenocortical carcinoma or metastasis in someone without a known prior diagnosis of malignancy were found.

Discussion

In our 2008 study evaluating the radiologic and hormonal evaluation of adrenal incidentalomas at a large metropolitan medical center, we found that compliance with the 2002 NIH guidelines by primary care clinicians was low. In that study, which examined a smaller patient population between 2003 and 2005, 24% of patients did not have a follow up scan and only 18% of patients who were not seen by an endocrinologist had testing for adrenal hormone hyperfunction [7]. This underscored the need for more education about recommendations for the appropriate workup of these lesions. After implementing a clinical algorithm in our radiology reports, we found that the rate of hormonal evaluation of adrenal incidentalomas increased significantly, regardless of whether the patient saw an endocrinologist. When scans that contained guidance about follow up imaging from the radiologist were separated out from the control group, the rate of follow up imaging also improved. When patients did see an endocrinologist, they had a significantly higher likelihood of having hormonal testing than when they did not see one. Since the algorithm/link has guidance for referring patients to Endocrinology, improved rates of hormone testing in the study group patients who saw an endocrinologist was not independent of the presence of the algorithm/link.

We found several reasons for the lack of hormone testing or imaging follow up, despite the use of a clinical algorithm to guide clinicians. In some cases, labs and imaging studies were ordered, but never completed by the patient. For patients that had evaluation of the adrenal nodule prior to the study period (in some cases up to 10 years prior), laboratory testing or imaging of a nodule previously shown to be stable in size and appearance, and not hormonally active, was not repeated since follow up testing may have been viewed as unnecessary or not cost-effective and an individualized approach to management based on the clinical findings was therefore utilized. [12–14] The different rates of follow up imaging could have also been affected by the higher rate of prior imaging in the control group (35% vs 24%, p 0.0057, Table 2) and

adaptation of imaging guidance from emerging guidelines in 2016.

While the study protocol included a search for imaging studies done outside our system, we may not have identified outside imaging studies in all cases. And for patients whose incidentaloma was identified near the end of the study period, a follow up scan may not yet have been scheduled or completed by the time the data was collected.

Some patients saw an endocrinologist during the study period and did not have imaging follow up or laboratory evaluation. This may have been due to a number of reasons, including seeing the patient for another diagnosis, or not being aware that the patient had an adrenal nodule.

The algorithm provides specific guidance about which laboratory tests to order and follow up imaging recommendations. Interestingly, we found a slightly higher rate of laboratory testing for patients whose scan reports quoted the clinical algorithm, as opposed to a link to the algorithm (Appendix Table 3). This difference may have been due to the fact that utilizing the link required an additional step for the clinician to open the URL and find the guidelines and suggests that embedding recommendations from the algorithm within the radiology report may be more useful than simply including a link.

There are several potential reasons why Radiology reports in this study did not contain the management algorithm: the scans were performed at an imaging center whose Radiology department protocol did not utilize the algorithm; the radiologist who interpreted the study made his or her own recommendation for imaging follow up interval and/or hormonal evaluation, the latter based on 2010 ACR guidelines, which only recommended hormone testing based on clinical signs or symptoms of adrenal hyperfunction [5]; or the imaging study was done for a specific diagnostic purpose (e.g. lung cancer screening or CT urogram for hematuria). The influence of the recommendations made by the reporting radiologist in turn may explain the low rates of investigation of adrenal incidentalomas, as Wikramarachchi also found [15]. When the Radiologist gave a diagnostic impression and follow up recommendation in the report, the rate of follow up imaging was improved.

The goal of evaluating adrenal incidentalomas is to identify malignancy or hormone-secreting lesions. We did not identify any cases of adrenal carcinoma or adrenal metastases in this study. Yet 42 of a total of 434 patients who had laboratory testing were found to have hormonal abnormalities in this study, or approximately 10%. 586 patients in this study did not have hormone testing. Assuming a rate of 10% comparable hormonal abnormalities in these 586 untested patients, 58 cases of patients with hormonal abnormalities would have been missed.

Although there is uncertainty about the clinical impact of subclinical Cushing's syndrome [16–23], at least 76% of the functional tumors in this study were pheochromocytomas, aldosteronomas or adenomas causing Cushing's syndrome, underscoring the importance of hormonal evaluation of adrenal incidentalomas.

Our study has several limitations. It was a retrospective review. Radiologic analyses were performed by multiple radiologists and were sometimes incomplete. Images that did not have HU density measurements or MRI signal intensity reported were not re-read or re-analyzed prior to inclusion in our database. Follow up periods were relatively short and only comprised one additional image. Guidance was based on older clinical guidelines that were in place during the study period.

Despite these limitations, we have demonstrated that use of our EMR tool led to improved rates of evaluation of adrenal incidentalomas and, most important, identification of functional tumors, many of which were clinically significant.

Conclusion and recommendations

We have shown that implementation of a clinical algorithm with guidelines for the evaluation of adrenal incidentalomas in the radiology reports identifying these lesions led to improved rates of hormone testing. Follow up imaging performance was improved by either the use of the algorithm-link or a recommendation by the radiologist. Our experience indicates that electronic medical record tools that provide guidance about how to evaluate incidentally discovered adrenal nodules, an area that we and others have previously shown is suboptimal, substantially increases the detection of clinically significant hormone secreting tumors. Adoption of an EMR algorithm within radiology reports, with revisions based on current clinical guidelines, and additional efforts to highlight this diagnosis within the medical record should lead to better detection of clinically significant adrenal nodules.

Declaration of interest

Funding for this project was provided by an unrestricted research grant from Corcept Therapeutics, Inc. The authors declare that there is no conflict of interest prejudicing the impartiality of the research reported here.

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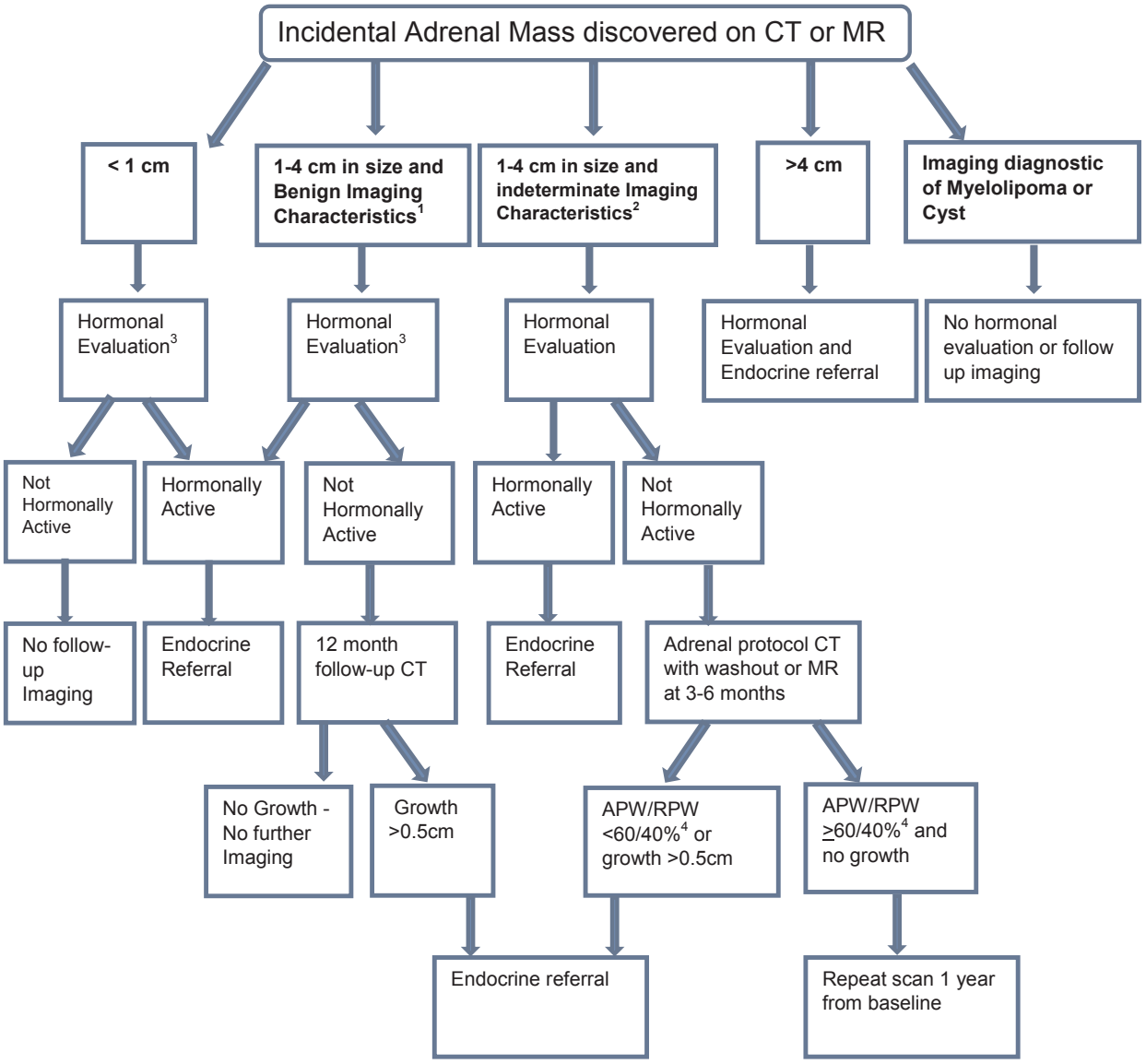
Appendix 1

See Appendix Fig. 1 and Table 1.



Legend:

1 Benign imaging characteristics: homogeneous, smooth borders, HU ≤ 10 on non-contrast CT or decreased signal intensity on chemical shift MRI

2 Indeterminate imaging characteristics: heterogeneous, necrosis, irregular margins, HU>10 or no loss of signal intensity on chemical shift MRI

3 Hormonal evaluation: 24 hour urine fractionated metanephrines, overnight 1 mg dexamethasone suppression test for cortisol, and in hypertensive patients, serum K and plasma aldosterone concentration/plasma renin activity (PAC/PRA) ratio

4 APW=Absolute Percentage Washout, RPW=Relative Percentage Washout

Appendix Fig. 1.

Appendix Table 1
Rate of Follow Up Imaging in Control Group, With or Without Guidance About Follow Up Imaging

Controls (710)	Follow up scan	No scan	P value
Guidance (126) (18%)	79 (63%)	47 (37%)	0.0027*
No guidance (584) (82%)	280 (48%)	304 (52%)	

* p value represents the rate of follow up scans in guidance vs no guidance

Appendix 2

See Appendix Table 2.

Appendix Table 2
Evaluation by Endocrinologists.

	Seen by Endocrinology (370 patients)	Not seen by Endocrinology (523 patients)	P value
Follow up Scan	216 (58%)	248 (47%)	< 0.0001
Labs	284 (77%)	150 (29%)	< 0.0001

Appendix 3

See Appendix Table 3.

Appendix Table 3
Use of Algorithm alone vs Link with Algorithm.

Total 893	Algorithm with link (n = 127) (14%)	Algorithm only (n = 56) (7%)	Control (n = 710) (79%)
Follow up scan	66/127 (52%)	39/56 (70%)	359/710 (51%)
Prior scan	35/127 (28%)	9/56 (16%)	247/710 (35%)
No prior or post scan	26/127 (20%)	8/56 (14%)	104/710 (15%)
Seen by Endocrinologist	53/127 (42%)	26/56 (46%)	291/710 (41%)
Labs	85/127 (67%)	41/56 (73%)	308/710 (43%)

Appendix 4. Algorithm for management of adrenal incidentalomas

Background

The definition of an incidentally discovered adrenal nodule applies to a clinically inapparent adrenal mass that is greater than 1 cm in size, found in the course of diagnostic testing or treatment for other clinical conditions, and not related to suspicion of adrenal disease. The definition excludes patients undergoing imaging procedures as a part of staging and workup for cancer. For incidentally discovered adrenal masses with diagnostic features of a myelolipoma or cyst, no hormonal evaluation or follow up imaging is needed. For all other incidental adrenal masses greater than 1 cm in size, biochemical evaluation for adrenal hormone hyperfunction should be performed.

Biochemical evaluation

Should include 24 h urine fractionated metanephrines, overnight 1 mg dexamethasone suppression test for cortisol, and in hypertensive patients, measurement of serum potassium and plasma aldosterone concentration /plasma renin activity ratio.

1–4 cm nodules with benign imaging characteristics

For incidentally discovered adrenal masses that are 1–4 cm in size with benign imaging characteristics (homogeneous, smooth borders and noncontrast HU ≤ 10 or decreased signal intensity on chemical shift MRI with in and out of phase T1 imaging), proceed to hormonal evaluation as above. If the hormone evaluation is negative, perform 12 month follow up noncontrast CT scan. If the one year follow up scan shows growth of the mass (greater than 0.5 cm), or if there is evidence of hormonal activity, refer to Endocrinology.

1–4 cm nodules with indeterminate imaging characteristics

For incidentally discovered adrenal masses that are 1–4 cm in size, but with indeterminate imaging characteristics (noncontrast HU > 10 or no loss of signal intensity on MRI, necrosis, heterogeneous density, or irregular margins), proceed to hormonal evaluation. If the hormone evaluation is negative, consider a dedicated adrenal CT with delayed washout or chemical shift MRI as the follow up study in 3–6 months. If the follow up scan shows growth of the mass (greater than 0.5 cm), or if there is evidence of hormonal activity, or if the washout study is not consistent with an adenoma, refer to Endocrinology. If there is no change in size, no hormonal activity, and washout study is consistent with a benign adenoma, repeat the scan one year after the baseline study.

Nodules > than 4 cm

For incidentally discovered adrenal masses that are > 4 cm in size, proceed to hormone testing, and then refer to Endocrinology.

Appendix 5. Radiology report terminology

The following 3 types of recommendations were included in the radiology reports following creation of algorithms

Lesion 1–4 cm consistent with adenoma

Hormonal Evaluation – plasma or urine metanephrines and normetanephrines; overnight 1 mg dexamethasone suppression test; in hypertensive patients, serum K and plasma aldosterone concentration/plasma renin activity (PAC/PRA) ratio. If NOT hormonally active → 12 month f/u NON-CONTRAST CT abdomen

Lesion 1–4 cm – Indeterminate

Hormonal Evaluation – plasma or urine metanephrines and normetanephrines; overnight 1 mg dexamethasone suppression test; in hypertensive patients, serum K and plasma aldosterone concentration/plasma renin activity (PAC/PRA) ratio. If NOT hormonally active → Adrenal CT washout or MRI with contrast at 3–6 months

Lesion > 4 cm

Hormonal Evaluation – plasma or urine metanephrines and normetanephrines; overnight 1 mg dexamethasone suppression test; in hypertensive patients, serum K and plasma aldosterone concentration/plasma renin activity (PAC/PRA) ratio. Endocrinology Consult

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jcte.2018.07.001.

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