Optimal follow-up strategies for adrenal incidentalomas: reappraisal of the 2016 ESE-ENSAT guidelines in real clinical practice

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Abstract

Objective: Recently, the European Society of Endocrinology (ESE), in collaboration with the European Network for the Study of Adrenal Tumors (ENSAT), asserted that adrenal incidentalomas (AIs) <4 cm and ≤10 Hounsfield units (HU) do not require further follow-up imaging. To validate the clinical application of the follow-up strategies suggested by the 2016 ESE-ENSAT guidelines, we explored the clinical characteristics and natural course of AIs in a single center over 13 years.

Design and methods: This retrospective cohort study included a total of 1149 patients diagnosed with AIs between 2000 and 2013 in a single tertiary center. Hormonal examination and radiological evaluations were performed at the initial diagnosis of AI and during the follow-up according to the appropriate guidelines.

Results: The mean age at diagnosis was 54.2 years, and the majority of AIs (68.0%) were nonfunctional lesions. Receiver operating curve analysis was used to discriminate malignant from benign lesions; the optimal cut-off value for mass size was 3.4 cm (sensitivity: 100%; specificity: 95.0%), and that for the pre-contrast HU was 19.9 (sensitivity: 100%; specificity: 67.4%). The majority of nonfunctional lesions did not change in size during the 4-year follow-up period. Applying a cut-off value of 1.8 μg/dL after a 1-mg overnight dexamethasone suppression test, 28.0% of all nonfunctional AIs progressed to autonomous cortisol secretion during the follow-up period. However, we observed no development of overt Cushing's syndrome in the study.

Conclusions: We advocate that no follow-up imaging is required if the detected adrenal mass is <4 cm and has clear benign features. However, prospective studies with longer follow-up are needed to confirm the appropriate follow-up strategies.

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Introduction

Adrenal incidentalomas (AIs) refer to adrenal masses discovered on imaging studies performed for conditions unrelated to suspected adrenal diseases. Owing to the wide use of imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI), the prevalence of AI has dramatically increased in recent years. AIs are detected in less than 1% of patients younger than 30 years old but in more than 7% of patients older than 70 years (1). While malignant and functional AIs that require active treatment must be identified, most AIs are benign and nonfunctional (2, 3, 4). With the increasing prevalence of AIs due to aging and improved health screenings, adequate follow-up strategies after the initial assessment are becoming increasingly important in clinical practice.

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Several recommendations and suggested strategies have been proposed for the diagnosis and management of AIs to identify clinically important adrenal lesions (1, 2, 3, 5, 6). However, there are considerable differences in the recommended biochemical tests and imaging studies for the detection of functional or malignant adrenal lesions. In addition, the follow-up strategies for surgically unresected AIs also differ between the various recommendations. This is likely because these strategies are based on multiple case series, among which the accuracy and availability of diagnostic tests varied widely.

Recently, the European Society of Endocrinology (ESE), in collaboration with the European Network for the Study of Adrenal Tumors (ENSAT), published new clinical practice guidelines regarding AI management (7). These new guidelines re-define the terminology and describe how to manage autonomous cortisol secretion and the follow-up strategy for typical benign AIs. They use the term (possible) autonomous cortisol secretion instead of subclinical Cushing's syndrome, which is considered as a spectrum of cortisol secretion. It is also noteworthy that, in contrast to previous guidelines, the 2016 ESE-ENSAT guidelines do not recommend further follow-up imaging for adrenal masses <4 cm and with clear benign features (≤10 Hounsfield units (HU)).

In the present study, we investigated the clinical characteristics of AIs in a large patient sample and followed their longitudinal course for up to 13 years in a single tertiary center (median follow-up duration, 4 years). We also evaluated the features of benign AIs in terms of mass size and pre-contrast HU to discriminate them from malignant AIs. Furthermore, we aimed to validate the follow-up strategies proposed by the new ESE-ENSAT guidelines.

Subjects and methods

Study subjects

We retrospectively reviewed the medical records of 1742 patients aged ≥20 years who were newly diagnosed with AIs between January 2000 and June 2013 at Seoul National University Hospital. We defined AI as an adrenal lesion discovered on CT performed for reasons other than suspected adrenal pathology, without any suspicious symptoms and signs related to hormone excess. We excluded patients without adequate biochemical evaluation (n=341). Among the eligible patients with AIs (n=1401), we further excluded patients with a history of extra-adrenal malignancy (n=252). Finally, a total of

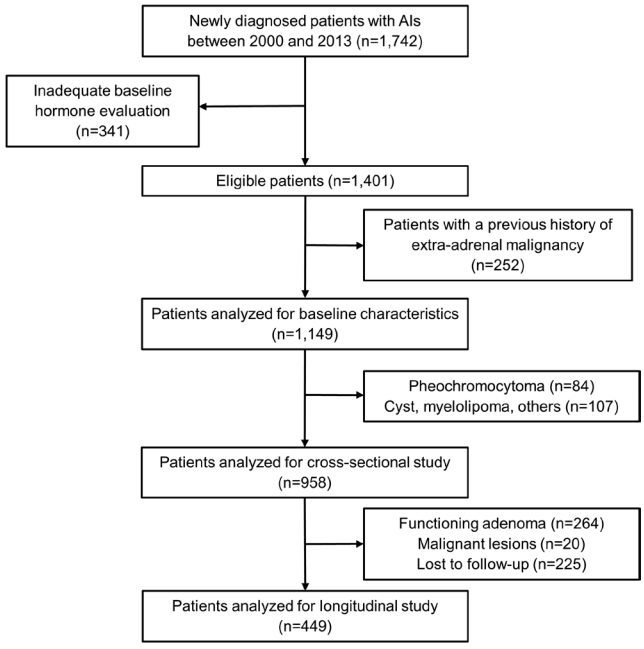

Figure 1
Flow diagram of the study subjects.

1149 patients were included in the analysis (Fig. 1). We collected the following data for all patients: age, sex, hormonal status, mass size and localization of the adrenal mass. We further examined the presence of combined comorbidities, including diabetes mellitus, hypertension and cardiovascular disease, at the time of initial imaging detection of AIs. The presence of hypertension was defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or as patients taking any antihypertensive medications. The presence of diabetes mellitus was determined by a fasting plasma glucose ≥126 mg/dL, HbA1c ≥6.5% or aspatients taking any oral antidiabetic drugs or on insulin therapy. We considered patients with stable angina, unstable angina or myocardial infarction noted on their medical records as having cardiovascular disease.

The study was approved by the Institutional Review Board of Seoul National University Hospital (No. H-1506-047-679) and was conducted in accordance with the Declaration of Helsinki. The requirement of informed consent from the study participants was waived, owing to the retrospective design of the study.

Biochemical evaluation and diagnostic criteria

Primary aldosteronism was diagnosed based on the Endocrine Society Guideline, as follows (8): plasma

aldosterone concentration (PAC) (ng/dL) and plasma renin activity (PRA) (ng/mL/h) were measured at the same time, and an aldosterone-to-renin ratio (ARR) >30 along with a PAC >15 ng/dL was considered a positive diagnosis. These criteria were adopted to reduce the risk of false-positive results for the diagnosis of primary aldosteronism, particularly considering the low diagnostic accuracy of ARR alone and the high sodium intake in the Korean population (9, 10). We performed the saline infusion test and/or captopril challenge test in all positive-screened patients to confirm the diagnosis of primary aldosteronism, except for in 1 patient with marked hypertension, in whom the ARR was >50 and an adrenal adenoma was lateralized with adrenal vein sampling. Of the 167 patients who tested positive for primary aldosteronism, 35 patients were finally considered to be negative for primary aldosteronism after confirmation tests.

PAC was measured by radioimmunoassay (RIA) using the SPAC-S aldosterone kit (TFB, Inc., Tokyo, Japan). The intra- and inter-assay coefficients of variation (CVs) were 4.7% and 4.5% respectively. Before 2011, the PRA was measured with Renin RIA beads (TFB, Inc.), for which the intra- and inter-assay CVs of PRA were 7.0% and 7.5% respectively. Thereafter, the PRA was measured with a PRA RIA kit (TFB, Inc.), with intra- and inter-assay CVs of 3.8% and 6.7% respectively.

The diagnosis of pheochromocytoma was based on the following combination of clinical signs and symptoms: elevated levels of 24-h urinary catecholamine (e.g., epinephrine and norepinephrine) or its metabolites (e.g., metanephrine, normetanephrine and dopamine), elevated plasma metanephrine or normetanephrine and pathological confirmation after surgical resection. Of the 122 patients with elevated levels of plasma or urine metanephrine, normetanephrine and catecholamines, 84 patients had pathologically confirmed pheochromocytoma. From 2012, plasma metanephrine and normetanephrine were measured using liquid chromatography–tandem mass spectrometry. Urinary catecholamine and its metabolites were measured by high-performance liquid chromatography during the entire study period.

Autonomous cortisol secretion was defined as a serum cortisol level >1.8 μg/dL following a 1-mg overnight dexamethasone suppression test (DST), and a lack of typical Cushingoid features such as moon face, buffalo hump, central obesity and easy bruising.

The diagnosis of overt Cushing's syndrome was based on the presence of Cushingoid features and a lack of serum cortisol suppression following a 1-mg DST, as well as on the 24-h urine free cortisol (UFC). Of the 132 patients who did not show serum cortisol suppression following the 1-mg DST, 50 patients were finally considered as having overt Cushing's syndrome. The serum cortisol and 24-h UFC were measured using a RIA kit (IMMUNOTEC, Prague, Czech Republic), with an intra-assay CV of 5.8% and an inter-assay CV of 9.2%. The reference range for the 24-h UFC was 19.4–115.2 μg/day. Plasma adrenocorticotropic hormone (ACTH) was measured by an immunoradiometric assay (CIS-Bio International, Saclay, France) with a reference range of 10.0–60.0 pmol/L. The intra- and inter-assay CVs of ACTH were 3.7% and 3.8% respectively.

Radiologic evaluation on CT scans

We used the largest transverse diameter of an adrenal lesion to represent the lesion size, and determined the pre-contrast HU on a non-contrast CT image. We excluded areas of necrosis or cystic changes from the pre-contrast HU measurements. In patients with a heterogeneous adrenal mass, the highest HU measurement was used, based on a previous study (11). A density of ≤10 pre-contrast HU was considered to indicate a lipid-rich adrenal adenoma. In patients who underwent dynamic adrenal CT imaging, the absolute percentage and relative percentage washouts were calculated. An absolute percentage washout of ≥60% and relative percentage washout of ≥40% were considered to indicate a benign cortical adenoma. We defined the follow-up duration as the interval from the initial CT scan to the final scan.

Based on the CT findings, malignant lesions were suspected if they showed a size change greater than 0.5 cm per 6 months. Metastasis was determined by the clinician's decision based on imaging and/or pathological findings in patients with a history of extra-adrenal malignancy.

Statistical analysis

Data are expressed as the mean ± standard deviation (s.d.), median (interquartile range), or *n* (%). Continuous variables were analyzed using either the Student *t*-test or Mann–Whitney test. Categorical variables were analyzed using the Chi-square test. We performed receiver operating curve (ROC) analyses to determine the discrimination values for malignant adrenal lesions. The optimal cut-off values of mass size and pre-contrast HU on CT for malignant lesions were chosen using the Youden

index (sensitivity + specificity − 1) (12). All statistical analyses were performed using PASW SPSS for Windows (Version 21, SPSS). A P value <0.05 was considered to be statistically significant.

Results

Initial biochemical and radiologic evaluations

The baseline characteristics of patients with AIs are shown in Table 1. The mean age at diagnosis was 54.2 years, and 45.1% were female patients. Nonfunctional adrenal lesions were observed in 781 (68.0%) patients, most of which were adrenal adenomas (n=674, 58.8%). Among patients with functional adrenal adenomas (n=348, 30.3%), 50 (4.4%) were diagnosed with overt Cushing's syndrome, 82 (7.1%) with autonomous cortisol secretion, 132 (11.5%) with primary aldosteronism and 84 (7.3%) with pheochromocytoma. Of the 132 patients with primary aldosteronism, 49 (37.1%) had hypokalemia (<3.5 mmol/L) at the time of AI diagnosis. The prevalence of malignant adrenal lesions, including adrenocortical carcinomas and lymphomas, was 1.7% (n=20). Of the 14 patients with adrenocortical carcinoma, 2 (16.7%) had hormonally active adrenocortical carcinomas, both of which were identified as Cushing's syndrome.

Table 1 Baseline characteristics of patients with adrenal incidentalomas (n=1149). Data are expressed as mean ± S.D. or median (interquartile range) or n (%).

Variables	Values
Age (years)	54.2 ± 12.4
Female, n (%)	518 (45.1)
Maximal diameter of adrenal mass at diagnosis (cm)	1.8 (1.3–2.7)
Etiology, n (%)	
Functioning	348 (30.3)
Cushing's syndrome	50 (4.4)
Autonomous cortisol secretion	82 (7.1)
Primary aldosteronism	132 (11.5)
Pheochromocytoma	84 (7.3)
Nonfunctioning	781 (68.0)
Adenoma	674 (58.8)
Cyst	29 (2.5)
Ganglioneuroma	25 (2.2)
Myelolipoma	19 (1.7)
Others (e.g., schwannoma)	34 (3.0)
Malignant	20 (1.7)
Adrenocortical carcinoma	14 (1.2)
Lymphoma	3 (0.2)
Leiomyosarcoma	2 (0.2)
Neuroblastoma	1 (0.1)
Metastasis	–

In the present study, 934 (81.3%) adrenal lesions showed homogenous appearances on the CT scan. However, among the 14 adrenocortical carcinomas, only 4 (28.6%) were homogeneous.

The annual incidence of AIs during the study period is presented in Supplementary Fig. 1 (see section on supplementary data given at the end of this article).

Calculation of cutoffs for mass size and HU

ROC analyses were used to assess the diagnostic accuracy of the mass size and pre-contrast HU on CT for differentiating malignant from benign lesions after excluding myelolipomas, pheochromocytomas and adrenal cysts (n=958) (Fig. 2 and Table 2). The areas under the curve (AUCs) for mass size and pre-contrast HU were 0.994 (95% confidence interval 0.989–1.000) and 0.909 (95% confidence interval 0.875–0.943) respectively (P<0.001 for both). The optimal cut-off value for mass size was 3.4 cm, with a sensitivity of 100% and specificity of 95.0%. The sensitivity and specificity with 4.0 cm as the cut-off value were 90.0% and 97.9% respectively. Of the 14 malignant adrenocortical carcinomas, 9 (64.3%) had a mass size in the range of 3.4–8.0 cm. Of these 9 patients, only 1 presented symptoms and signs of Cushing's syndrome; the remaining 8 patients did not show any clinical features related to hormone excess or elevated hormone levels, including cortisol, sex hormone and aldosterone levels. The optimal cut-off value for the pre-contrast HU was 19.9, with a sensitivity of 100% and specificity of 67.4%. With a pre-contrast HU value of 10 as the cut-off value, the sensitivity and specificity were 100% and 45.4% respectively. In the present study, 19 (95.0%) of 20 malignant lesions were ≥4 cm in size and had a pre-contrast HU value >10, whereas all malignant lesions were included with the criteria of size ≥3.4 cm and pre-contrast HU value >19.9. When we applied the diagnostic criteria for malignant lesions as mass size ≥4 cm and pre-contrast HU value >10, the specificity increased to 98.1%, which was better than the specificity obtained from mass size or pre-contrast HU alone. With a mass size ≥3.4 cm and pre-contrast HU value >19.9 as the diagnostic criteria, the specificity also increased to 98.1%. Of the 41 patients with an adrenal mass size between 3.4 and 4.0 cm, 1 patient had a malignant lesion, with a size of 3.5 cm, and a pre-contrast HU value of 38.2; this lesion was confirmed as neuroblastoma after surgical resection.

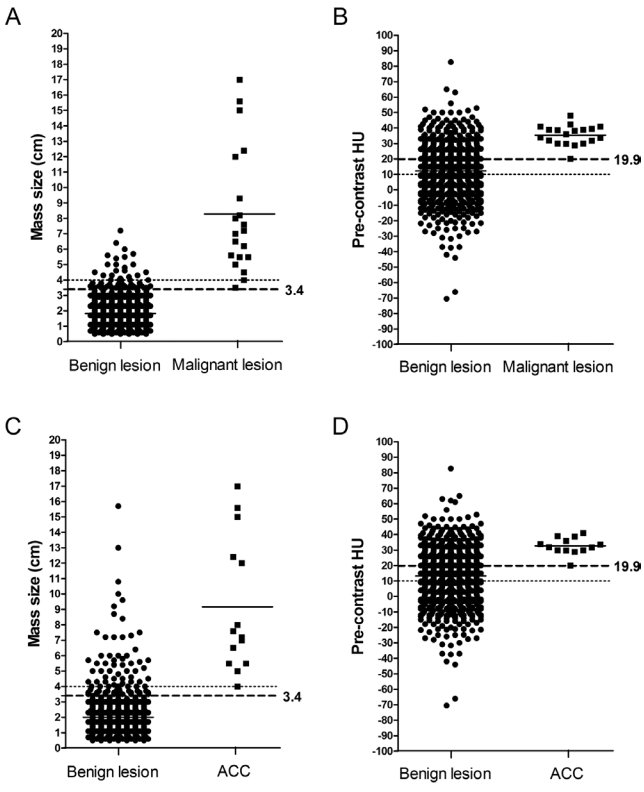

Figure 2
Distribution of (A) mass size and (B) pre-contrast Hounsfield units (HU) on computed tomography between benign and malignant lesions of any etiology in patients without a history of extra-adrenal malignancy ($n=958$). Distribution of (C) mass size and (D) pre-contrast HU between benign lesions and adrenocortical carcinoma ($n=14$). ACC, adrenocortical carcinoma. (Dotted lines: the 2016 ESE/ENSAT guidelines; dashed lines: newly established cutoffs).

Radiologic evaluation during the follow-up

Longitudinal analysis was performed only in patients with nonfunctional adrenal adenomas who were followed-up for at least 6 months ($n=449$) (Supplementary Fig. 2). There were no significant differences in the baseline characteristics between patients with and without repeated CT measurements, except for the pre-contrast HU (Supplementary Table 1). The median follow-up duration of radiologic evaluation was 4.0 years (interquartile range, 2.0–6.0). We compared the changes in size according to the initial maximal diameter (<2, 2–3, ≥3 cm; Table 3) and pre-contrast HU (≤10 vs >10) (Table 4). Overall, the mean change in diameter was 0.14 cm during the entire follow-up period, and the annual change was 0.03 cm. Only 9 (2.0%) patients had adrenal enlargement >0.5 cm/year. Figure 3 shows that there was little change in size with a longer follow-up period, even in patients followed-up for more than 5 years. Two patients with adenomas <4 cm and a pre-contrast HU value >10 experienced significant growth of their mass (≥1 cm/year); however, these cases were pathologically confirmed as benign after surgical resection. Of the 197 patients with nonfunctional adrenal adenomas <4 cm and ≤10 pre-contrast HU, there was no change in size in 72 (36.5%) patients, whereas the size decreased in 31 (15.7%) patients.

Biochemical evaluation during the follow-up

We also analyzed the hormone changes in 193 patients with nonfunctional adrenal lesions who underwent repeated hormone tests. The mean follow-up period was 2.9 years (interquartile range: 1.6–4.9). Among these 193 patients, no patients developed pheochromocytoma, primary aldosteronism or overt Cushing's syndrome. However, 4 (2.0%) patients exhibited serum cortisol levels >5 μg/dL after the 1-mg DST. Given that the cut-off value for autonomous cortisol secretion is 1.8 μg/dL, 54 (28.0%) patients did not show suppression after dexamethasone at the last follow-up visit. Repeated 1-mg DST was performed in 46.3% (25/54) of these patients to validate that the test results were not a consequence of inadequate intake of dexamethasone. We compared the prevalence of diabetes mellitus, hypertension and cardiovascular

Table 2 Diagnostic accuracy of mass size and pre-contrast HU for differentiation of malignant from benign lesions in patients with adrenal incidentalomas ($n=958$). Data were analyzed after excluding cases with pheochromocytoma, cyst, myelolipoma, and others ($n=191$).

	AUC	95% CI	*P*	Cut-off value	Sensitivity (%)	Specificity (%)
Mass size (cm)	0.994	0.989–1.000	<0.001	3.4	100	95.0
				4.0	90.0	97.9
Pre-contrast HU	0.909	0.875–0.943	<0.001	19.9	100	67.4
				10.0	100	45.4

AUC, area under the curve; CI, confidence interval.

Table 3 Radiographic changes of nonfunctional adrenal lesions according to initial maximal diameter (*D*). Data are expressed as mean ± S.D. or *n* (%).

(a)	Total (*n* = 449)	*D* < 2 cm (*n* = 302)	2 ≤ *D* < 3 cm (*n* = 131)	*D* ≥ 3 cm (*n* = 16)	*P*
Age at diagnosis (years)	57.2 ± 10.7	57.7 ± 10.3	56.5 ± 10.9	53.4 ± 14.1	0.441
Final diameter (cm)	1.79 ± 0.70	1.45 ± 0.45	2.42 ± 0.45	3.23 ± 0.89	<0.001
Follow-up duration (years)	4.31 ± 2.76	4.23 ± 2.69	4.51 ± 2.88	3.97 ± 3.22	0.543
Change in diameter (cm)	0.14 ± 0.34	0.15 ± 0.33	0.12 ± 0.36	0.14 ± 0.51	0.183
Growth velocity (cm/year)	0.03 ± 0.18	0.04 ± 0.17	0.01 ± 0.17	0.08 ± 0.32	0.102
Change in diameter >0.5 cm/year	9 (2.0%)	5 (1.7%)	2 (1.5%)	2 (12.5%)	0.095

diseases between patients who remained nonfunctional and those who showed conversion to autonomous cortisol secretion (Supplementary Table 2). However, we did not find any metabolic differences between the two groups. Meanwhile, of the 82 patients regarded as having possible or definite autonomous cortisol secretion at the initial biochemical evaluation, repeated 1-mg DST was performed in 50 patients. Of these patients, 9 (18.0%) were re-classified into nonfunctional adenomas after the second 1-mg DST.

Discussion

In this large cohort of 1149 patients with AIs, nonfunctional adrenal lesions were the most common etiology, and the prevalence of malignancy was 1.7%. The optimal cut-off values of mass size and pre-contrast HU to distinguish malignant from benign lesions were 3.4 cm and 19.9 respectively. Longitudinal analysis of 449 patients with nonfunctional AIs revealed that no patients developed malignant transformation or overt hormone-secreting adenomas. Moreover, there was no significant change in the observed adenoma size over the 4-year follow-up period. We observed the development of autonomous cortisol secretion from nonfunctional lesions in 28.0% (54/193) of patients according to a cut-off value of 1.8 μg/dL; however, only 2.0% developed autonomous cortisol secretion when using a cut-off value of 5.0 μg/dL.

In this cohort of 1149 patients with AIs, we showed that the majority of AIs were nonfunctional adrenal adenomas, which was consistent with previous reports (13, 14). A discriminating feature of our study was the high prevalence of primary aldosteronism (up to 11.5%), which was much higher than the prevalence rates previously reported (1.6–3.3%) (13, 14). While it is difficult to clarify the reason for the difference in ours and previous findings, one possibility is that although the current guidelines recommend biochemical tests for aldosterone secretion in patients with hypertension or unexplained hypokalemia, screening tests for hyperaldosteronism were widely performed in our institution during the study period, even in patients without any suspicion for the disease. This may have contributed to the early detection of primary aldosteronism even in patients with a mild degree of aldosterone excess. As the present study was conducted in a single center, this may represent a bias that could lead to difficulties in the accurate interpretation of our findings.

Table 4 Radiographic changes of nonfunctional adrenal lesions according CT attenuation. Data are expressed as mean ± S.D. or *n* (%).

	≤10 HU (*n* = 199)	>10 HU (*n* = 250)	*P*
Age at diagnosis (years)	57.5 ± 10.0	57.0 ± 11.2	0.441
CT attenuation (HU)	−2.7 ± 10.6	23.3 ± 10.1	<0.001
Initial diameter (cm)	1.70 ± 0.67	1.61 ± 0.61	0.184
Final diameter (cm)	1.83 ± 0.73	1.77 ± 0.68	0.340
Follow-up duration (years)	4.21 ± 2.56	4.38 ± 2.92	0.534
Change in diameter (cm)	0.13 ± 0.32	0.15 ± 0.37	0.610
Growth velocity (cm/year)	0.03 ± 0.12	0.04 ± 0.21	0.616
Change in diameter >0.5 cm/year	7 (2.8%)	2 (1.0%)	0.310

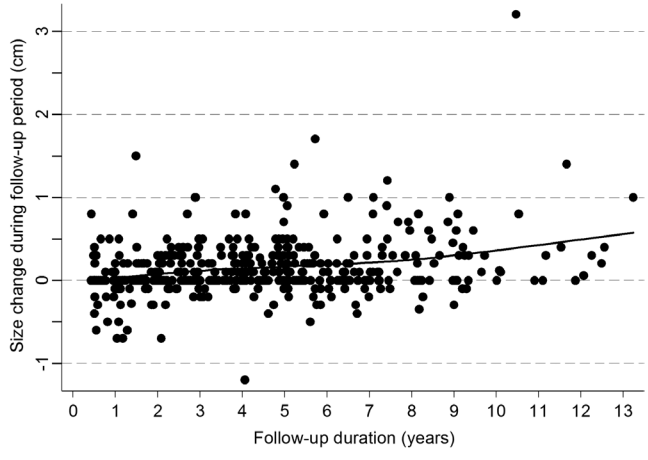

Figure 3
Natural history of nonfunctional adrenal lesions (*n* = 449) during the follow-up period.

Our cross-sectional study excluded patients with a history of extra-adrenal malignancy. In these patients, the prevalence of malignancy (e.g., adrenocortical carcinoma or metastasis) was 1.7% ($n=20$). The current guidelines suggest a pre-contrast HU value >10 and mass size ≥4 cm as criteria for discriminating malignant from benign lesions (2, 5, 7). In the present study, we re-analyzed data from 958 patients to evaluate the diagnostic powers of pre-contrast HU and mass size for detecting malignant lesions. The diagnostic power of mass size was higher than that of pre-contrast HU. Based on our data, we estimated that patients with an adrenal mass ≥3.4 cm and/or a pre-contrast HU value >20 should be closely evaluated, and, if necessary, further examinations should be performed to characterize the suspicious malignant lesion. This supports our previously published radiographic findings of adrenal metastasis in oncologic patients, which also advocated a CT attenuation of >20 HU for adrenal metastasis (15).

Considering the recent concept of a biological continuum whereby there is no clear border between nonfunctional adenomas and cortisol-secreting adenomas, the debate as to whether a serum cortisol post-dexamethasone of 1.8 or 5 µg/dL is the most appropriate criterion of autonomous cortisol secretion is likely to be ongoing. However, previous studies have reported increased morbidity and mortality in patients with cortisol values of >1.8 µg/dL following the 1-mg DST (16, 17). This indicates that adopting a value of >5 µg/dL could result in an underestimation of the clinical risk for patients with cortisol suppression level of 1.8–5 µg/dL. Hence, in the present study, we determined the level of post-dexamethasone cortisol suppression to be 1.8 µg/dL. However, the results of the 1-mg DST could be influenced by various factors, especially medications, which may result in false-positive or -negative responses. In particular, estrogen increases the cortisol-binding globulin concentration, which causes about 50% of false-positive reports for the 1-mg DST in women taking oral contraceptive pills (7). Medications affecting the CYP3A4 enzyme could cause false-negative responses by reducing the plasma dexamethasone concentration. As we diagnosed the autonomous cortisol secretion based solely on the 1-mg DST results in this study, we avoided this issue by excluding patients taking medications, including oral contraceptive pills or CYP3A4 inducers, as well as patients with inadequate intake of dexamethasone for the test (all of which we categorized as 'inadequate baseline hormone study'), from the final analysis (Fig. 1).

Previous guidelines have suggested at least one follow-up imaging study for adrenal masses <4 cm and a pre-contrast attenuation value of ≤10 HU (2, 4, 11, 18, 19). Furthermore, the American Medical Guidelines recommend that patients with adrenal masses <4 cm in size and a pre-contrast attenuation value of >10 HU should undergo a follow-up CT study at 3–6 months and then once a year for 2 years (2). In contrast, the 2016 ESE-ENSAT guidelines recommend that adrenal masses <4 cm with clear benign features do not require follow-up imaging, regardless of the history of extra-adrenal malignancy (7). In the present study, most nonfunctional adrenal masses remained stable in size during the long-term follow-up period. Even in patients in whom a significantly increasing mass (≥1 cm/year) was observed, the final pathological diagnosis was confirmed as benign after surgical resection. The majority of previous cohort studies, which comprised sample sizes of 24–187 patients and had median follow-up periods of 1.8–7.5 years, similarly revealed no malignant transformation in typical benign nonfunctional AIs (20, 21, 22, 23, 24, 25, 26). One systematic review including data from 1081 patients reported an incidence of adrenal malignancy of 0.2% (only 1 case) (4). In addition, only a few studies have reported a change from benign-looking adenoma to adrenocortical carcinoma (27, 28, 29). As a single-center longitudinal study, we explored the largest study population to date ($n=449$), with a median follow-up duration of 4 years, including 163 patients that were followed-up for more than 5 years. Based on our data, we advocated that no further follow-up imaging is required in patients with typical benign adenomas <4 cm in size and with a CT attenuation value of ≤10 HU.

Our findings showed that 28.0% (54/193) of initially nonfunctional AIs progressed to autonomous cortisol secretion during a median follow-up of 3 years. The progression rate to autonomous cortisol secretion varies among previous studies (0–12%), with median follow-up periods of 1.8–7.5 years (17, 22, 30, 31). This may be attributed to the differences in the diagnostic criteria for autonomous cortisol secretion and follow-up durations. In our study, we defined autonomous cortisol secretion based on one measurement of the cortisol level after the 1-mg DST alone, owing to a lack of data, while previous researchers used various combinations of the 1-mg DST, plasma ACTH, and 24-h UFC. Therefore, the present study could have overestimated the development of autonomous cortisol secretion compared to previous studies. However, no patients developed overt Cushing's syndrome from nonfunctional AIs during the follow-up in our study. This was consistent with previous reports that followed-up patients for 3, 6.9, and 7.5 years, respectively (17, 22, 23). Furthermore, no patient developed functional AIs such as

primary aldosteronism or pheochromocytoma in the present study. Similarly, a previous meta-analysis reported that the risk of developing an overt hormone-secreting tumor is <0.3% (4, 32). Based on the present study, we agree with the 2016 ESE-ENSAT guidelines for AIs, which suggest that repeated hormonal testing is not needed in patients with nonfunctional AIs at initial evaluation if new symptoms do not appear (7). Previous data have demonstrated an increased risk for autonomous cortisol secretion, especially if the tumor is >3 cm in size (33, 34). On the contrary, we found no difference in mass size and comorbidities between patients with nonfunctional adenomas and autonomous cortisol secretion at the last follow-up.

There are several limitations of the present study. First, although the total sample size was large in the cross-sectional analysis, a substantial number of patients were lost to follow-up. Second, the AIs without follow-up data had higher pre-contrast HU values than those with follow-up data (Supplementary Table 1). Although we could not evaluate the outcomes of AIs without follow-up, among AIs with available follow-up data, there was no significant difference in the change in diameter (Table 3) between those with ≤10 HU and >10 HU (Table 4). Third, the median follow-up durations of imaging and hormone assessments were 4.0 and 2.9 years respectively, which may not have been sufficient to evaluate long-term changes, particularly with regards to the progression to autonomous cortisol secretion. Fourth, apart from the pre-contrast HU, it was difficult to statistically analyze the radiologic characteristics of the abdominal CT, such as the absolute/relative percentage washout, because dynamic adrenal imaging was only performed in 121 patients (10.5%). Furthermore, ^{18}F-FDG-positron emission tomography/CT and ^{123}I- or ^{131}I-meta-iodobenzylguanidine scans were obtained only in 6.0% (69/1149) and 1.5% (17/1149) of patients respectively. Fifth, the diagnosis of autonomous cortisol secretion requires measurements of plasma ACTH and 24-h UFC in addition to the 1-mg DST; however, we were unable to present additional data, owing to the lack of these tests. Finally, we did not compare the development of autonomous cortisol secretion between patients with AIs and a control group.

Taken together, initial radiographic and hormonal evaluations of AIs are crucial for determining the appropriate follow-up strategies. Our results suggest that typical benign AIs with a size <4 cm and a pre-contrast HU value of ≤10 do not need to be followed-up with repeated CT measurements, as most remain stable in size for a long time. Nonfunctional AIs rarely evolve to become overt hormone-secreting tumors; however, attention should be paid to the development of autonomous cortisol secretion. Further long-term prospective longitudinal studies are required to confirm our findings and validate these follow-up strategies.

Supplementary data

This is linked to the online version of the paper at http://dx.doi.org/10.1530/EJE-17-0372.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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