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Clinical Guidelines for the Management of Adrenal Incidentaloma

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An adrenal incidentaloma is an adrenal mass found in an imaging study performed for other reasons unrelated to adrenal disease and often accompanied by obesity, diabetes, or hypertension. The prevalence and incidence of adrenal incidentaloma increase with age and are also expected to rise due to the rapid development of imaging technology and frequent imaging studies. The Korean Endocrine Society is promoting an appropriate practice guideline to meet the rising incidence of adrenal incidentaloma, in cooperation with the Korean Adrenal Gland and Endocrine Hypertension Study Group. In this paper, we discuss important core issues in managing the patients with adrenal incidentaloma. After evaluating core proposition, we propose the most critical 20 recommendations from the initially organized 47 recommendations by Delphi technique.

Keywords: Adrenal incidentaloma; Adrenal disease; Clinical guideline

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INTRODUCTION

An adrenal incidentaloma is an adrenal mass found in an imaging examination performed for other reasons, typically without clinical symptoms of adrenal disease. Generally, tumors less than 1 cm are not considered adrenal incidentalomas, and additional diagnostic tests are recommended for tumors larger than 1 cm in the absence of clinical symptoms or signs of excess adrenal hormone. Because the prevalence of adrenal incidentaloma increases with age and it often accompanies obesity, diabetes mellitus, or hypertension [1], we expect that the prevalence of adrenal incidentaloma in Korea will rise as the population ages and obesity and diabetes mellitus increase. In addition, the rapid development of imaging technology increases the chances of discovering adrenal incidentalomas. Therefore appropriate practice guidelines are needed, so we, the committee for clinical practice guidelines of the Korean Endocrine Society, have established these practice guidelines for adrenal incidentaloma in Korea.

EPIDEMIOLOGY OF ADRENAL ADENOMA

The prevalence of adrenal incidentaloma in Korea has never been precisely investigated, but a review of the literature reveals an average prevalence as 2% in foreign populations, with a range of 1.0% to 8.7% [1,2]. The prevalence of adrenal incidentaloma increases with age, and there is no difference between genders. It frequently accompanies obesity, diabetes mellitus, or hypertension [1]. With advances in imaging technology, the prevalence of adrenal incidentaloma increases to 4% in middle age and up to 10% in the elderly [3-5]. It is very low in childhood and adolescence. Non-functional benign adenoma is found in 80% of adrenal incidentaloma cases. The prevalence of other disease causes varies by study due to differences in selection criteria and patterns in moving patients to advanced hospitals: the prevalence of pheochromocytoma is 1.5% to 23.0% and that of adrenocortical carcinoma is 1.2% to 12.0%. The types of adrenal incidentaloma reported from abroad are shown in Table 1 [6]. The prevalence of cancer and functional tumors might be exaggerated because previous research included many patients with surgery or a past history of cancer. Recent studies reported the prevalence of adrenocortical carcinoma to be 2.0% to 5.0%, adrenal metastases as 1.0% to 2.0%, and pheochromocytoma as 3.0% to 6.0% [1,5,7,8]. Other causes are cysts, ganglioneuroma, myelolipoma, hematoma, etc. An adrenal gland is a location of metastasis for a variety of cancers (lung cancer, breast cancer, renal cancer, melanoma, lymphoma, etc.), and one cancer patient cohort study claimed that 50% to 75% of adrenal incidentalomas were metastases [9].

Table 1. Frequency of the Different Types of Adrenal Incidentaloma

Type	Average, %	Range, %
Clinical studies		
Adenoma	80	33–96
Non-functioning	75	71–84
Cortisol secreting	12	1.0–29
Aldosterone secreting	2.5	1.6–3.3
Pheochromocytoma	7.0	1.5–14
Carcinoma	8.0	1.2–11
Metastasis	5.0	0–18
Surgical studies		
Adenoma	55	49–69
Non-functioning	69	52–75
Cortisol secreting	10	1.0–15
Aldosterone secreting	6.0	2.0–7.0
Pheochromocytoma	10	11–23
Carcinoma	11	1.2–12
Myelolipoma	8.0	7.0–15
Cyst	5.0	4.0–22
Ganglioneuroma	4.0	0–8.0
Metastasis	7.0	0–21

Similar results were found in studies of Korean patients with adrenal incidentaloma. The incidence of functional adrenal tumors was reported to be 41.3% in Kim's study of 80 patients [10], but it was 13.6% to 18.7% in other studies [11-14]. There are several types of functional tumors: pheochromocytomas, with an average incidence of 6.2% (range, 2.1% to 20.0%); Cushing's syndrome (including symptom-free), with an average of 8.1% (range, 3.0% to 11.3%); and hyperaldosteronism, with an average of 3.9% (range, 1.5% to 10.0%). Malignant tumors (adrenal cortical carcinoma and adrenal metastases) averaged 2.6% (range, 0.7% to 15.0%).

A non-functional adrenal incidentaloma that is 4 cm or less and positively identified in imaging tests should be checked periodically via radiological imaging and hormone evaluation. It has been reported that the risk for tumors to increase in size in 1, 2, and 5 years is 6%, 14%, and 29%, respectively, and the possibility of finding a concomitant hormone secretion disorder is 17%, 29%, and 47%, respectively [15]. If a tumor becomes a functional tumor, subclinical hypercortisolism is the most com-

mon finding; overproduction of catecholamine or aldosterone is rarely seen during follow-up. The incidence of overt Cushing's syndrome is less than 1%, and that of asymptomatic hormone abnormality has been reported to be up to 11% [5,16]. A relatively large tumor, larger than 3 cm, has a high potential to cause asymptomatic hormone hypersecretion, with the risk peaking 3 to 4 years later [15]. Also, when there is an increase in uptake on an NP-59 scan, there is a higher incidence of asymptomatic hypercortisolism [17]. One hundred and fifty-nine patients with non-functioning adrenal tumors were monitored (for an average of 15.0 to 23.1 months) in parts of the Korean studies mentioned above. Subclinical hypercortisolism was diagnosed in three patients, and pheochromocytoma was diagnosed in one patient [10,13,14]. The tumors increased by more than 1 cm in size in three patients, but they were not malignant.

Table 2. Clinical Key Questions

1. What is the prevalence of adrenal incidentaloma, and what is the frequency of malignant tumors and functional tumors among adrenal incidentaloma patients?
2. What testing is required when an adrenal incidentaloma is found?
3. What testing is to be performed if an additional test is needed for an adrenal incidentaloma?
4. What is the confirming test when the adrenal incidentaloma is a functional tumor?
5. What is the treatment if the adrenal incidentaloma is a functional tumor?
6. What clinical findings suggest malignancy in an adrenal incidentaloma?
7. When is surgery indicated in adrenal incidentaloma?
8. How should a non-functioning benign adrenal incidentaloma be monitored?
9. How should adrenal incidentaloma patients in special situations (the elderly or people under the age of 40) be managed?

METHOD FOR DEVELOPING THESE GUIDELINES FOR THE MANAGEMENT OF ADRENAL INCIDENTALOMA

The committee for clinical practice guidelines of the Korean Endocrine Society developed the following recommendations with help from the Korean Adrenal Gland and Endocrine Hypertension Study Group. Because no Korean practice guidelines for adrenal incidentaloma have previously been developed, and few domestic research studies or data on adrenal incidentaloma are available, we decided to adapt and modify existing foreign guidelines rather than develop a completely new guideline. Therefore, our research focused on deciding which recommendations to use as source material.

Because a specialty in endocrinology is needed to treat adrenal incidentaloma patients, we originally targeted endocrinologists, but we later decided to include primary health care providers because they also encounter affected patients.

As a first step, we discussed the many important issues physicians must understand in managing adrenal incidentaloma patients, and we collected the core propositions most important to the medical professionals who directly treat and manage adrenal incidentaloma patients. By deleting duplicates and integrating similar propositions, we selected nine core propositions through the Delphi technique (Table 2). We then searched key overseas practice guidelines and papers and domestic papers related to the selected core propositions. We used "adrenal incidentaloma" as a search keyword on all data published in English or Korean from 2000 to the present, targeting meta-analyses, practice guidelines, reviews, etc., on humans (not animal experiments or *in vitro* studies). We used the databases of KoreaMed, KMbase, and RISS for domestic articles and the databases of PubMed, Embase, Scopus, and Cochrane Library for overseas articles.

After the reference search was completed, we excluded redundancies and collected abstract information for the primary screening. From the domestic literature, we collected 59 cases, excluding four duplicates out of 63 cases. From the overseas literature, we selected 340 cases from the original 3,117 cases collected, and we finalized the selection at 333 cases, excluding seven duplicates. After searching the articles, we reviewed articles and selected seven published guidelines that were established by evidences. Three committee members graded each guideline by the Korean Appraisal of Guidelines for Research & Evaluation II (K-AGREE II) which was developed as a Korean version of AGREE 2.0 by the Clinical Practice Guideline Executive Committee of the Korean Academy of Medical Sciences. Finally, we chose two published guidelines for guideline adaptation. And we continued to make an effort to find more recent systematic review and articles supporting evidences.

We used collected cases to write the PICO (Participant, Intervention, Comparison, Outcomes) associated with the core propositions, and we wrote the recommendations by evaluating the outcomes. We originally selected 47 recommendations, including particulars from the initially organized list, through the Delphi technique. Then we organized the final 20 recommendations, which focus on the core propositions. As defined in Table 3, we set the recommendation levels depending on strength of the selected literature.

Table 3. Definition of Recommendation Levels

Recommendation level	Definition
A	When there is a clear rationale for the recommendations: When manifold randomized controlled trials that can be generalized because they have sufficient test or meta-analysis results support a recommendation
B	When there is a reliable basis for the recommendations: When reasonable grounds support this through well-performed cohort studies or patient—control group studies
C	When there is a possible basis for the recommendations: When relevant grounds are seen through randomized clinical studies or case reports and observational studies carried out in a small institution, despite their inherent unreliability
E	Expert recommendations: There is no basis to support the recommendations, but they are supported by expert opinion or expert clinical experience

SUMMARY OF RECOMMENDATIONS

Q. What testing is required when an adrenal incidentaloma is found?

R1. (C) All patients found to have an adrenal incidentaloma should undergo clinical, biochemical, and imaging examinations to determine the presence/absence of symptoms and signs caused by an excess of adrenal hormone and to determine whether the tumor is malignant.

R1-1. (C) A 1 mg overnight dexamethasone suppression test (DST) is recommended for all adrenal incidentaloma patients to exclude asymptomatic hypercortisolism. (C) According to the 1mg overnight DST, it is possible to rule out autonomous cortisol secretion if the blood level of cortisol is 1.8 μg/dL (50 nmol/L) or less; autonomous cortisol secretion is possible if the level is 1.9 to 5.0 μg/dL (51 to 140 nmol/L); and can be seen as an evidence of autonomous cortisol secretion if the level is higher than 5.0 μg/dL (140 nmol/L).

R1-2. (A) A catecholamine metabolites test, including plasma metanephrine or 24-hour urinary fractionated metanephrine, should be performed from all adrenal incidentaloma patients to rule out pheochromocytoma.

R1-3. (C) For those patients who also have hypertension or hypokalemia, determination of the plasma aldosterone/renin activity ratio is recommended to exclude primary aldosteronism.

R1-4. (C) Non-contrast computed tomography (CT) is recommended as an initial imaging study to determine whether the adrenal tumor is benign.

R1-5. (E) Levels of sex hormones and steroid precursors should be checked in all patients who show imaging findings of suspected adrenal cancer.

R2. (E) Clinical examination, biochemical tests, and imaging studies should proceed, just as in a unilateral adrenal tumor, for all patients with bilateral adrenal tumors. Also, consider the possibility of adrenal metastases and pheochromocytoma in patients with a history extra-adrenal cancers.

R2-1. (E) If bilateral adrenal metastases, invasive disease, or bleeding is suspected, we recommend testing for hypoadrenalism.

R2-2. (E) We recommend an early morning basal 17-hydroxyprogesterone test in all patients with bilateral adrenal tumors to differentiate congenital adrenal hyperplasia.

Q. What test is to be performed if an additional test is needed in adrenal incidentaloma?

R3. (C) If a malignant adrenal tumor is suspected, but CT results are uncertain, positron emission tomography using ^{18}F-2-deoxy-D-glucose (^{18}F-FDG-PET) or PET/CT can be performed selectively.

R4. (C) In patients with an extra-adrenal malignant tumor, a biopsy can be performed when a rare tumor is suspected or imaging tests are ambiguous.

R5. (C) Pheochromocytoma has to be ruled out before biopsy.

Q. What testing confirms that an adrenal incidentaloma is functioning?

R6-1. (B) Cushing's syndrome can be diagnosed when serum cortisol is 1.8 μg/dL (50 nmol/L) or more in a 2-day low dose DST. (C) Patients with clinical signs such as hypertension, obesity, diabetes mellitus, and osteoporosis can also be examined with tests such as saliva cortisol, DST, and urinary free-cortisol.

R6-2. (E) Asymptomatic hypercortisolism can be diagnosed when plasma cortisol is 5.0 μg/dL or higher after a 1 mg DST in adrenal adenoma patients without the characteristic symptoms of hypersecretion of cortisol.

R7. (C) Aldosterone-secreting adenomas can be diagnosed if aldosterone is not suppressed after saline or a high salt load.

Q. What is the treatment if the adrenal incidentaloma is a functional tumor?

Asymptomatic hypercortisolism

R8-1. (C) Carry out screening tests for hypertension, type 2 diabetes mellitus, and asymptomatic vertebral fractures in patients with autonomous cortisol secretion, and treat appropriately.

R8-2. (E) Whether adrenal surgery is needed in patients with autonomous cortisol secretion should be individualized based on age, excess cortisol level, general health status, comorbidities, and the patient's opinion.

R8-3. (E) Consider surgical treatment when hypertension, impaired glucose tolerance, dyslipidemia, or osteoporosis worsens in patients with asymptomatic hypercortisolism.

R8-4. (C) After removal of the adrenal glands in cases of cortisol secreting adenoma, patients should be treated with glucocorticoid until the hypothalamus-pituitary-adrenal axis recovers.

R8-5. (C) Pre- and postoperative glucocorticoid treatment and testing for the recovery of the hypothalamus-pituitary-adrenal axis should be carried out.

Cortisol-producing adenoma

R9-1. (E) We recommend examination for several conditions that can be caused by hypercortisolism such as diabetes mellitus and hypertension.

R9-2. (C) Preoperative administration of prophylactic broad-spectrum antibiotics can reduce the risk of infection when performing adrenalectomy in patients with cortisol-producing adrenal adenoma.

R9-3. (B) Steroid administration is needed before and after adrenalectomy for cortisol-producing adrenal adenomas.

R9-4. (B) Patients who undergo surgery for cortisol-producing adrenal adenoma should take steroids until the hypothalamus-pituitary-adrenal axis has recovered.

R9-5. (C) To prevent venous thromboembolism, intermittent air compression devices or compression stockings should be worn during and after the surgery, or low-molecular-weight heparin or unfractionated heparin can be administered until the patient can move freely.

Pheochromocytoma

R10-1. (C) We recommend α-blocker therapy prior to surgery for all patients with functioning pheochromocytoma to prevent cardiovascular complications.

R10-2. (C) A liberal sodium diet and fluid intake are recommended before surgery to restore blood volume contraction caused by catecholamines and to prevent severe postoperative hypotension.

R10-3. (C) Seven to 14 days of medical treatment are suggested to allow sufficient time for the normalization of preoperative blood pressure and pulse rate.

R10-4. (C) Minimally invasive technique, such as laparoscopic adrenalectomy, is recommended in most cases of pheochromocytoma.

R10-5. (E) Abdominal adrenalectomy should be considered to ensure complete resection of the tumor and prevention of tumor rupture or local recurrence in tumors larger than 6 cm with infiltrative pheochromocytoma.

R10-6. (C) Monitor the blood pressure, pulse rate, and blood glucose immediately after surgery and treat appropriately when indicated.

R10-7. (C) Follow-up measurements of plasma or urinary fractionated metanephrine are recommended to diagnose whether the disease persists after surgery.

R10-8. (C) Annual biochemical tests for life are recommended to evaluate for recurrence or metastases.

Aldosterone-producing adenoma

R11-1. (C) Once an adrenal incidentaloma has been diagnosed as a unilateral aldosterone-producing adenoma, laparoscopic adrenalectomy is recommended.
R11-2. (C) If the aldosterone-producing adenoma patient does not want surgery or surgery is impossible, treat with a mineralocorticoid receptor antagonist.
R11-3. (C) Treat with a mineralocorticoid receptor antagonist when the plasma aldosterone/renin activity ratio is positive in a screening test but additional tests to confirm primary aldosteronism or distinguish subtypes are unavailable or unwanted by the patient.

Q. What clinical findings suggest a malignancy in adrenal incidentaloma?

R12. The following indicate malignant adrenal incidentaloma.
(1) (C) When it is large (≥4 cm).
(2) (E) When the Hounsfield unit (HU) value is high on a non-contrast CT scan (≥10 HU).
(3) (C) When the contrast washout rate is low in the delayed view of a contrast CT scan (absolute washout <60%, relative washout <40%).
(4) (C) If the margin of the tumor is irregular, the contents are not homogeneous, there is non-uniform enhancement, or if there is surrounding tissue invasion or metastasis.
(5) (E) When there is an abnormal increase in metabolites of steroids, such as dehydroepiandrosterone sulfate (DHEA-S).

Because none of those findings is definitive, and no one finding has high discriminatory power, all findings should be considered in determining malignancy.

R13. When adrenal incidentaloma is found in a patient with a history of other malignancy.
(1) (C) Plasma or urine fractionated metanephrine tests should be done to rule out pheochromocytoma, even when metastatic cancer seems likely.
(2) (C) If CT findings suggest a benign tumor, additional imaging tests are not recommended.
(3) (C) ^{18}F-FDG-PET/CT can be considered as an additional diagnostic method.
(4) (E) When all of the following criteria are met, an adrenal biopsy can be conducted:
  1) When it is a non-functional tumor.
  2) When it is a non-benign tumor in imaging.
  3) When the treatment varies depending on the biopsy results.
(5) (C) Residual adrenal function assessment is recommended when bilateral metastasis is suspected.

Q. When is surgery indicated in adrenal incidentaloma?

R14. Surgical treatment standards for adrenal incidentaloma.
(1) (A) Regardless of the tumor size, surgery should be performed in all cases of hormone-hypersecreting tumors accompanied by clinical symptoms caused by the hypersecretion.
(2) (C) Regardless of hormonal hypersecretion, surgery should be considered in adrenal incidentaloma larger than 4 cm because of the possibility of malignancy.
(3) (B) If CT findings indicate malignant adrenal incidentaloma (see R12), surgery should be considered as a treatment option.
(4) (C) Surgery should be considered when findings suggest abnormally increased adrenal function or malignancy during the follow-up period.
(5) (E) Surgery should be considered when an increase in size is observed during a follow-up period of 4 years.
(6) (E) Surgery should be considered when symptoms of organ rupture, bleeding, etc., occur.

R15. Tests and pretreatment should be performed when adrenal incidentaloma is found in patients prior to surgery or procedure.
(1) (A) Patients with adrenal incidentaloma must undergo biochemical tests for excessive secretion of adrenal hormones or adrenal insufficiency before proceeding with surgery.
(2) (C) If pheochromocytoma is suspected or cannot be completely ruled out, treat with an α-receptor blocker for 7 to 14 days before proceeding with surgery.

(3) (C) When findings, such as high blood pressure accompanied by hypokalemia, suggest an aldosterone-producing adenoma, correcting the hypokalemia and hypertension before surgery is recommended. An aldosterone antagonist is recommended in this case.

Q. How should follow-up tests for nonfunctioning benign adrenal incidentaloma be conducted?

R16. (C) We recommend annual hormone tests for 4 to 5 years to check the functionality of the tumor.

R17. (C) Follow-up imaging studies to differentiate malignancy are recommended 3 to 6 months after the initial study and continuing for 1 to 2 years. Considering adrenalectomy if the mass enlarges by 1 cm or more and/or changes its appearance during observation.

Q. How should adrenal incidentaloma patients in special situations (the elderly or people under age 40) be managed?

R18. (E) Immediate testing of adrenal incidentaloma in children, adolescents, adults under the age of 40, and pregnant women is recommended because of the high risk of malignancy.

R19. (E) If additional imaging tests are needed for children, adolescents, adults under the age of 40, and pregnant women, magnetic resonance imaging (MRI) is recommended rather than CT.

R20. (E) Further examinations of adrenal incidentaloma should be performed with a consideration of the clinical benefits in elderly patients and patients with poor general health status.

RATIONALE FOR THE RECOMMENDATIONS

What testing is required when an adrenal incidentaloma is found?

Biochemical examination

Hypersecretion of glucocorticoid, mineralocorticoid, sex steroids, and catecholamines not only causes clinical syndromes but can also be related to morbidity and premature mortality [18]. According to some studies, hypersecretion of hormones such as aldosterone, cortisol, or catecholamines has been found in 12% to 23% of adrenal incidentaloma patients without a history of malignant disease [19]. Therefore, it is important to determine whether the lesion is malignant and whether hormonal hypersecretion is present at the initial diagnosis of adrenal incidentaloma [20].

Clinical, biochemical, and imaging studies for asymptomatic hypercortisolism, pheochromocytoma, and malignancy should be performed in all adrenal incidentaloma patients, and evaluation for aldosteronism is also recommended when hypertension or hypokalemia is present [6].

However, biochemical exams are not essential because myelolipoma can be diagnosed by the observation of low HU (≤ –30 HU) in a CT scan [21]. Screening tests for Cushing's syndrome are extremely important because it is the most common diagnosis with adrenal incidentaloma. Although there is some controversy about the ideal screening test for asymptomatic hypercortisolism, we recommend a 1 mg overnight DST rather than a 24-hour urinary free-cortisol measurement or a midnight (late-night) cortisol measurement [20,22]. Despite continuing disagreement about the reference range, the sensitivity of the DST is higher than 95%, and its specificity is 70% to 80% when the serum cortisol baseline is set at 1.8 μg/dL (50 nmol/L); its specificity is higher than 95% but sensitivity decreases when the baseline is set at 5.0 μg/dL (138 nmol/L) [6,23]. A test value of less than 1.8 μg/dL is generally normal; a value of 5.0 μg/dL or more implies asymptomatic hypercortisolism; and a middle range of 1.8 to 5.0 μg/dL requires additional examination for diagnosis [6,23]. More accurate diagnosis is possible by checking for a low adrenocorticotropic hormone (ACTH) level [2]. Although plasma free metanephrine is known to be the most sensitive screening test for pheochromocytoma, plasma free normetanephrine, 24-hour urinary total metanephrine, and 24-hour urinary fractionated metanephrine can also be performed [24]. The plasma aldosterone/renin activity ratio is the best initial screening test for primary aldosteronism [25].

Imaging test

The main purpose of imaging studies in adrenal incidentaloma is to identify malignant tumors for early detection through biopsy and to make a cure through surgical resection possible [26]. Typical tests used to determine the characteristics of adrenal tumors include CT, MRI, and ^{18}F-FDG-PET [6,26]. The non-con-

trast (or un-enhanced) CT attenuation coefficient, expressed in HU, is the best way to distinguish between benign and malignant tumors [27]. Past studies mostly used an attenuation coefficient of ≤10 HU in a non-contrast CT as the diagnostic criterion for benign adenoma, and the specificity of this criterion was 71% to 79% with a sensitivity of 96% to 98% [6,28]. However, 10% to 40% of adrenal masses have low fat content and thus show an HU value >10. Therefore other findings should also be considered when making a diagnosis [21]. The size of the lesion and pattern after contrast enhancement (called washout) is also an important criterion to distinguish between benign and malignant lesions [22].

A size greater than 4 to 6 cm on a CT scan, a tumor with an irregular margin or heterogeneity, an attenuation coefficient of 10 HU or higher in a non-contrast CT, washout of the contrast agent after 10 or 15 minutes of less than 40%, calcification, and invasion into surrounding tissue all suggest malignancy [18,26,29].

Some studies have proposed that a low attenuation coefficient on a CT scan before injection of contrast reflects high fat content [30], which makes it a better tool than the size of the tumor in differentiating malignancy [6,22]. Contrast washout should be measured in addition to HU when the initial CT finding is indefinite because many malignant lesions appear to be benign [20]. The percentage of washout can be determined in imaging delayed 10 to 15 minutes after contrast administration, and the two methods, absolute percentage washout (APW) and relative percentage washout (RPW), can be calculated using the following respective formulas [31].

APW = 100×(EA–DA)/(EA–PA)

RPW = 100×(EA–DA)/EA

(EA, attenuation coefficient 60 to 70 seconds after contrast administration; DA, attenuation coefficient 10 or 15 minutes after contrast administration; PA, attenuation coefficient before contrast administration)

Generally, adrenal adenomas show typical rapid washout after contrast administration [18], whereas malignant lesions usually show fast contrast enhancement but slow contrast washout. Therefore, findings such as APW >60%, RPW >40% most likely indicate benign lesions [29,32].

Sex steroids or steroid precursors

Preoperative biochemical evaluation for excessive hormonal levels is necessary in patients with suspected adrenal carcinoma to identify the origin of the tumor and determine whether steroid replacement therapy is needed before or after surgery, as for hypercortisolism patients. About 60% of adrenocortical carcinomas are functional tumors, and more than half of functional tumor patients have ACTH-independent Cushing's syndrome [33]. High blood steroid precursor levels have also been observed in patients without clear clinical findings. According to a recent study, adrenal adenomas can be distinguished from adrenal cancer by analysing a urine steroid metabolomics [34].

In addition, about 10% of functional adrenocortical carcinomas over-secrete different types of hormones, such as corticosteroids and androgens, with masculinization in women with a tumor that secretes only androgen and feminization in men with a tumor that secretes only estrogen reported to occur in 20% and 10% of cases, respectively [35]. There is a much higher risk of malignancy with findings such as masculinization or feminization, increased 17-ketosteroids, or simultaneous hypersecretion of multiple hormones [35]. Therefore, measurement of sex steroids and steroid precursors, such as androstenedione, testosterone, DHEA-S, and 17β-estradiol, can prove the adrenocortical nature of the adrenal mass. Also, the results can also be used as tumor markers after surgery [36].

Bilateral adrenal incidentaloma

Fewer than 15% of adrenal incidentaloma cases are bilateral [37]. Most are benign lesions, such as bilateral cortical adenoma or nodular hyperplasia, but metastatic lesions, invasive diseases, congenital adrenal hyperplasia, and bilateral pheochromocytoma can also appear as bilateral adrenal hyperplasia [8]. Metastatic lesions are usually heterogeneous and have irregular margins, but they are bilateral in only 10% to 15% of cases [38]. Patients previously diagnosed with cancer require special attention. In consultation with an oncologist, tumor-specific marker tests, contrast-enhanced CT, and location-specific MRI of the chest/abdomen/pelvis should be performed. FDG-PET/CT can be helpful in finding metastatic lesions outside the adrenal gland in cancers with good affinity to FDG, such as lung or breast cancer. Although fine needle aspiration biopsy (FNAB) can be used to confirm the diagnosis of metastatic lesions, a biochemical evaluation for pheochromocytoma must be performed first [39]. Additionally, all patients with bilateral adrenal involvement should undergo assessment for adrenal insufficiency [38,40].

Congenital adrenal hyperplasia, which occurs primarily in infants, is a rare cause of adrenal incidentaloma and accounts for less than 1% of all cases [41]. An adrenal tumor is found in approximately 80% of patients with congenital adrenal hyperplasia [42], and most such tumors are benign [43]. Diagnosis is made by identifying the accumulation of each steroid prior to the affected enzyme, and levels of cortisol precursors such as

17-hydroxyprogesterone should be measured during the ACTH stimulation test to rule out 21-hydroxylase deficiency, which accounts for 90% to 95% of all such cases [44].

What test is to be performed if an additional test is needed in adrenal incidentaloma?

MRI or PET scan

Too few studies compare CT and MRI, and there is no evidence that a CT scan is superior to an MRI scan in patients with adrenal incidentaloma. CT scans are typically recommended as the primary imaging study when treating adrenal incidentaloma. An MRI exam is used only in very limited cases. In a study that involved adenomas with little fat and ≥10 HU on a CT scan before contrast administration, the sensitivity was 67% when all tumors ≥10 HU were included in the study, and sensitivity and specificity were 89% and 100%, respectively, when only tumors with HU values of 10 to 30 were included [45]. Therefore MRI may be used selectively when the CT finding is ambiguous. Various studies have used MRI to distinguish between adenomas and non-adenomas [46], but they found no significant advantage for MRI over a CT scan, and the expense of an MRI was considered a weakness. Chemical shift MRI is better at diagnosing adrenal incidentaloma than conventional MRI, with findings such as reduced T1 signal and increased T2 signal suggestive of malignancy or pheochromocytoma [47,48].

An ^{18}F-FDG-PET or PET/CT scan is helpful in potentially diagnosing malignant tumors when an adrenal tumor is difficult to identify from other imaging tests [49-51]. The sensitivity of an ^{18}F-FDG-PET or PET/CT is moderate, and the fact that some adrenal adenoma and pheochromocytoma show false positive results should be taken into account. However, unnecessary surgery can be avoided for nonfunctional tumors with low ^{18}F-FDG uptake, and similarly, surgery can be considered when ^{18}F-FDG uptake is increased because the negative predictive values of those exams are excellent [52]. One study reported that an ^{18}F-FDG-PET scan was more sensitive than an $^{131/123}$I-MIBG (metaiodobenzylguanidine) scan in finding tumor metastases in 17 patients with metastatic pheochromocytoma [53]. But an ^{18}F-FDG-PET scan cannot distinguish malignancy. Therefore, an ^{18}F-FDG-PET scan can be used as a secondary method of inspection when pheochromocytoma is suspected but no mass is found on other imaging studies.

Fine needle aspiration biopsy

The sensitivity and specificity of FNAB in diagnosing malignancy among patients with adrenal incidentaloma are known to be 81% to 96% and 99% to 100%, respectively [54,55]; however, 6% to 50% of tissue is reported to show indefinite biopsy results. Side effects vary depending on the skill of the operator and are reported to occur in 2.8% to 14% cases. Although rare, serious side effects such as pneumothorax, bleeding, infection, and pancreatitis can occur [56]. Also, cases have been reported in which adrenal cancer spread into the peritoneal cavity via the biopsy needle [8]. The need for FNAB has decreased as the accuracy of imaging tests for the adrenal glands has improved [57].

FNAB is not accurate in differentiating between primary adrenal cancer and benign tumors. However, FNAB can be performed in the rare cases of a malignant tumor outside the adrenal gland, imaging studies that show inaccurate results, or when a rare tumor is suspected [57,58]. It is important to rule out pheochromocytoma before performing FNAB [40].

What testing confirms that an adrenal incidentaloma is functioning?

A confirmative test is needed when hypercortisolism is suspected when screening for Cushing's syndrome, but no additional tests for hypercortisolism are needed in cases of severe Cushing's syndrome. A 2-day low dose DST is performed when the findings are ambiguous. Hypercortisolism can be diagnosed when serum cortisol is 1.8 μg/dL (50 nmol/L) or higher after administering 0.5 mg of dexamethasone orally every 6 hours for 48 hours. A sensitivity of 95% or higher has been reported in adult patients when the cutoff value was set at 1.8 μg/dL [59]. The serum cortisol test has a higher diagnostic accuracy than the urinary free-cortisol test [60].

The confirmative test for pheochromocytoma is controversial, and no single test can confirm the diagnosis. It is not much different from the screening test, but repetition of the test is important. Examination for pheochromocytoma includes measurements of 24-hour urine normetanephrine concentration, metanephrine concentration, vanillylmandelic acid concentration, and plasma metanephrine concentration. There is a high possibility of pheochromocytoma if the 24-hour urinary normetanephrine concentration is higher than 1,500 μg. Pheochromocytoma can generally be diagnosed when the 24-hour urine metanephrine concentration is 1,800 μg or higher, and a 24-hour urine vanillylmandelic acid concentration has diagnostic value when it is 11 mg or higher [58]. Plasma catecholamine measurements can be helpful when pheochromocytoma is strongly suspected but the urine test result is ambiguous.

When the plasma aldosterone/renin activity ratio increases accompanied by hypertension with hypokalemia in patients

with adrenal incidentaloma, an aldosterone-producing adrenal adenoma can be diagnosed after checking that plasma aldosterone was not abnormally suppressed. Any medication that can affect the renin-angiotensin-aldosterone axis should be stopped several weeks before the examination, and hypokalemia should also be corrected. Diagnosis can be made when the 24-hour urine aldosterone excretion is 12 μg/day (33.3 nmol/day) or more even after 3 days of high salt intake. An aldosterone-secreting adrenal adenoma can also be diagnosed when aldosterone-renin activity is not reduced after intravenous administration of 2 L of normal saline for 4 hours. Plasma aldosterone concentration is normally reduced to less than 5 ng/dL, but it does not drop below 10 ng/dL in patients with an aldosterone-producing adrenal adenoma [61-63].

Q. What is the treatment if the adrenal incidentaloma is a functional tumor?

Asymptomatic hypercortisolism

Asymptomatic hypercortisolism patients do not show the typical symptoms or signs caused by high cortisol, but they do show cortisol hypersecretion [63]. This is the most common type of functional adrenal incidentaloma, accounting for 5% to 25% [20,22] or 6.0% to 9.9% of adrenal incidentaloma patients [12,14]. That great difference in prevalence is mainly due to inconsistent diagnosis criteria.

Asymptomatic hypercortisolism patients can be exposed to excess cortisol that is often weak but chronic. Therefore, typical complications of Cushing's syndrome, such as high blood pressure, dyslipidemia, and diabetes mellitus, can develop, but little research has been done on the long-term effects [6,64]. Many retrospective studies and cross-sectional studies have reported an increased incidence of high blood pressure, central obesity, impaired glucose tolerance, diabetes mellitus, dyslipidemia, osteoporosis, and fractures in asymptomatic hypercortisolism patients [16,65,66].

In a recent retrospective study that observed 198 people for an average period of 7.5 years, asymptomatic hypercortisolism patients had a higher rate of cardiovascular disease than nonfunctional adenoma patients. Of the 21 fatalities, 48% died of cardiovascular disease, 43% died of cancer, and the mortality rates from both all causes and cardiovascular diseases were elevated among asymptomatic hypercortisolism patients [67]. A retrospective cohort study of 206 people observed an increased mortality rate among asymptomatic hypercortisolism patients, and the main causes of death were cardiovascular and infectious diseases [68]. However, most research in this area has been limited to retrospective studies, so whether asymptomatic hypercortisolism patients face an increased mortality rate compared to the general population is not yet known [64,69].

Cases have been reported in which hypertension or hyperglycemia improved after adrenalectomy in asymptomatic hypercortisolism patients, but the level of basis is low [65,70]. In another retrospective study of 20 patients, eight of the 10 patients who received an adrenalectomy showed improved hypertension or hyperglycemia, and those that did not receive surgery deteriorated [71]. A prospective randomized controlled study of 45 asymptomatic hypercortisolism patients for an average follow-up period of 8 years found that two-thirds of the 23 patients who received surgery showed improved diabetes mellitus and hypertension, but some of the patients who received conservative treatment showed worsened blood glucose levels or blood pressure. Three patients underwent surgery due to an increase in the size of the adrenal tumor without progression to overt Cushing's syndrome [72]. On the other hand, another retrospective study reported no difference in metabolic indicators or risk factors for atherosclerosis between patients who received an adrenalectomy and those who did not [73].

Due to those inconsistent and incomplete findings, it is difficult to propose a clear recommendation for asymptomatic hypercortisolism treatment. Previous studies have used inconsistent definitions of asymptomatic hypercortisolism, small study samples, a retrospective approach, uncontrolled variables, diverse follow-up periods, and inaccurately defined research goals. Long-term prospective studies on the proper treatment of asymptomatic hypercortisolism are warranted [6,16].

As of now, surgery is considered when diseases thought to be caused by excess cortisol, such as hypertension, diabetes mellitus, central obesity, dyslipidemia, and osteoporosis, newly occur or become aggravated.

When surgery is performed for asymptomatic hypercortisolism, corticosteroid replacement therapy should be initiated the morning after surgery after blood is drawn for the serum cortisol test, and follow-up tests should be conducted until the hypothalamus-pituitary-adrenal axis is recovered.

Although there is no consistent recommendation about the follow-up period for asymptomatic hypercortisolism patients who do not undergo surgery, we recommend performing annual hormone tests (1 mg DST and additional tests when necessary) for 5 years and performing follow-up imaging studies 3 to 6 months after the initial imaging study and annually for another 1 to 2 years. Also, bone density, fasting blood glucose, blood pressure, and cholesterol tests should be carefully monitored,

and the adequacy of medication should be evaluated annually. When complications worsen in spite of medication, consider surgery [23,74].

Cortisol-producing adrenal adenoma

This disease requires a many-sided approach. Hypercortisolism can induce or aggravate diabetes mellitus, hypertension, dyslipidemia, hypokalemia, osteoporosis, and mental disorders. Therefore, patients might require regulation of blood sugar and blood pressure, correction of hypokalemia, etc., before surgery. It has even been reported that hypercortisolism patients are vulnerable to infection because of immune deficiency. The prophylactic administration of a wide range of antibiotics before anesthesia can reduce the risk of infection [75]. Any patient who has undergone unilateral or bilateral adrenalectomy for a cortisol-producing adrenal adenoma will need steroid replacement therapy to prevent hypoadrenalism after surgery [76,77]. Because ACTH secretion is suppressed by hypercortisolism, cortisol stimulation is insufficient after surgery. Cortisol secretion after surgery can be lower than normal because of atrophy in the opposite adrenal gland [78]. However, little research has been done on steroid replacement therapy during surgery for a cortisol-producing adrenal adenoma, and no clear guideline exists for steroid replacement therapy before and after surgery. For patients undergoing major surgery, endogenous cortisol generally increases with the start of anesthesia to reach a blood concentration of 75 to 150 μg/dL and then returns to preoperative the plasma concentration 24 to 48 hours after surgery [79,80]; therefore, 100 mg of hydrocortisone is usually administered intravenously right before anesthesia so cortisol in the blood will reach a maximum concentration at the time of the adrenal resection. An additional 100 mg of hydrocortisone is administered right after the adrenal gland resection or every 8 hours after the dose immediately before anesthesia for 24 hours [75]. However, excessive steroid medication should be avoided because it could slow recovery, increase the risk of infection at the surgical site, and lead to hyperglycemia during and after surgery.

Venous thromboembolism is more likely to occur for the first 4 weeks after surgery [81,82]. To prevent venous thromboembolism, have patients wear an intermittent air compression device or compression stockings during and after surgery or administer low-molecular-weight heparin or unfractionated heparin until they can move completely.

Current research offers a wide variety of tapering methods for steroid replacement therapy after surgery. Most sources agree that steroid supplements should be rapidly reduced within 3 or 4 days after surgery, followed by maintenance of a physiological dose of steroids adjusted to match the state of each patient [77]. Patients and their families should be educated about the symptoms of and remedies for hypoadrenocorticism [77]. If cortisol secretion is normal, steroid replacement therapy is to be discontinued [5] after performing an adrenal cortical function assessment via morning cortisol, an ACTH stimulation test, and an insulin-induced hypoglycemia-induction test on steroid replacement therapy. It usually takes 18 months for cortisol secretion to recover to normal after resection of a cortisol-producing adrenal tumor [83].

Hydrocortisone, which has a short half-life, is preferred for steroid replacement therapy to reduce suppression of the hypothalamic-pituitary-adrenal axis. Begin with separate doses administered two to three times a day for a total of 10 to 12 mg/m^2/day, and then reduce and maintain dosages and administration in accordance with the patient's condition [84]. Vaccination can be considered during steroid replacement therapy, depending on the age of the patient [77].

The management of diabetes mellitus and hypertension might be required after surgery. Patients exposed to hypercortisolism should be evaluated for cardiovascular disease and osteoporosis and treated if necessary.

Pheochromocytoma

Selective α1-blockers correlate with a reduction in preoperative diastolic blood pressure, low pulse rate during surgery, and hemodynamic recovery after surgery, and fewer harmful effects such as reactive tachycardia and continuous postoperative hypotension were observed than seen with the use of non-selective α-blockers [85]. Therefore, treatment to reduce pre-/postoperative cardiovascular complications in pheochromocytoma patients before surgery should be conducted, and α-blockers are recommended as the drug of choice. No randomized clinical study has compared the efficacy of non-selective α-blockers with that of selective α1-blockers [86]. A calcium channel blocker is the drug most commonly added to improve the regulation of blood pressure in patients already receiving α-blockers [87]. Calcium channel blocker monotherapy is not recommended unless the patient has very mild hypertension or severe orthostatic hypotension when treated with α-blockers. Simultaneous preoperative administration of β-blockers can be used only to control tachycardia after α-blocker administration. The use of β-blockers without α-blockers is not recommended because of the risk of a hypertensive crisis caused by unilateral stimulation of the α-receptor. No evidence suggests that non-selective or se-

lective β-blockers are superior to each other. Metyrosine inhibits the synthesis of catecholamines and can thus be used preoperatively with α-blockers to reduce blood loss and volume deficiency during surgery and to stabilize blood pressure [88].

Retrospective studies suggest that starting a high-sodium diet a few days after the initiation of α-blockers helps restore the blood volume contraction caused by catecholamines and prevents severe hypotension after tumor resection [89]. In addition, injecting 1 to 2 L of normal saline the day before surgery can help. A high-sodium diet and normal saline injection before surgery is recommended because α-blockers alone can restore blood volume contraction in only about 60% of patients [90]. Special attention is needed when volume loading in patients with heart failure or renal insufficiency.

Based on retrospective studies, we recommend 7 to 14 days of medical treatment to allow sufficient time for the normalization of blood pressure and pulse before surgery [91,92].

Although no randomized clinical study has been done to find an appropriate preoperative target blood pressure, retrospective studies and clinical experience suggest that it be below 130/80 mm Hg when sitting, with systolic blood pressure higher or equal to 90 mm Hg when standing, and that the heart rate be 60 to 70 per minute when sitting and 70 to 80 per minute when standing. These goals should be modified in accordance with the patient's age and accompanying cardiovascular disease [93]. Understand that hypertension and tachycardia during surgery cannot be completely prevented, even when a combination therapy of antihypertensive drugs and other medications is administered.

The surgical methods for pheochromocytoma include abdominal adrenalectomy and laparoscopic adrenalectomy. Although no prospective randomized study compares those two methods, large, single-institution studies reported that laparoscopic adrenalectomy is associated with reduced pain, bleeding, hospital stay, and postoperative complications [94,95]. Thus, minimally invasive adrenal surgery, such as laparoscopic adrenalectomy, is recommended for most adrenal pheochromocytoma. Open adrenal surgery is recommended for tumors larger than 6 cm and infiltrative pheochromocytoma to guarantee complete resection of the tumor and prevent tumor rupture and local recurrence. No studies have yet compared the difference between the recurrence rates after different types of surgery.

There are two methods of laparoscopic adrenalectomy. The transabdominal/transperitoneal approach (Gagner) is more advantageous to resect large tumors than the retroperitoneal approach (Walz) because it allows evaluation of the peritoneal space and is spacious [95]. The retroperitoneal approach is better for patients who have previously received abdominal surgery or those who need bilateral adrenal resection [96,97].

We recommend partial adrenalectomy only in special cases, such as when a hereditary pheochromocytoma patient has a small tumor after the other adrenal gland has already been removed, to preserve the adrenal cortex and prevent permanent adrenal insufficiency.

The main complications that can occur after surgery are hypertension, hypotension, and hypoglycemia. Based on retrospective studies and clinical experience, we recommend close monitoring of the blood pressure, pulse, and plasma glucose for 24 to 48 hours [89]. There are many reports about hypoglycemia after surgery, but no research has been done on the exact prevalence.

Randomized clinical studies have not been conducted to determine whether the disease persists after surgery, but based on the experience of individuals and medical institutions, we recommend taking plasma or urine metanephrine measurements 2 to 4 weeks after the surgery. Because there are many reports about recurrence and metastases after surgery, lifetime annual biochemical tests should be done to look for recurrence or metastases [85,98,99].

Aldosterone-producing adrenal adenoma (primary aldosteronism)

Once an adrenal incidentaloma is diagnosed as primary aldosteronism, it should be treated with an adrenalectomy [24,100-102] or a mineralocorticoid receptor antagonist [103,104]. Medication, including a mineralocorticoid receptor antagonist, should be considered even when the plasma aldosterone/renin activity ratio is positive, but no additional tests to confirm the presence of an aldosterone-producing adrenal adenoma or evaluate the subtype are available [105]. Treatment for excess aldosterone is necessary because complications such as myocardial fibrosis, left ventricular hypertrophy, arrhythmia, myocardial infarction, stroke, chronic kidney disease, and cardiovascular mortality increase even when hypertension and hypokalemia are controlled, if excess aldosterone is not corrected. Primary aldosteronism patients should have their blood pressure and serum potassium corrected before surgery, and surgery should be postponed if hypertension and hypokalemia are not regulated. Use antihypertensive drugs, including a mineralocorticoid receptor antagonist, for hypertension and hypokalemia correction.

Assess biochemical response by measuring plasma aldosterone concentration and plasma renin activity immediately after surgery [61]. Potassium supplements and mineralocorticoid re-

ceptor antagonist therapy should be discontinued the day after surgery. Adjust the dosage of antihypertensive drugs according to the change in blood pressure after surgery. To prevent hyperkalemia caused by hypoaldosteronism, which is a result of chronic inhibition of the contralateral adrenal gland in aldosterone-producing adrenal adenomas, allow free ingestion of salt for several weeks after surgery. Continuous hypoaldosteronism that requires fludrocortisone replacement therapy can occur in up to 5% of patients who received an adrenalectomy. Creatinine elevation and microalbuminuria after surgery and a decreased glomerular filtration rate before surgery are meaningful predictors of postoperative hyperkalemia [106,107].

What clinical findings suggest a malignancy in adrenal incidentaloma?

When an adrenal incidentaloma is first found, one of the most important issues for both physicians and patients is the possibility of malignant disease. Adrenocortical carcinoma is rare, with incidence of 4% to 5% among adrenal incidentaloma patients, but the prognosis is poor because it is generally far advanced when it is found, and recurrence is common [3,31]. A malignant tumor of the adrenal gland accidentally discovered through imaging does not present any symptoms when there is no abnormality in hormone secretion. In some cases, flank pain, obscure abdominal discomfort, fever due to internal bleeding, and abdominal distension caused by pushing on the surrounding tissues can occur, but it is impossible to differentiate malignant tumors based only on clinical features. However, if a patient has a history of extra-adrenal malignant tumors, the chance that an adrenal incidentaloma will be metastatic cancer is nearly half, so it is important to check patient history of malignancy [108]. Metastatic cancers of the adrenal gland are often from lung, kidney, colon, breast, esophagus, pancreas, liver, or stomach cancer, and the metastases are often bilateral.

The most useful tool to determine whether an adrenal tumor is malignant is a CT scan. When the tumor is <4 cm, the risk of adrenal cancer is less than 2%, but when the size is ≥6 cm, the risk increases to 25%. Therefore, surgical removal is recommended when an adrenal tumor is ≥4 cm [109,110]. When suggesting surgical treatments, consider the age of the patient and the associated disease.

In many adenomas, more than 50% of the contrast agent disappears 10 to 15 minutes after the administration of contrast agent. Adrenal cancer, pheochromocytoma, and metastatic cancer all show less than a 50% loss. This finding has very high sensitivity and specificity [111].

There is the possibility of malignancy when a CT scan shows an irregular tumor margin, heterogeneous content, non-uniform enhancement, or invasion of the surrounding tissue [112].

It is generally impossible to distinguish between pheochromocytoma and metastatic cancer by imaging. It is important to conduct blood and urine tests to rule out pheochromocytoma even though metastatic cancer is more likely. Additional hormone tests can proceed based on the clinician's judgment.

The approach to adrenal incidentaloma in patients with a history of cancer is not much different from that in those who have no such history. The major difference is that in patients with a previous malignancy, ^{18}F-FDG-PET/CT is an effective alternative to other diagnostic imaging [109,110].

FNAB may be performed to verify whether an adrenal incidentaloma is a metastatic tumor in the absence of evidence of metastases in other regions in patients with lung, breast, or kidney cancer or melanoma. It is a good option if the attenuation value prior to contrast is >10 HU and washout is <60% in a CT scan. It also is carried out if the diagnosis can change the direction of treatment in a patient with an unknown primary cancer.

When is surgery indicated in adrenal incidentaloma?

Consider an adrenalectomy in cases with malignant image findings or functional adrenal tumors accompanied by clinical symptoms. The possibility of malignancy increases with the size of the tumor, so size is also an indication for surgical treatment [6]. The laparoscopic adrenalectomy is the most useful treatment for excising tumors. It generally shows better results than open surgery in terms of hospital stay and recovery speed when it is performed by experienced surgeons. Open surgery is still recommended when the tumor is large or suspected to be malignant, but that recommendation remains controversial [2].

In the absence of indications for surgery, tracking observation should proceed, keeping the surgical standard in mind as imaging and biochemical tests accrue during the tracking observation. It is rare for non-functional tumors to change into functional tumors or for a malignancy to be reversed. Nonetheless, surgical treatment is needed upon findings of abnormal adrenal hypersecretion or findings that suggest malignancy during the tracking observation period. Tumors increase in size in 5% to 20% of patients during 4 years of monitoring [8]. The possibility of malignancy increases if the tumor grows more than 1 cm, so tumor growth above that size should trigger consideration of surgical resection [109]. Surgical treatment should also be considered in the presence of symptoms such as pain, organ rupture, or bleeding caused by other tumors.

Table 4. Recommendations for Tracking Adrenal Incidentaloma

Recommendation	Who to image	Image follow-up period	Hormone tracking test	Hormone test follow-up period
NIH consensus statement, 2002	Monitor those <4 cm	Two CTs, at least 6 months apart, if there is no change in size, there is no basis for further follow-up	1 mg DST Plasma free metanephrine K^+ and renin/aldosterone ratio (when accompanied by high blood pressure)	Every year for 4 years
Young, NEJM, 2007		Repeat imaging at 6, 12, and 24 months		
AACE/AAES guidelines, 2009		Imaging at 3–6 months, then annually for 1–2 years		Every year for 5 years

NIH, National Institutes of Health; CT, computed tomography; DST, dexamethasone suppression test; NEJM, *New England Journal of Medicine*; AACE, American Association of Clinical Endocrinologists; AAES, American Association of Endocrine Surgeons.

An assessment of adrenal function and hormone treatment is required before, during, and after surgery for all patients in accordance with their respective situations. In particular a biochemical test for pheochromocytoma must be performed before an adrenalectomy or diagnostic procedure because pheochromocytoma can cause a life-threatening, spasmodic increase in blood pressure if surgical treatment is performed without sufficient pretreatment. Therefore, if pheochromocytoma is suspected or has not been completely ruled out, surgery should proceed only after minimizing any increase in blood pressure and seizure risk by using α-receptor blockers for at least 2 weeks [113]. Typically phenoxybenzamine has been recommended as the primary drug, though doxazosin can also be used. Aldosterone-producing adenomas also require preoperative treatment for high blood pressure and hypokalemia [24,109].

How should follow-up tests for nonfunctioning benign adrenal incidentaloma be conducted?

Benign adrenal adenomas rarely become malignant, and the transformation of a non-functioning adenoma to a functional adenoma cannot cause serious clinical problems. Therefore, there is controversy about the recommendation for regular follow-up after initial tests [6-8,109]. Considering the increases in health care costs, the relatively common false-positive results, and the risk associated with radiation exposure from CT scans, follow-up test is unnecessary in some cases [7]. When the tumor is less than 2 cm and the non-enhanced attenuation value is ≤10 HU, repeated imaging tests are of limited utility. If the tumor does not change in size over a period of more than 1 year, we recommend no further follow-up [6].

In the case of an adenoma smaller than 4 cm with a non-enhanced attenuation value of >10 HU, we recommend a follow-up CT be conducted 3 to 6 months after the initial exam and annually for 1 to 2 years after that. According to the up-to-date guideline for adrenal incidentaloma by European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network, they do not recommend further imaging study during follow-up in patients with an adrenal mass <4 cm with clear benign features on initial work-up [114].

In a study analyzing 75 patients undergoing adrenal surgery who had two or more radiologic exam sources, a size increase of more than 0.8 cm showed the highest sensitivity (60%) and specificity (85%) in distinguishing between malignant and benign tumors [115]. If an adrenal incidentaloma with indeterminate radiological features increases in size more than 0.8 to 1.0 cm during 3 to 12 months of follow-up, consider an adrenalectomy [116].

The possibility that a non-functional adrenal incidentaloma will become a functional tumor is 3.8% a year later and 6.6% 5 years later, and most such tumors cause asymptomatic hypercortisolism [117]. Relatively large tumors, larger than 3 cm, have a high possibility of causing asymptomatic hormone hypersecretion, and that risk reaches its peak in 3 to 4 years. Therefore, it is reasonable to conduct annual hormone tests for at least 5 years when the tumor is larger than 3 cm (Table 4).

How should adrenal incidentaloma patients in special situations (the elderly or people under the age of 40) be managed?

The incidence of adrenal incidentaloma in the whole population is 1% to 4%, but it is more than 10% in people older than 70 years and very low in people younger than 40. Immediate assessment of adrenal incidentaloma in adults <40 years of age and pregnant women is needed because the malignant risk is relatively high. On the other hand, small adrenal incidentaloma in people older than 70 are unlikely to be malignant. Therefore,

additional tests should be performed in the elderly only when the original findings suggest malignancy or the clinician expects clinical benefit after checking the patient's overall status of body performance.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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