Management of the Clinically Inapparent Adrenal Mass ("Incidentaloma")

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The National Institutes of Health Consensus Development Program convened surgeons, endocrinologists, pathologists, biostatisticians, radiologists, oncologists, and other health care professionals, as well as members of the general public, to address the causes, prevalence, and natural history of clinically inapparent adrenal masses, or "incidentalomas"; the appropriate evaluation and treatment of such masses; and directions for future research. Improvements in abdominal imaging techniques have increased detection of adrenal incidentalomas, and because the prevalence of these masses increases with age, appropriate management of adrenal tumors will be a growing challenge in our aging society.

To address six predetermined questions, the 12-member nonfederal, nonadvocate state-of-the-science panel heard presentations from 21 experts in adrenal incidentalomas and consulted a systematic review of medical literature on the topic provided by the Agency for Healthcare Research and Quality and an extensive bibliography developed by the National Library of Medicine. The panel recommended a 1-mg dexamethasone suppression test and measurement of plasma-free metanephrines for all patients with an adrenal incidentaloma; additional measurement of serum potassium and plasma aldosterone concentration–plasma renin activity ratio for patients with hypertension; and surgery for patients with biochemical evidence of pheochromocytoma, patients with tumors greater than 6 cm, and patients with tumors greater than 4 cm who also meet other criteria. The panel also advocated a multidisciplinary approach to managing adrenal incidentalomas.

This statement is an independent report of the panel and is not a policy statement of the National Institutes of Health or the federal government.

 NIH Conference

A 2.5-day National Institutes of Health (NIH) state-of-the-science conference, Management of the Clinically Inapparent Adrenal Mass ("Incidentaloma"), was convened on 4–6 February 2002 to explore and assess the current knowledge regarding adrenal incidentalomas, so that health care providers and the general public can make informed decisions about this important public health issue.

After 1.5 days of expert presentations and questions and public discussion by members of the panel and the audience of interested attendees on incidental adrenal masses, an independent, nonfederal panel weighed the evidence and drafted a statement that was presented on the third day of the conference. Expert presentations and the panel’s statement addressed the following questions: 1) What are the causes, prevalence, and natural history of clinically inapparent adrenal masses? 2) Based on available scientific evidence, what is the appropriate evaluation of a...
clinically inapparent adrenal mass? 3) What criteria should guide the decision on surgical versus nonsurgical management of these masses? 4) If surgery is indicated, what is the appropriate procedure? 5) What is the appropriate follow-up for patients for each management approach? and 6) What additional research is needed to guide practice?

The panel’s draft statement was posted on the NIH Consensus Program Web site (http://consensus.nih.gov) on 6 February 2002.

The primary sponsors of this meeting were the National Institute of Child Health and Human Development and the NIH Office of Medical Applications of Research. Cosponsors included the National Cancer Institute and the National Institute of Diabetes and Digestive and Kidney Diseases.

1. WHAT ARE THE CAUSES, PREVALENCE, AND NATURAL HISTORY OF CLINICALLY INAPPAINT ADRENAL MASSES?

Clinically inapparent adrenal masses are detected incidentally with imaging studies conducted for other reasons. They may be clinically important because some are caused by adrenal cortical carcinomas (estimated prevalence, 4 to 12 per million), which have a high mortality rate. The other medical concern is hormone overproduction from pheochromocytomas, aldosteronomas, and subclinical hypercortisolism, which may be associated with morbidity if untreated.

Prevalence of Clinically Inapparent Adrenal Masses

In autopsy series, the prevalence of clinically inapparent adrenal masses is about 2.1%. Because of increased use of noninvasive high-resolution imaging technology, clinically inapparent adrenal masses are being recognized more often. Estimates range from 0.1% for general health screening with ultrasonography to 0.42% among patients evaluated for nonendocrinologic symptoms to 4.3% among patients who have a previous diagnosis of cancer.

In addition to source of data (autopsy versus clinical series) and reasons for imaging (cancer work-up, nonendocrinologic symptoms, and general health screening), the prevalence of clinically inapparent adrenal masses varies with age. The prevalence of clinically inapparent adrenal masses detected at autopsy is less than 1% for patients younger than 30 years of age and increases to 7% in patients 70 years of age or older. Many of these lesions detected at autopsy are very small. More patients with clinically inapparent adrenal masses are women. This probably reflects the sex distribution of the population undergoing imaging procedures. Autopsy studies or general health examinations show no evidence of difference in prevalence between men and women. There is insufficient information to determine whether the prevalence of clinically inapparent adrenal masses differs by the initial diagnostic test.

Causes of Clinically Inapparent Adrenal Masses

Clinically inapparent adrenal masses can be benign or malignant. These include adenomas, pheochromocytomas, myelolipomas, ganglioneuromas, adrenal cysts, hematomas, adrenal cortical carcinomas, metastases from other cancers, and other rare entities.

The distributions of the pathologic origins of clinically inapparent adrenal masses vary with several clinically important factors, including cancer history and mass size. Three fourths of clinically inapparent adrenal masses among patients with cancer are metastatic lesions. In contrast, two thirds of clinically inapparent adrenal masses in populations with no history of cancer are benign tumors. Prevalence of primary adrenal cortical carcinoma is clearly related to the size of the tumor. Adrenal cortical carcinoma accounts for 2% of tumors that are 4 cm or less, 6% of tumors that are 4.1 to 6 cm, and 25% of tumors that are greater than 6 cm.

Among unselected patients and those with nonendocrinologic symptoms, clinically inapparent adrenal masses are most often nonfunctioning tumors (approximately 70%). Approximately 5% to 10% of patients being evaluated for nonendocrinologic symptoms have subclinical hypercortisolism (sometimes called “subclinical Cushing syndrome”). The percentage of patients with subclinical hypercortisolism depends on the testing methods and cortisol levels achieved after dexamethasone suppression.

The distribution of clinically inapparent adrenal masses derived from surgical series will overestimate the prevalence of adrenal cortical carcinoma, since suspicion of adrenal cortical carcinoma is an indication for surgery. Moreover, the reported frequency of adrenal cortical carcinoma is derived from highly selected patient populations and does not reflect the prevalence rates seen in population-based studies. The age and sex of the patient do not seem to help predict the presence of adrenal cortical carcinoma. Distribution estimates from autopsy studies are not biased by surgical indications but may not reflect the risk for adrenal cortical carcinoma among the subset of people undergoing abdominal imaging studies. A precise estimate of the risk for adrenal cortical carcinoma that could guide clinical decision making may not be possible. Almost all the reported large studies used imaging equipment that is now considered obsolete. The use of contemporary equipment may increase the prevalence of detected clinically inapparent adrenal masses and enhance our ability to differentiate adrenal cortical carcinomas from adenomas. In addition, the literature comprises mainly small, retrospective studies with variable definitions of clinically inapparent adrenal masses, which cause variation in the relative proportions of adrenal pathologic classifications.

Natural History of Clinically Inapparent Adrenal Masses

The observed natural history of clinically inapparent adrenal masses varies, depending on the composition of the study sample and the size and pathologic classification of...
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the adrenal mass. Patients with or without a previous cancer diagnosis found to have adrenal gland metastatic lesions will have a clinical course defined by the stage, grade, and site of the primary tumor. Usually, large clinically inapparent adrenal masses (>6 cm) are treated surgically. Approximately 25% of masses greater than 6 cm in diameter are adrenal cortical carcinomas, and these patients have poor clinical outcomes. Most studies report less than 50% 5-year overall survival for adrenal cortical carcinoma, and several report less than 50% 2-year overall survival. Inconclusive evidence suggests that adrenalectomy at stage 1 or 2 may improve the survival rate.

Follow-up of patients with nonfunctioning adrenal masses suggests that 5% to 25% of masses increase in size by at least 1 cm. The threshold for clinically significant increase in size is unknown. The risk for malignancy is about 1 out of 1000. Up to 20% of patients develop hormone overproduction. Masses of 3 cm or greater are more likely to develop hyperfunction than smaller tumors. Interpretation of these follow-up studies is affected by their variable length of follow-up and variable follow-up strategies.

Most studies indicate that the transformation rate of small (<3 cm) nonfunctioning nodules to functional tumors is low. This may suggest that only limited follow-up is necessary to detect the clinically inapparent adrenal masses that become biochemically active. Similarly, the high growth rate (or short doubling time) and extremely low incidence of adrenal cortical carcinomas suggest that a judicious follow-up strategy is sufficient to reassure concerned patients.

2. BASED ON AVAILABLE SCIENTIFIC EVIDENCE, WHAT IS THE APPROPRIATE EVALUATION OF A CLINICALLY INAPPARENT ADRENAL MASS?

The patient with a clinically inapparent adrenal mass revealed by an imaging study requires a complete history and physical examination, a biochemical evaluation for hormone excess, and possible additional radiologic studies. The goal is to determine whether the patient has pheochromocytoma, subtle glucocorticoid excess, primary aldosteronism (Conn syndrome), or virilizing or feminizing tumors.

Hormonal Evaluation

Available evidence suggests that an overnight (1-mg) dexamethasone suppression test and determination of fractionated urinary or plasma metanephrines should be performed. Exceptions would include patients with imaging characteristics of myelolipoma or an adrenal cyst. In patients with hypertension, serum potassium and a plasma aldosterone concentration–plasma renin activity ratio should be determined to evaluate for primary aldosteronism. A plasma aldosterone concentration–plasma renin activity ratio greater than 30 and a plasma aldosterone concentration of greater than 0.5 nmol/L is highly suggestive of autonomous aldosterone production.

The sensitivity and specificity of 24-hour urine catecholamines for the diagnosis of pheochromocytoma are high, but this test is less sensitive than the determination of free metanephrines, a test now available in commercial laboratories in the United States. Plasma free metanephrines (normetanephrine and metanephrine) can be measured with high diagnostic sensitivity (99%) and good specificity (approximately 89%) and is recommended, on the basis of a multicenter study of biochemical tests for the detection of a pheochromocytoma, as the test of choice for excluding or confirming the diagnosis of pheochromocytoma. The rationale for the 1-mg dexamethasone suppression test is to detect subclinical hypercortisolism. After dexamethasone administration, most normal individuals have serum cortisol concentrations suppressed to less than 139.75 nmol/L. Some experts, however, propose further testing of individuals with serum cortisol values between 49.7 nmol/L and 139.75 nmol/L, in addition to patients with the more traditional cut-off of greater than 139.75 nmol/L, to increase the detection of subclinical hypercortisolism. However, specificity decreases when lower cutpoints are used, which results in more false-positive test results. Unfortunately, this subclinical syndrome has not been adequately characterized, and its natural history is unknown. A better term for this condition might be "subclinical autonomous glucocorticoid hypersecretion." It is controversial whether this disorder is associated with long-term morbidity and whether treatment to reverse subtle glucocorticoid excess is beneficial.

Radiologic Evaluation

The size and appearance of an adrenal mass on computed tomography (CT) or magnetic resonance imaging (MRI) may help distinguish between benign and malignant lesions. The available data suggest that nearly all lesions smaller than 4 cm are benign. A standardized measure of radiograph absorption known as CT attenuation value, conventionally expressed in Hounsfield units (HU), may differentiate between benign and malignant lesions. A homogeneous mass with a smooth border and an attenuation value of less than 10 HU on unenhanced CT strongly suggests a benign adrenal adenoma. The optimal diagnostic evaluation has not been established for adrenal masses between 4 and 6 cm. If these lesions are hormonally inactive and exhibit a benign imaging appearance as described above, they can be monitored. Lesions greater than 6 cm are more likely to be malignant; therefore, surgery should be considered.

Magnetic resonance imaging is as effective as CT in distinguishing benign from malignant lesions. A benign adenoma exhibits a signal drop on chemical-shift imaging and has an intensity similar to that of the liver on a T2-weighted image. Although chemical-shift MRI is commonly performed, it does not provide additional informa-
tion beyond that already available on unenhanced CT. The following tests are not widely available, and data on their clinical usefulness are insufficient: radionuclide scintigraphy using iodocholesterol for evaluating adrenocortical lesions, I-131 metaiodobenzyl guanidine for evaluating pheochromocytoma, and positron emission tomography.

**Fine-Needle Aspiration**

Computed tomography–guided fine-needle aspiration may be helpful in the diagnostic evaluation of patients with a history of cancer (particularly lung, breast, and kidney), no other signs of metastases, and a heterogenous adrenal mass with a high attenuation value (>20 HU). Pheochromocytoma should always be excluded before fine-needle aspiration biopsy of an adrenal mass is attempted in order to avoid the potential for hypertensive crisis. A benign cytologic diagnosis on fine-needle aspiration does not, of course, exclude malignancy because of the high false-negative rate of this procedure.

There are few data on the use of fine-needle aspiration in patients without a history of malignancy who have an incidentally found adrenal mass.

3. **WHAT CRITERIA SHOULD GUIDE THE DECISION ON SURGICAL VERSUS NONSURGICAL MANAGEMENT OF THESE MASSES?**

The major issues to be addressed in formulating a therapeutic plan are whether the lesion is clinically or biochemically active (functional) and whether the lesion is likely to be benign or malignant.

If history or physical examination of a patient with a unilateral incidentaloma shows signs and symptoms suggestive of glucocorticoid, mineralocorticoid, adrenal sex hormone, or catecholamine excess that is confirmed biochemically, adrenalectomy is often considered the treatment of choice. However, medical therapy may be appropriate in several situations. For instance, the use of inhibitors of adrenal cortical steroid hormone biosynthesis may be useful when patients with the Cushing syndrome are poor surgical candidates. Similarly, aldosterone antagonists may be used to treat an aldosterone-secreting tumor.

In the absence of clinical symptoms, treatment decisions for patients with biochemical evidence of adrenal hormone excess are not always straightforward. Patients with “silent” pheochromocytomas are at risk for a hypertensive crisis and should undergo adrenalectomy. Adrenalectomy is an option for an individual with hypertension and aldosterone excess. Patients with subclinical autonomous glucocorticoid hypersecretion present a vexing problem. Data indicate that some patients with subtle glucocorticoid excess may develop metabolic derangements, including insulin resistance, that could be attributable to autonomous cortisol hypersecretion or, rarely, may progress to overt Cushing syndrome. The long-term effects of these derangements on the patient are unknown. Adrenalectomy or careful observation has been suggested as a treatment option. However, while adrenalectomy has been demonstrated to correct the biochemical abnormalities, its effect on long-term outcome and quality of life is unknown.

In patients with nonfunctioning incidentalomas, distinguishing between malignant and benign primary adrenal tumors guides subsequent management. Variables to consider are the size of the lesion, its imaging characteristics, and its growth rate. Traditionally, the size of the lesion has been considered to be the major determinant of the presence of a malignant tumor. More than 60% of incidentalomas less than 4 cm are benign adenomas, while less than 2% represent primary adrenal carcinomas. In contrast, the risk for adrenal carcinoma increases to 25% in lesions that are greater than 6 cm, while benign adrenal adenomas account for less than 15%. Therefore, the generally accepted recommendation is to excise lesions that are larger than 6 cm. Lesions that are less than 4 cm and are defined as low risk by imaging criteria are unlikely to have malignant potential and are generally not resected. The need and strategy for routine follow-up in this group are unclear. For lesions between 4 cm and 6 cm, either close follow-up or adrenalectomy is considered a reasonable approach. Adrenalectomy should be strongly considered if the imaging findings, including rapid growth rate, decreased lipid content, and other features described previously, suggest that the lesion is not an adenoma. It is important to recognize that the size criteria discussed above are arbitrary to some degree, and treatment recommendations are based on data derived from highly selected series of patients. Data from several small series of patients indicate that fewer than 30% of incidentalomas increase in size and fewer than 20% develop biochemical abnormalities when followed for up to 10 years. In studies that monitored patients for many years, the risk for the lesion’s being an adrenal cortical carcinoma was extremely low. Clinicians should consider the clinical condition and personal concerns of an individual patient when making treatment recommendations. Future efforts should define the true natural history of adrenal incidentalomas as a function of size based on properly designed prospective clinical studies.

Finally, adrenalectomy has no known benefits for patients who, during work-up for a clinically inapparent adrenal mass, receive a diagnosis of metastasis from a known or unknown primary neoplasm.

4. **IF SURGERY IS INDICATED, WHAT IS THE APPROPRIATE PROCEDURE?**

Either open or laparoscopic adrenalectomy is an acceptable procedure for resection of an adrenal mass. No randomized trials have compared open adrenalectomy with laparoscopic adrenalectomy. Operative mortality associated with adrenalectomy is less than 2%. However, the laparoscopic approach may have advantages over the open ap-
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Table. Take-Home Points

1. All patients with an incidentaloma should have a 1-mg dexamethasone suppression test and measurement of plasma free metanephrines.
2. Patients with hypertension should also undergo measurement of serum potassium and plasma aldosterone concentration–plasma renin activity ratio.
3. A homogeneous mass with a low attenuation value (<10 HU) on computed tomography is probably a benign adenoma.
4. Surgery should be considered in all patients with functional adrenal cortical tumors that are clinically apparent.
5. All patients with biochemical evidence of pheochromocytoma should undergo surgery.
6. Data are insufficient to indicate the superiority of a surgical or nonsurgical approach to manage patients with subclinical hyperfunctioning adrenal cortical adenomas.
7. Recommendations for surgery based on tumor size are derived from studies not standardized for inclusion criteria, length of follow-up, or methods of estimating the risk for carcinoma. Nevertheless, patients with tumors >6 cm usually are treated surgically, while those with tumors <4 cm are generally monitored. In patients with tumors between 4 and 6 cm, criteria in addition to size should be considered in the decision to monitor or proceed to adrenalectomy.
8. The literature on adrenal incidentaloma has proliferated in the last several years. Unfortunately, the lack of controlled studies makes formulating diagnostic and treatment strategies difficult. Because of the complexity of the problem, the management of patients with adrenal incidentalomas will be optimized by a multidisciplinary team approach involving physicians with expertise in endocrinology, radiology, surgery, and pathology. The paucity of evidence-based data highlights the need for well-designed prospective studies.
9. Open or laparoscopic adrenalectomy is an acceptable procedure for resection of an adrenal mass. The procedure choice will depend on the likelihood of an invasive adrenal cortical carcinoma, technical issues, and the experience of the surgical team.
10. In patients with tumors that remain stable on two imaging studies done at least 6 months apart and do not exhibit hormonal hypersecretion over 4 years, further follow-up may not be warranted.

5. What Is the Appropriate Follow-up for Patients for Each Management Approach?

Recommendations for follow-up are designed to detect interval changes in tumor size or the development of hormone overproduction. Long-term follow-up studies suggest that most adrenal lesions remain stable, whereas 5% to 25% enlarge and 3% to 4% decrease in size. However, the limited and incomplete evidence available precludes making specific recommendations regarding serial imaging and biochemical evaluation. In patients whose lesions have not been excised, CT repeated 6 to 12 months after the initial study is reasonable. For lesions that do not increase in size, no data support continued radiologic evaluation. This observation is based on longitudinal studies of up to 10 years reporting that the risk for developing adrenal cortical carcinoma is extremely low.

Hormone excess may develop in up to 20% of patients during follow-up but is unlikely in a patient with a lesion smaller than 3 cm. Cortisol hypersecretion is the most likely disorder that may ensue and is subclinical in two thirds of cases. Catecholamine overproduction or hyperaldosteronism rarely develops during long-term follow-up. Few data are available that guide recommendations for periodic hormonal testing. One current approach is an overnight 1-mg dexamethasone suppression test and measurement of urine catecholamines and metabolites at yearly intervals or earlier if clinically indicated. The risk for tumor hyperfunction seems to plateau after 3 to 4 years; however, these data are based on a small number of patients with variable follow-up.

Patients with subclinical hypercortisolism should receive perioperative glucocorticoids because they are at risk for hypoadrenalism after removal of the functioning mass. They should be monitored for subsequent hypothalamic–pituitary–adrenal axis recovery and clinical improvement. Guidelines for follow-up of other patients who have undergone resection have not been defined.

6. What Additional Research Is Needed to Guide Practice?

Additional research needed to guide practice should be led by the establishment of an international collaborative study group whose charge is to develop a database of patients with clinically inapparent adrenal masses. The database would need to have clearly defined entry criteria, variables to be collected, guidelines for follow-up, and so forth.

The purpose would be to provide longitudinal data to help address several important questions: 1) What is the natural history of clinically silent adrenal masses? 2) Can we identify patients who are at high risk for developing adrenal cortical carcinoma? 3) How long should patients be monitored before concluding that they are not at risk for adrenal cortical carcinoma or emergence of endocrine hyperfunction? 4) What is the optimal follow-up strategy for patients with incidentally discovered adrenal masses?

Proposed studies are 1) a study of perioperative and postoperative outcomes designed to define the risks and benefits of the various surgical procedures; 2) studies of physical and mental health outcomes and quality of life among patients with conservatively managed clinically inapparent adrenal masses; 3) a study of the effect of surgical removal of tumors on evolution of common chronic dis-
eases, such as obesity, diabetes, osteoporosis, hypertension, and psychiatric conditions; 4) a prospective study at centers conducting screening whole-body scanning to learn more about the prevalence and natural history of incidentalomas and the psychosocial effect on the patient; and 5) a prospective study to characterize subclinical hypercortisolism, including the evaluation of diagnostic tests, possible associated morbidity, and the benefits of treatment; and 6) a study to validate the reproducibility of size measurements in serial imaging examinations for ultrasonography, CT, and MRI and to determine what constitutes a clinically significant change. In addition, markers sensitive and specific for adrenal cortical carcinoma need to be identified.

There is a need to better define the various diagnostic tests that have been advocated for evaluating adrenal masses and their translation to clinical practice. These include positron emission tomography, delayed enhanced CT for distinguishing between benign and malignant adrenal neoplasms, adrenal biopsies with immunostaining for tumor markers, 3-mg dexamethasone suppression test versus the 1-mg overnight dexamethasone suppression test, and use of plasma free metanephrine measurements for the diagnosis of an adrenal incidentaloma that is a pheochromocytoma. Finally, the appropriate specialty and surgical societies should develop minimal criteria that define proficiency in the performance of laparoscopic adrenalectomy.

**CONCLUSIONS**

The management of clinically inapparent adrenal masses is complicated by limited studies of incidence, prevalence, and natural history, including the psychological effect on the patient who is informed of the diagnosis. Improvements in the resolution of abdominal imaging techniques combined with increased use of abdominal imaging suggest that the prevalence of clinically inapparent adrenal masses will continue to escalate. The low prevalence of adrenal cortical carcinomas and the relatively low incidence of progression to hyperfunction call into question the advisability of the current practice of intense long-term clinical follow-up of this common condition. See the Table for a summary of conclusions.

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Current author addresses and a list of conference speakers and conference planning committee members are available at www.annals.org.
APPENDIX
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