DRAFT STATEMENT
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NATIONAL INSTITUTES OF HEALTH
STATE-OF-THE-SCIENCE CONFERENCE STATEMENT
Management of the Clinically Inapparent Adrenal Mass ("Incidentaloma")
February 4–6, 2002

NIH Statements are prepared by a nonadvocate, non-Federal panel of experts, based on (1) presentations by investigators working in areas relevant to the questions during a 2-day public session; (2) questions and statements from conference attendees during open discussion periods that are part of the public session; and (3) closed deliberations by the panel during the remainder of the second day and morning of the third. This statement is an independent report of the panel and is not a policy statement of the NIH or the Federal Government.

Introduction

The adrenals are triangular glands that sit atop each kidney. They influence or regulate the body's metabolism, salt and water balance, and response to stress by secreting a variety of hormones. Based on autopsy studies, adrenal masses are among the most common tumors in humans: adrenal masses occur in at least 3 percent of persons over age 50 at autopsy. Most adrenal masses cause no health problems. A small proportion, however, can lead to a number of serious hormonal diseases; approximately one out of every 4,000 adrenal tumors is malignant.

Clinically inapparent adrenal masses are discovered inadvertently in the course of diagnostic testing or treatment for other clinical conditions that are not related to suspicion of adrenal disease and, thus, are commonly known as incidentalomas. The definition of incidentaloma excludes patients undergoing imaging procedures as part of staging and workup for cancer. Improvements in abdominal imaging techniques and technologies have resulted in the

detection of an increasing number of adrenal incidentalomas. Increasing clinical and scientific interest is reflected in a twentyfold increase in publications about this condition over the past decades.

When detected, clinically inapparent adrenal masses raise challenging questions for physicians and their patients. Diagnostic evaluation is performed to determine whether the lesion is hormonally active or nonfunctioning and whether it is malignant or benign. The results from these tests will influence whether the mass is removed surgically or treated nonsurgically. Because the prevalence of these masses increases with age, appropriate management of adrenal tumors will be a growing challenge in our aging society.

Over the past 3 decades, new information has become available regarding the epidemiology, biology, screening, treatment, and followup of adrenal tumors. For example, recent refinements in the field of minimally invasive surgery have made laparoscopic adrenalectomy a more frequently used method for removing adrenal masses. Recent reports suggest that up to 20 percent of patients with adrenal incidentaloma have some form of subclinical hormonal dysfunction and may represent a population at higher risk for metabolic disorders and cardiovascular disease. It is important to determine whether groups of patients with subclinical disease benefit from treatment. The psychological impact on the patient of knowing that he or she harbors an adrenal incidentaloma, an incompletely understood clinical problem, merits investigation.

This two-and-a-half-day state-of-the-science conference on Management of the Clinically Inapparent Adrenal Mass (“Incidentaloma”) was convened on February 4–6, 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 a day-and-a-half of expert presentations and public discussion on incidental adrenal masses, an independent, non-Federal 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 followup for patients for each management approach?

6. What additional research is needed to guide practice?

The panel's draft statement was posted to the Consensus Program Web site—http://consensus.nih.gov—on Wednesday, February 6, 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 inapparent 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 of 4–12 per million), which have a high mortality rate. The other clinical concern is hormone overproduction from pheochromocytomas, aldosteronomas, and subclinical Cushing syndrome, 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 percent. Because of increased use of noninvasive high-resolution imaging technology, clinically inapparent adrenal masses are being recognized more often. Estimates range from 0.1 percent for general health screening with ultrasound, to 0.42 percent among patients evaluated for nonendocrinologic complaints, to 4.3 percent among patients who have a previous diagnosis of cancer.

In addition to source of data (autopsy versus clinical series) and reasons for imaging (cancer workup, nonendocrinologic complaints, 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 percent for ages younger than 30 years and

increases to 7 percent in those 70 years of age or older. Many of these lesions detected at autopsy are very small. Among patients with clinically inapparent adrenal masses, more are women. This probably reflects the sex distribution of the population undergoing imaging procedures. There is no evidence of a sex difference in prevalence from autopsy studies or general health exams. 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 either 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. Among cancer patients, three-fourths of clinically inapparent adrenal masses are metastases. In contrast, in populations with no history of cancer, two-thirds of clinically inapparent adrenal masses are benign tumors. Prevalence of primary adrenal cortical carcinoma is clearly related to the size of the tumor. Adrenal cortical carcinoma accounts for 2 percent of tumors less than or equal to 4 cm, 6 percent of tumors 4.1–6 cm, and 25 percent of tumors greater than 6 cm.

Among unselected patients and those with nonendocrinologic complaints, clinically inapparent adrenal masses are most often nonfunctioning tumors (approximately 70 percent). Among patients being evaluated for nonendocrinologic complaints, approximately 5–10 percent have subclinical hypercortisolism (subclinical Cushing syndrome). The percent of patients with

subclinical hypercortisolism depends on the testing methods and cortisol levels achieved after dexamethasone suppression.

The distribution of clinically inapparent adrenal mass pathologies 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 carcinomas 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 appear to be helpful in predicting the presence of adrenal cortical carcinoma. Distribution estimates from autopsy studies are not biased by surgical indications but may not reflect the risk of adrenal cortical carcinoma among the subset of people undergoing abdominal imaging studies. A precise estimate of the risk of adrenal cortical carcinoma that could guide clinical decision-making may not be possible. Almost all the reported large studies used imaging equipment that would now be considered obsolete. The use of contemporary equipment may increase the prevalence of detected clinically inapparent adrenal masses and may 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 pathological 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 population and the size and pathological classification of the adrenal mass. Patients with or without a previous cancer diagnosis found to have adrenal gland metastases will have a clinical course defined by the stage, grade, and site of the primary tumor.

Usually, large clinically inapparent adrenal masses (greater than 6 cm) are treated surgically. Approximately 25 percent of masses greater than 6 cm in diameter are adrenal cortical carcinomas, and these patients have very poor clinical outcomes. The overwhelming majority of studies report less than 50 percent 5-year overall survival for adrenal cortical carcinoma, and several report less than 50 percent 2-year overall survival. There is no evidence that early detection of adrenal cortical carcinoma decreases the mortality rate.

Followup of patients with nonfunctioning adrenal masses suggests that 5–25 percent of masses increase in size by at least 1 cm. The threshold for clinically significant increase in size is unknown. The risk of malignancy is about 1/1,000. Up to 20 percent of patients develop hormone overproduction. Masses greater than or equal to 3 cm are more likely to develop hyperfunction compared to smaller tumors. Interpretation of these followup studies is affected by variable length of followup and variable followup strategies.

Most studies indicate that the transformation rate of small (less than 3 cm) nonfunctioning nodules to functional tumors is low. This may suggest that only limited followup 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 followup 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 (Cushing syndrome), primary aldosteronism (Conn syndrome), or virilizing or feminizing tumors.

Hormonal Evaluation

Available evidence suggests that an overnight (1-mg) dexamethasone suppression test and fractionated urinary plasma metanephrine should be performed. Exceptions would include patients with imaging characteristics of myelolipoma and 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 20 ng/dL is highly suggestive of autonomous aldosterone production. The sensitivity and specificity of measuring 24-hour fractionated urine metanephrines for the diagnosis of pheochromocytoma are also high. Emergency data suggest that plasma metanephrines can be measured with high diagnostic accuracy and may eventually replace or complement the measurement of urine metanephrines. The rationale for the 1-mg dexamethasone suppression test is to detect subclinical Cushing syndrome. Following dexamethasone, normal individuals generally suppress their serum cortisol to less than 5 mg/dl. Unfortunately, this syndrome has not been adequately characterized, and the 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 the 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 X-ray 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 an unenhanced CT study strongly suggests the diagnosis of a benign adrenal adenoma. The optimal diagnostic evaluation has not been established for adrenal masses between 4–6 cm. If these lesions are hormonally inactive and exhibit a benign imaging appearance as described above, they can be followed. Lesions greater than 6 cm are more likely to be malignant; therefore, surgery should be considered.

Although chemical shift MRI is commonly performed, it does not provide additional information beyond that which is already available on unenhanced CT. The following tests are not widely available, and there are insufficient data regarding clinical utility: radionuclide scintigraphy using iodocholesterol (NP59) for evaluating adrenocortical lesions, I-131 metaiodobenzyl guanidine (MIBG) for evaluating pheochromocytoma, and positron emission tomography (PET).

Fine Needle Aspiration

CT-guided fine needle aspiration (FNA) may be helpful in the diagnostic evaluation of patients with a history of cancer (particularly lung, breast, and kidney), with no other signs of metastases, and a heterogenous adrenal mass with a high attenuation value (greater than 20 HU). It is important to note that a benign cytologic diagnosis on FNA does not totally exclude malignancy because of its high false negative rate.

There are few data regarding the utility of FNA in patients without a history of malignancy who have an incidentally found adrenal mass.

3. <u>What criteria should guide the decision on surgical versus nonsurgical management of these masses</u>?

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 a patient with a unilateral incidentaloma is found on history or physical examination to have the 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 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 those 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 exist that 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 have been suggested as treatment options. 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 potential presence of a malignant tumor. More than 60 percent of incidentalomas less than 4 cm are benign adenomas, while less than 2 percent represent primary adrenal carcinomas. In contrast, the risk of adrenal carcinoma increases to 25 percent in lesions that are greater than 6 cm while benign adrenal adenomas account for less than 15 percent. Therefore, the generally accepted recommendation is to excise lesions that are larger than 6 cm. Lesions that are less than 4 cm and appear to be defined as low risk by imaging criteria are unlikely to have malignant potential and are generally not resected.

The need and strategy for routine followup in this group are unclear. For lesions between 4 and 6 cm, either close followup 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 to some degree arbitrary, and treatment recommendations are based upon data derived from highly selected series of patients. Data from several small series of patients indicate that less than 30 percent of incidentalomas increase in size and less than 20 percent develop biochemical abnormalities when followed for up to 10 years. It is reassuring to note that in studies in which patients were monitored for many years, the risk of the lesion being an adrenal cortical carcinoma was extremely low. The clinical condition and personal concerns of an individual patient should be taken into account when making treatment recommendations. Future efforts should be directed toward defining the true natural history of adrenal incidentalomas as a function of size based upon properly designed prospective clinical studies.

Finally, there is no known benefit from adrenalectomy for patients who, during their workup for a clinically inapparent adrenal mass, are diagnosed with metastasis from a known or unknown primary neoplasm.

4. <u>If surgery is indicated, what is the appropriate procedure</u>?

Either open or laparoscopic adrenalectomy is an acceptable procedure for resection of an adrenal mass. There are no prospective, randomized trials comparing open with laparoscopic adrenalectomy. Operative mortality associated with adrenalectomy is less than 2 percent. However, the laparoscopic approach may have advantages over the open approach when

performed by a surgical team experienced in advanced laparoscopic techniques. These advantages include decreased postoperative pain, reduced time to return of bowel function, decreased length of hospital stay, and the potential for earlier return to work. At present, relative contraindications to laparoscopic adrenalectomy are a definitive or presumed diagnosis of invasive adrenal cortical carcinoma or circumstances that make a minimally invasive approach technically difficult, for example, large tumors. There are no studies that demonstrate a consistent benefit of one laparoscopic approach (transabdominal or retroperitoneal) over another.

5. What is the appropriate followup for patients for each management approach?

Recommendations for followup are designed to detect interval changes in tumor size or the development of hormone overproduction. Long-term followup studies suggest that the vast majority of adrenal lesions remain stable, whereas 5–25 percent enlarge, and 3–4 percent 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, a CT study repeated 6–12 months after the initial study is reasonable. For lesions that do not increase in size, there are no data to support continued radiologic evaluation. This observation is based on longitudinal studies of up to 10 years reporting that the risk of developing adrenal cortical carcinoma is extremely low.

Hormone excess may develop in up to 20 percent of patients during followup, but is unlikely in a patient with a lesion less than 3 cm. Cortisol hypersecretion is the most likely disorder that may ensue and is subclinical in two-thirds of cases. The onset of catecholamine overproduction or hyperaldosteronism during long-term followup is rare. There are few data that would guide recommendations for periodic hormonal testing. One current approach would be to

perform an overnight 1 mg dexamethasone suppression test and urine catecholamines/metabolites at yearly intervals or earlier if clinically indicated. The risk of tumor hyperfunction appears to plateau after 3–4 years; however, these data are based on a small number of patients with variable followup.

Patients with subclinical Cushing syndrome should receive perioperative glucocorticoids and should be monitored for hypothalamic-pituitary-adrenal axis recovery and clinical improvement. Guidelines for followup 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 followup, and so forth.

The purpose would be to provide longitudinal data to help address several important questions. These include:

- What is the natural history of clinically silent adrenal masses?
- Can we identify patients who are at high risk for developing adrenal cortical carcinoma?
- How long should patients be followed before concluding that they are not at risk for adrenal cortical carcinoma or emergence of endocrine hyperfunction?

- What is the optimal followup 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 diseases such as obesity, diabetes, osteoporosis, hypertension, and psychiatric conditions

4. A prospective study at centers conducting screening whole body scans to learn more about the prevalence and natural history of incidentalomas and the psychosocial effect on the patient

5. A prospective study to characterize subclinical Cushing syndrome, including the evaluation of diagnostic tests, possible associated morbidity, and the benefits of treatment

6. A study to validate the reproducibility of size measurements in serial imaging exams for ultrasound, CT, and MRI and to determine what constitutes a significant change

Additionally, 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 computed tomography 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
- Utility of plasma free metanephrines measurements for the diagnosis of 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. 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 clinical followup of this common condition.

- All patients with an incidentaloma should have a 1-mg dexamethasone suppression test and measurement of urine or plasma free metanephrines.

- Patients with hypertension should also undergo measurement of serum potassium and plasma aldosterone concentration/plasma renin activity ratio.

- A homogeneous mass with a low attenuation value (less than 10 HU) on CT scan is likely a benign adenoma.

- Surgery should be considered in all patients with functional adrenal cortical tumors that are clinically apparent.

- All patients with biochemical evidence of pheochromocytoma should undergo surgery.

- Data are insufficient to indicate the superiority of a surgical or nonsurgical approach to manage patients with subclinical hyperfunctioning adrenal cortical adenomas.

- Recommendations for surgery based upon tumor size are derived from studies not standardized for inclusion criteria, length of followup, or methods of estimating the risk of carcinoma. Nevertheless, patients with tumors greater than 6 cm usually are treated surgically, while those with tumors less than 4 cm are generally followed. In

patients with tumors between 4 and 6 cm, criteria in addition to size should be considered in making the decision to monitor or proceed to adrenalectomy.

- 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.

- Either open or laparoscopic adrenalectomy is an acceptable procedure for resection of an adrenal mass. The choice of procedure will depend upon the likelihood of an invasive adrenal cortical carcinoma, technical issues, and the experience of the surgical team.

- In patients with tumors that remain stable on two imaging studies carried out at least 6 months apart and do not exhibit hormonal hypersecretion over 4 years, further followup may not be warranted.

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