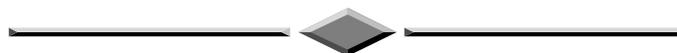
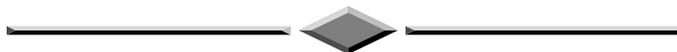


NIH State-of-the-Science Conference on Management of the Clinically Inapparent Adrenal Mass (“Incidentaloma”)



**February 4–6, 2002
William H. Natcher Conference Center
National Institutes of Health
Bethesda, Maryland**



Sponsored by:

- ◆ National Institute of Child Health and Human Development ◆ Office of Medical Applications of Research ◆

Cosponsored by:

- ◆ National Cancer Institute ◆ National Institute of Diabetes and Digestive and Kidney Diseases ◆



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Introduction

The National Institutes of Health (NIH) will convene a State-of-the-Science Conference on Management of the Clinically Inapparent Adrenal Mass (“Incidentaloma”), on February 4–6, 2002.

The adrenals are triangular glands that sit atop each kidney. They influence or regulate the body’s metabolism, salt and water balance, response to stress, and other important functions by secreting a variety of hormones. Adrenal masses are among the most common tumors in humans, occurring in at least 3 percent of persons over age 50, according to recent estimates. Most adrenal masses cause no health problems. A small proportion, however, can lead to a number of serious hormonal diseases, and approximately one out of every 4,000 adrenal tumors is cancerous.

Clinically inapparent adrenal masses are discovered inadvertently, in the course of diagnostic testing or treatment for other conditions, and thus are commonly known as incidentalomas. Improvements in abdominal imaging techniques and technologies have resulted in the detection of an increasing number of adrenal incidentalomas.

When detected, the clinically inapparent adrenal mass raises challenging questions for physicians and their patients. For example, should the mass be removed? Is a nonsurgical approach indicated? What risks are associated with either approach? Because the incidence of these masses increases with age, appropriate management of adrenal tumors will be a growing challenge in our aging society.

Over the past several years, significant 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 general surgery have made laparoscopic adrenalectomy a widely used method for removing adrenal masses. Moreover, recent reports suggest that 5 to 25 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 will be important to identify those groups with subclinical disease that will benefit from treatment.

This two-and-a-half-day conference will explore and assess the current scientific knowledge regarding adrenal incidentalomas, so 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 will weigh the scientific evidence and draft a statement that will be presented on the third day of the conference. Expert presentations, and the panel’s statement, will address the following questions:

- What are the causes, prevalence, and natural history of clinically inapparent adrenal masses?
- Based on available scientific evidence, what is the appropriate evaluation of a clinically inapparent adrenal mass?

- What criteria should guide the decision on surgical versus nonsurgical management of these masses?
- If surgery is indicated, what is the appropriate procedure?
- What is the appropriate followup for patients for each management approach?
- What additional research is needed to guide practice?

The panel's draft statement will be posted to the Consensus Program Web site—<http://consensus.nih.gov>—on Wednesday, February 6, 2002.

General Information

Conference sessions will be held in the Natcher Conference Center, National Institutes of Health, Bethesda, Maryland. Sessions will run from 8:30 a.m. to 5:30 p.m. on Monday, February 4, 2002; from 8:30 a.m. to 12:30 p.m. on Tuesday, February 5, 2002; and from 9 a.m. to 11 a.m. on Wednesday, February 6, 2002. The telephone number for the message center is (301) 496-9966; the fax number is (301) 480-5982.

Cafeteria

The cafeteria in the Natcher Conference Center is located one floor above the auditorium on the main floor of the building. It is open from 7 a.m. to 2 p.m., serving breakfast and lunch.

Sponsors

The primary sponsors of this meeting are the NIH Office of Medical Applications of Research and the National Institute of Child Health and Human Development. Supporting agencies include the National Cancer Institute and the National Institute of Diabetes and Digestive and Kidney Diseases.

Statement of Interest

Each speaker presenting at this conference has been asked to submit documentation outlining all outside involvement pertaining to the subject area. Please refer to the chart in your participant packet for details.

Agenda

Monday, February 4, 2002

- 8:30 a.m. Opening Remarks
Duane Alexander, M.D., Director
National Institute of Child Health and Human Development
National Institutes of Health
- 8:40 a.m. Charge to Panel
Barnett S. Kramer, M.D., M.P.H., Director
Office of Medical Applications of Research, Office of the Director
National Institutes of Health
- 8:50 a.m. Conference Overview and Panel Activities
Melvin M. Grumbach, M.D., Panel and Conference Chairperson
Edward B. Shaw Professor of Pediatrics Emeritus
Department of Pediatrics
University of California, San Francisco

I. Overview

- 9:00 a.m. Clinically Inapparent Adrenal Mass: A Challenge for Modern Medicine
Stefan R. Bornstein, M.D., Ph.D., Professor of Medicine and Associate Director
Department of Endocrinology
University of Düsseldorf

II. Methods

- 9:20 a.m. Methods of the Evidence Report
Joseph Lau, M.D., Director
New England Medical Center Evidence-Based Practice Center
Tufts University School of Medicine

III. Causes, Prevalence, and Natural History of Clinically Inapparent Adrenal Masses

- 9:40 a.m. Adrenal Pathology and Causes of Adrenal Masses
Clara S. Heffess, M.D., Chief
Endocrine Division
Armed Forces Institute of Pathology

Monday, February 4, 2002 (continued)

III. Causes, Prevalence, and Natural History of Clinically Inapparent Adrenal Masses (continued)

- 10:00 a.m. Prevalence and the Natural Course of Adrenal Incidentaloma
Luisa Barzon, M.D., Research Associate
Department of Histology, Microbiology, and Medical Biotechnologies
University of Padova
- 10:20 a.m. Recent Update of Histopathology of Adrenocortical Incidentaloma—
Changes in the Concept
Hironobu Sasano, M.D., Ph.D., Director
Department of Pathology
Tohoku University School of Medicine
- 10:40 a.m. Discussion

IV. Evaluation of Clinically Inapparent Adrenal Masses

- 11:30 a.m. Test Performance for Evaluating Incidentaloma
Ethan M. Balk, M.D., M.P.H., Assistant Director
New England Medical Center Evidence-Based Practice Center
Tufts University School of Medicine
- 11:50 a.m. Endocrine and Biochemical Evaluation of Adrenal Incidentaloma
William F. Young, Jr., M.D., Consultant
Department of Endocrinology and Metabolism
Mayo Clinic and Foundation
- 12:10 p.m. Imaging of Adrenal Incidentaloma
Melvyn Korobkin, M.D., Professor of Radiology and Director of
Abdominal Imaging
Department of Radiology
University of Michigan Medical School
- 12:30 p.m. Lunch
- 1:30 p.m. Pathologic Evaluation of Adrenal Incidentaloma
Ernest E. Lack, M.D., Professor of Anatomic Pathology
Department of Pathology
Washington Hospital Center
- 1:50 p.m. Discussion

Monday, February 4, 2002 (continued)

V. Surgical Versus Nonsurgical Management

- 2:30 p.m. When Should an Adrenal Incidentaloma Be Operated On—Survey From the Italian Study Group
Franco Mantero, M.D., Professor of Endocrinology
Department of Endocrinology
University of Padova
- 2:50 p.m. Criteria for Surgery
Anna A. Kasperlik-Zaluska, M.D., Ph.D., Professor of Medicine
Department of Endocrinology
Centre for Postgraduate Medical Education
- 3:10 p.m. Considerations in the Management of Adrenal Incidentalomas:
A Practical Algorithm
David E. Schteingart, M.D., Professor
Department of Internal Medicine
University of Michigan Medical School
- 3:30 p.m. Discussion

VI. Conventional Versus Minimally Invasive Surgery

- 4:00 p.m. Adrenal Incidentaloma: Surgical Progress or Status Quo?
Allan E. Siperstein, M.D., Head, Section of Endoscopic Surgery
Department of General Surgery
Cleveland Clinic Foundation
- 4:20 p.m. Laparoscopic Adrenalectomy
Robert Udelsman, M.D., M.S.B., M.B.A., F.A.C.S., Lampman Professor of
Surgery and Oncology
Chairman, Department of Surgery
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- 4:40 p.m. Risk and Complication Rate of Different Surgical Techniques
Michael Rothberg, M.D., M.P.H., Consultant
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Tufts University School of Medicine
- 5:00 p.m. Discussion
- 5:30 p.m. Recess until Tuesday

Tuesday, February 5, 2002

VII. Followup of Adrenal Incidentaloma

- 8:30 a.m. Evidence for Followup Strategies
Joseph Lau, M.D., Director
New England Medical Center Evidence-Based Practice Center
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- 8:50 a.m. The Long-Term Complications of Incidentally Discovered Adrenal Mass
(Adrenal Incidentaloma)
Alberto Angeli, M.D., Full Professor of Internal Medicine
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San Luigi Hospital
- 9:10 a.m. The Adrenal Incidentaloma: Public Health Dimensions and Followup
David C. Aron, M.D., M.S., Associate Chief of Staff/Education
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- 9:30 a.m. Cost-Effectiveness Analysis of Diagnosis and Treatment of Adrenal
Incidentaloma
Job Kievit, M.D., Ph.D., Director
Department of Medical Decision Making
Leiden University Medical Center
- 9:50 a.m. Discussion

VIII. Perspectives and Future Directions

- 10:30 a.m. Novel Tumor Markers in the Adrenal Gland
Sandra Ann Murray, Ph.D., Professor
Department of Cell Biology and Physiology
University of Pittsburgh School of Medicine
- 10:50 a.m. Novel Biochemical Markers and Imaging Techniques for Diagnosis of
Pheochromocytoma in Patients with an Incidentally Discovered Adrenal Mass
Karel Pacak, M.D., Ph.D., D.Sc., Tenure-Track Investigator
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- 11:10 a.m. Subclinical Endocrine Activity and Adrenal Biopsy
Martin Reincke, M.D., Professor of Medicine
University of Freiburg
- 11:30 a.m. Discussion

Tuesday, February 5, 2002 (continued)

IX. Public Presentations

12:00 p.m. Presentations by Public

12:15 p.m. Recess until Wednesday—Panel Meets in Executive Session

Wednesday, February 6, 2002

9:00 a.m. Presentation of the State-of-the-Science Statement

9:30 a.m. Public Discussion

11:00 a.m. Panel Meets in Executive Session

1:00 p.m. Press Conference

2:00 p.m. Adjournment

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Abstracts

The following are abstracts of presentations to the NIH State-of-the-Science Conference on Management of the Clinically Inapparent Adrenal Mass (“Incidentaloma”). They are designed for the use of panelists and participants in the conference and as a reference document for anyone interested in the conference deliberations. We are grateful to the authors for their participation and for supplying these summaries.

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Clinically Inapparent Adrenal Mass: A Challenge for Modern Medicine

Stefan R. Bornstein M.D., Ph.D.

Although a comparatively recent clinical phenomenon, the impact of the clinically inapparent adrenal mass, or incidentaloma, on health and vitality is now gaining widespread acceptance. Despite the rarity of endocrine cancers of the adrenal, adrenal masses are in fact one of the most prevalent of all human tumors. Indeed the prevalence of adrenal incidentaloma approaches 3 percent in middle age, and increases to 10 percent in the elderly. Therefore the diagnosis and management of incidentaloma will become an increasingly important aspect of health care within our progressively aging population. Recent advances and availability in imaging technology may reveal a still higher incidence, making incidentaloma a still greater challenge to modern medicine.

Most of these nodules, until now, have been regarded as being benign and endocrinologically inactive with only a small fraction developing into malignant tumors. However, clinicians will be increasingly presented with cases of incidentaloma and, therefore, should become increasingly vigilant for new developments. Currently there is considerable confusion among contemporary clinicians as to the relevance of and best approaches to the diagnosis and treatment of incidentaloma. Diagnostic and therapeutic strategies vary from extensive treatment and/or an early operation to a complete ignorance of the problem. Studies in different countries have recommended different size criteria for surgery; for instance, in Italy it is 4 cm, in Germany 6 cm, in the United States 5 cm, and so forth. This confusion, combined with a lack of knowledge, also opens the doors for inappropriate procedures, malpractice, and a further explosion of health care costs.

Fresh insights into the diagnosis, biology, and epidemiology of incidentaloma have recently arisen, and more funding and the stagelight of public attention should lead to a more complete comprehension of the role of incidentaloma in the perturbation of adrenal function.

In recent years, several of the molecular and cellular mechanisms involved in adrenal cell regulation and tumorigenesis have begun to be unraveled. As a result, alterations in intercellular communication, in the local production of growth factors and cytokines, and in the aberrant expression of ectopic receptors on adrenal tumor cells have been implicated in adrenal cell growth, hyperplasia, tumor formation, and autonomous hormone production. Genetic and chromosomal abnormalities involving several chromosomal loci and the genes coding for p53, p57, and insulin-like growth factor II have been reported in adrenal tumors. In addition, chromosomal markers have been identified in several familial syndromes associated with adrenal tumors; these include *menin*, which is responsible for multiple endocrine neoplasia type I, and the hybrid gene that causes glucocorticoid remediable hyperaldosteronism. Algorithms for endocrine testing and imaging procedures are now available to encompass screening for, confirmation of, and differentiation of the underlying causes of adrenal masses, including primary hyperaldosteronism, pheochromocytoma, and Cushing's syndrome. Improved radiologic, computerized radiologic, and magnetic resonance imaging techniques, as well as

selective catheterization studies, are proving useful in localizing adrenal tumors and in distinguishing between benign and malignant lesions, and between functional and nonfunctional nodules. Finally, recent refinements in the field of minimally invasive general surgery have made laparoscopic adrenalectomy an attractive method for removing adrenal tumors; this type of surgery allows shorter hospital stays, lower rates of morbidity, and faster recovery.

Indeed, advances in noninvasive laparoscopic adrenalectomy have made the removal of adrenal masses possible for extensive molecular, endocrine, and physiological analysis. It is perhaps only a matter of time before a global database of incidentaloma tissue and clinical histories becomes available to hasten the unravelling of the pathology and molecular mechanisms of this clinical conundrum. The impact of incidentaloma on medicine will become increasingly apparent as patients presenting subclinical symptoms are shown to be at higher risk for metabolic disorders such as diabetes mellitus, osteoporosis, and hypercortisolemia. It is obvious that the surge of interest and investment in the adrenal would be enormous if current studies suggesting a role for adrenal incidentaloma in the causation of metabolic syndromes were confirmed in large prospective studies. The true clinical impact of incidentaloma will depend not only on improvements in the sensitivity of screening for such endocrine perturbations and their clinical manifestations, such as decreases in bone density or peripheral insulin insensitivity, but also on the shifts in the defined thresholds at which such perturbations are demonstrated to have clinical significance.

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Methods of the Evidence Report

Joseph Lau, M.D.

Introduction

The National Institutes of Health (NIH) Office of Medical Applications of Research (OMAR) requested that the Agency for Healthcare Research and Quality produce an evidence report for this State-of-the-Science Conference on Management of the Clinically Inapparent Adrenal Mass (“Incidentaloma”). This evidence report was conducted by the New England Medical Center Evidence-Based Practice Center (EPC).

EPCs review relevant scientific literature on assigned clinical care topics and produce evidence reports and technology assessments, conduct research on methodologies and the effectiveness of their implementation, and participate in technical assistance activities. Public and private sector organizations may use the reports and assessments as the basis for their own clinical guidelines and other quality improvement activities.

This evidence report is a systematic review of the literature summarizing evidence on several key questions developed in conjunction with the staff at the National Institute of Child Health and Human Development (NICHD) and OMAR.

Key Questions

1. What are the causes, prevalence, and natural history of clinically inapparent adrenal masses?
2. What is the diagnostic accuracy (sensitivity, specificity) of evaluation modalities (fine needle aspiration/biopsy, CT, MRI, US, biochemical tests) used to differentiate adrenal masses (e.g., adrenal carcinoma, pheochromocytoma, adenoma, adrenal hyperplasia)? What is the risk of metastatic spread of adrenal carcinoma by FNA?
3. What are the surgical complication rates for various approaches used to excise adrenal masses; specifically laparoscopic, transabdominal, and retroperitoneal approaches?
4. What are the patient outcomes after surgical excision of adrenal cortical carcinoma (morbidity and mortality)? Are there data on the influence of age and tumor size on the outcomes?
5. What evidence is there to support the use of periodic biochemical and imaging studies to follow untreated adrenal masses?
6. What additional research is needed to guide practice?

Literature Search

The staff at the National Library of Medicine (NLM) conducted a search of Medline, PreMedline, BIOSIS, and Embase in September 2000. EPC conducted an additional search in March 2001 because of modifications to the key questions. Additional subject headings were included to address questions on diagnostic accuracy, surgical complications rates as well as morbidity and mortality outcomes for adrenal masses, and monitoring technologies for untreated adrenal masses. A total of 5,586 abstracts were obtained from the literature searches. After screening the abstracts for potentially relevant studies, staff retrieved 602 articles for further evaluation.

Inclusion Criteria

We developed specific inclusion and exclusion criteria for each of the key questions. In general, we accepted English language studies with at least 10 human subjects. There was no age limit.

Summarizing the Literature

About 200 articles met the inclusion criteria for one of the key questions and were included in the evidence report. We performed data extraction on these articles and created evidence tables and summarized their results. More than 50 studies provided data about the prevalence of incidentaloma or the distribution of adrenal pathologies. Twenty-three studies evaluated various diagnostic tests to differentiate malignant lesions from benign tumors. More than 70 studies provided outcome information on various adrenal surgical techniques. Thirty-two studies reported prognostic information on patients with adrenal carcinoma after surgical excision, and eight articles reported results of followup strategies.

Evidence tables were created to provide detailed information about the study design, patient characteristics, inclusion and exclusion criteria, intervention or test evaluated, and the outcomes. Where appropriate, we graded the studies according to the methodological quality, applicability, size, and the effect or test performance.

The specific methodologies and the results for each of the key questions are presented in respective sections in the evidence report and will be presented at the meeting.

Adrenal Pathology and Causes of Adrenal Masses

Clara S. Heffess, M.D.

Tumors of the adrenal cortex and medulla are uncommon in general surgical pathology. They can be grouped into adrenal cortical tumors, adrenal medullary tumors, and miscellaneous neoplasms and tumor-like lesions. These include (1) adrenal cortical proliferations (functional and nonfunctional), including nodular cortical hyperplasia, cortical adenoma, and cortical carcinoma, (2) adrenal medullary proliferations, including adrenomedullary hyperplasia, pheochromocytoma, neuroblastoma, ganglioneuroblastoma, ganglioneuroma, composite tumors of the adrenal medulla, and primary malignant melanoma, (3) combination cortical and medullary tumors, the so-called corticomedullary tumors, and (4) miscellaneous tumors and tumor-like lesions, including myelolipoma, cysts, hemangiomas, angiosarcomas, benign and malignant mesenchymal and neural tumors, metastasis from nonadrenal tumors, and other rare tumors. A significant number of adrenal lesions are discovered incidentally during evaluation (e.g., abdominal CT scan) performed for unrelated reasons. The incidence of such incidentalomas ranges from 0.6 percent to 1.4 percent. The differential diagnosis of an incidentally discovered adrenal mass requires thorough clinical examination and biochemical evaluation for adrenal abnormalities in the differential diagnosis of a primary adrenal lesion versus metastatic disease to the adrenal gland. If the initial screening tests show biochemical abnormalities, further directed tests are indicated. It is clearly evident that a nonfunctioning mass constitutes a major diagnostic challenge.

A very common incidental finding during surgery or during a radiographic procedure is the presence of nonfunctioning adrenocortical nodules, perhaps representing the most common cause of adrenal enlargement. There is an increased incidence of nodularity with age and in association with diabetes mellitus, hypertension, and chronic diseases. Incidental nodules larger than 1.5 cm in diameter are found in 20 percent of hypertensive patients at autopsy. No clinical significance has been assigned to these lesions. These nodules are usually multiple and bilateral with significant disparity between glands in regard to weight. The size of the nodules ranges from 1 mm to 3 cm in diameter. Histologically, the cortex is nodular. These nodules are circumscribed and nonencapsulated. The cells resemble the zona fasciculata with abundant pale-staining finely vacuolated cytoplasm. The cortical tissue between the nodules appears normal. There are instances in which nodular hyperplasia presents as a dominant nodule accompanied by a modest nodularity of the remaining cortex. Obviously, there is a gradation between hyperplastic nodules and adenomas, and at times the pathologist must be arbitrary in assigning the process to a particular category.

Adrenocortical adenomas consist of a benign proliferation of adrenocortical cells almost always associated with endocrine hyperfunction. Some cortical adenomas produce little steroid hormone to effect biochemically diagnostic elevations, and the only evidence of hyperfunction in those cases may be the histologic evidence of atrophy of the adjacent cortex. Endocrine disorders associated with adenomas include, in order of frequency, hyperaldosteronism (80 percent of cases), Cushing's syndrome (5 percent to 10 percent of cases), and virilizing and feminizing tumors. The macroscopic appearance of adenomas varies to some degree with the steroid hormone production. Aldosterone-producing adenomas are solitary and unilateral with an

average size of 1.5 cm, of yellow color, frequently unencapsulated, and the remaining cortex can show mild nodularity, most probably related to the patient's hypertension. In hyperaldosteronism due to hyperplasia there is a diffuse process involving the zona glomerulosa rather than a multinodular process. Adenomas with hypercortisolism are larger with an average size of 4 cm, mottled yellow-brown in color, usually encapsulated, and the remaining cortex appears atrophic. Adrenal cortical adenomas, especially large silent ones can measure from 5 cm to 20 cm in diameter and may undergo a variety of retrogressive changes. They contain extensive regions of hyalinized collagen or sometimes fibrin deposits, dilated blood vessels, and cystic changes. Necrosis, when apparent, is localized in the center of the tumor and usually is the result of a previous vascular diagnostic procedure. Hemorrhage can be massive, increasing the size and weight of the adenoma and masking the true neoplastic process. Myelolipomatous foci are common. Although the presence of necrosis is considered a criterion for malignancy, this finding is not always indicative of malignancy. The necrosis evident in cortical carcinomas is patchy and not localized to the center of the tumor, as occurs with adenomas. Radiologists should be aware of the heterogeneous appearance of these tumors.

Adrenal cortical carcinomas (ACC) may manifest endocrinopathic syndromes or may be clinically nonfunctional. The weight of ACC may be quite variable, ranging from less than 40 gm to more than 3,000 gm. **Weight has been used as a predictor of behavior in cortical neoplasms, but it has become clear that weight, by itself, is not a reliable criterion for malignancy, since tumors of small size have metastasized.** Grossly, ACC are encapsulated and the larger ones can be infiltrative. According to Weiss's criteria, the histologic indicators of malignancy in ACC include nuclear grade, high mitotic rate, presence of atypical mitoses, cells with eosinophilic cytoplasm, diffuse growth pattern, necrosis, and capsular and vascular invasion. Staging is useful in predicting survival. More than 60 percent of the patients have metastatic disease at the time of diagnosis. The mortality rate for adult patients with ACC ranges from 50 percent within two years to 84 percent within five years. Death due to metastatic disease occurs within the first 12 months after diagnosis.

Oncocytic adrenal tumors are rare. Most tumors are nonfunctional and are found incidentally. Although all these tumors were considered benign, they can be locally aggressive and invade vascular structures and adjacent organs. These tumors tend to be large and weigh as much as 800 gm. Grossly, oncocytic tumors have a tan color. Histologically, these tumors are characterized by the presence of a diffuse proliferation of cells with abundant granular eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli. Foci of necrosis and mitoses are rarely seen. The criteria set forth by Weiss relative to determining malignancy in adrenal cortical (non-oncocytic) neoplasms are also used in the histologic evaluation of adrenal oncocytic neoplasms. There are no specific criteria for oncocytic tumors that are helpful in predicting their biologic behavior.

Pheochromocytomas can occur at any age (range from 12 to 80 years) and may be familial or sporadic in their occurrence. The most common symptom is headache and clinically sustained or paroxysmal hypertension. Abnormal laboratory findings include increased catecholamines, metanephrines, and VMA in the urine. These neoplasms tend to be encapsulated and on cross section appear dark red in color. Benign tumors have a nested pattern of growth with polygonally shaped cells, abundant granular cytoplasm, and distinct cell borders. The nuclei

are oval with vesicular chromatin and may demonstrate the presence of nuclear pseudoinclusions and cytoplasmic hyaline globules.

According to many investigators malignant pheochromocytomas are difficult to recognize unless there are metastatic foci; the presence of metastasis is the sine qua non for malignancy in pheochromocytomas.

In our experience, however, we have observed several histologic features that are associated with a more aggressive biologic outcome. Malignant pheochromocytomas are of a larger size than conventional pheochromocytomas. Further, malignant pheochromocytomas tend to appear as lobulated masses with foci of hemorrhage, necrosis, and cyst formation. The presence of vascular or capsular invasion, or infiltration of the normal surrounding tissues, is indicative of malignancy. Other features that suggest malignancy include (1) diffuse growth pattern with larger interconnected islands of cells that vary in size, (2) foci of (central) necrosis (necrosis may be minimal or extensive), (3) a distinct tendency toward cellular monotony or spindling of the cells, and (4) the presence of increased mitotic figures. In general, patients with malignant pheochromocytomas are associated with a poor prognosis.

The adrenal glands are frequently involved in metastatic tumors. The adrenal gland is the fourth most common organ targeted for metastatic disease following the lung, liver, and bone. Lung and breast are the most common tumors to metastasize to the adrenal glands. Adrenal metastases are present in 9 to 27 percent of patients with cancer, and bilateral involvement is found in 40 percent of the cases. Most metastatic tumors are clinically silent with regard to adrenal function; however, rare cases of adrenal insufficiency have been reported when there is substantial destruction of more than 90 percent of the cortex. Metastatic disease in both adrenal glands, even relatively small lesions, can be detected by CT scan; however, unilateral metastasis cannot be easily distinguished from primary adrenal neoplasms. CT-directed fine needle aspiration (FNAB) is a potentially valuable tool in the preoperative differentiation of metastatic disease versus a primary adrenal neoplasm. Further, preoperative CT-directed FNAB may be helpful in determining the source of metastasis when the primary site is unknown. Macroscopically, metastasis to the adrenal glands may be unilateral or bilateral, represent a single mass or multiple masses, and if large, may be partially necrotic. Histologically, metastatic tumors are recognizable as secondary lesions. Occasionally, some tumors are difficult to distinguish from primary adrenal cortical or medullary tumors; therefore, the use of special techniques (e.g., histochemistry and immunohistochemistry) may help in the diagnosis.

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Prevalence and the Natural Course of Adrenal Incidentaloma

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Prevalence

The prevalence of adrenal incidentalomas has been estimated about 1 percent (range, 0.35–4.4 percent) in computed tomography (CT) series (Table 1) and 5.9 percent (range, 1.1–32 percent) in autopsy series (Table 2). Because most published studies of abdominal CT were performed with obsolete scanners, the prevalence is probably underestimated and it is expected to approach that of autopsy studies using contemporary high-resolution CT scanning technology. The prevalence of adrenal incidentalomas increases with patients' age, being 0.2 percent in young subjects compared with 6.9 percent in subjects older than 70 years of age. Clinical studies show that adrenal incidentalomas are more frequent in females (mean female/male ratio, 1:4; range 0.9–2.5 percent); however, no sex differences have been reported in autopsy series (Table 2). Thus, the higher prevalence of adrenal incidentalomas in females could be attributed to a higher rate of abdominal diagnostic procedures in women than in men. Autoptic studies also show no apparent variation in the prevalence of adrenal incidentalomas over time (Table 2), whereas the discovery of adrenal incidentalomas has increased in the past decades with the widespread application of high-resolution imaging techniques. No significant geographic or ethnic variability has been reported.

Adrenal masses are found in the right adrenal gland in 50–60 percent of cases, in the left adrenal gland in 30–40 percent, and bilaterally in 10–15 percent. This difference can be attributed to the widespread use of ultrasonography for diagnosis of abdominal complaint, as a similar distribution between the two adrenal glands has been reported in CT-scan and autopsy series. Mean diameter of adrenal masses is 3 cm, ranging from 0.5 to 25 cm.

Table 1. Prevalence of adrenal incidentalomas in CT-scan series

Study	No. adrenal masses/ No. scans	Prevalence (%)
Glazer et al., 1982	16/2,200	0.7
Printz et al., 1982	4/1,423	0.3
Abecassis et al., 1985	19/1,459	1.3
Baldegrun et al., 1986	88/12,000	0.7
Herrera et al., 1991	259/61,054	0.4
Caplan et al., 1994	33/1,779	1.9

Table 2. Prevalence of adrenal incidentalomas in autopsy series

Study	No. pts	Prevalence (%)		
		Overall	Females	Males
Russi and Blumenthal, 1945	9,000	1.45	1.2	2
Commons and Callaway, 1948	7,437	2.86	2.88	2.84
Schroeder, 1953	4,000	1.38	–	–
Devenyi, 1967	5,120	3.55	3.61	3.62
Kokko et al., 1967	2,000	1.05	–	–
Granger and Genest, 1970	2,425	2.52	2.58	2.43
Russell et al., 1972	35,000	1.97	1.92	2.05
Abecassis et al., 1985	988	1.90	–	–
Reinhard et al., 1996	498	5.0	–	–

The etiology covers a wide range of pathology (Table 3). In the vast majority of cases, these masses are nonhypersecreting adrenocortical adenomas. However, they may represent primary or metastatic malignancies and show minor endocrine abnormalities or subclinical hyperfunction (Table 4). The prevalence of adrenocortical carcinoma is not low, accounting for 4.7 percent of cases in a recent meta-analysis of 13 published series and for 13 percent of patients operated on in a multicenter study from Italy. The probability of malignancy increases as a function of mass size. In this regard, Herrera et al. reported a ratio of 8:1 and 3:1 benign to malignant masses at a cut-off of greater than 4 and 5 cm in diameter, respectively. This association between mass size and risk of malignancy has been reported in other series, including the multicenter study of the Italian Society of Endocrinology. However, adrenal mass size should not be used as the only criterion of malignancy, as malignant tumors less than 3 cm in diameter are not uncommon.

Natural History

The natural course of adrenal incidentalomas and the risk that such lesions evolve toward hormonal hypersecretion or malignancy are still under evaluation. Although there are few studies in the literature reporting long-term followup observation of adrenal incidentalomas, it seems that the majority of masses, classified as benign and nonhypersecreting at diagnosis, subsequently remain hormonally and morphologically unchanged. Nonetheless, some patients develop adrenal hyperfunction and/or mass enlargement, in a percentage that varies in different series, ranging from 0 to 11 percent and from 0 to 26 percent, respectively (Table 5). Controversy exists on the risk of progression from asymptomatic hormonal abnormalities to overt endocrine hyperfunction. Terzolo et al. reported a spontaneous endocrine normalization in 50 percent of patients with subclinical hypercortisolism, whereas no patients developed clinical Cushing's syndrome.

Table 3. Diagnosis of adrenal incidentalomas

Etiology	Prevalence
Adrenal cortical tumors	
Adenoma	36–94%
Nodular hyperplasia	7–17%
Carcinoma	1.2–11%
Adrenal medullary tumors	
Pheochromocytoma	1.5–23%
Ganglioneuroma	0–6%
Ganglioneuroblastoma, neuroblastoma, carcinoma	Rare
Other adrenal tumors	
Myelolipoma	7–15%
Lipoma	0–11%
Lymphoma, hemangioma, angiomyolipoma, hamartoma, liposarcoma, myoma, fibroma, neurofibroma, teratoma	Rare
Cysts and pseudocysts	4–22%
Hematoma and hemorrhage	0–4%
Infections, granulomatosis	Rare
Metastases (breast, kidney, lung, ovary, melanoma, lymphoma, leukemia)	0–21%
Pseudoadrenal masses (stomach, pancreas, kidney, liver, lymph node, vascular lesions, and technical artefacts)	0–10%

Table 4. Hormonal findings in adrenal incidentalomas

Endocrine state	Prevalence
Nonhypersecreting adenoma	65–90%
Hypercortisolism	5–14%
Hyperaldosteronism	1–3.3%
Hyperandrogenism	0–11%
Hyperestrogenism	Rare
Congenital adrenal hyperplasia	Rare
Pheochromocytoma	1.5–25%

Table 5. Long-term followup of adrenal incidentalomas

Study	Followup yrs (range %)	Mass size enlargement	Mass size reduction	Hyperfunction
Raincke et al., 1989	1.2 (0.5–4)	0/11	0/11	0/11
Virkkala et al., 1989	2 (0.8–4.1)	0/12	1/12	0/12
Herrera et al., 1991	2 (0.1–5.6)	5/159	4/159	0/287
Jockenovel et al., 1992	2.7 (1–8.4)	1/18	2/18	2/18
Osella et al., 1994	1.0	2/9	0/9	1/9
Bencsik et al., 1995	1.5 (0.3–3.4)	1/27	0/27	0/27
Courtade et al., 1997	3.6 (0.3–6.3)	0/25	10/25	0/32
Bastounis et al., 1997	3.6 (1–5.3)	2/60	0/60	0/60
Bondanelli et al., 1997	(0.5–1.5)	1/14	0/14	0/14
Barry et al., 1998	7 (0.1–11.7)	4/91	0/91	0/224
Terzolo et al., 1998	>1	0/53	0/53	0/53
Barzon et al., 1999	4 (2–10)	2/75	2/75	6/75
Siren et al., 2000	7 (2–16.3)	4/21	7/21	0/27
Mantero et al., 2000	>1	4/53	NA	2/53
Barzon et al., in press	4.6 (2–12)	9/130	3/130	10/130
Total		65/758 (8.6%)	29/705 (4.1%)	21/1032 (2%)

At variance, in other series, hormonal abnormalities tended to persist unchanged throughout followup. Moreover, endocrine hyperfunction, such as hypercortisolism or high catecholamine levels, became clinically evident in some patients. Our recent followup study in 130 non-operated patients with adrenal incidentalomas, including nine with subclinical hypercortisolism at diagnosis, demonstrated the estimated cumulative risk for a nonsecreting adrenal incidentaloma to develop either subclinical or overt glucocorticoid hypersecretion was 3.8 percent after one year and 6.6 percent after five years. When considering only masses with subclinical autonomous glucocorticoid overproduction at diagnosis, the estimated cumulative risk to develop overt Cushing's syndrome was 11 percent after one year and 26 percent after five years. An amelioration of clinical or biochemical abnormalities in patients with subclinical hypercortisolism is obtained after surgery.

The likelihood of malignant transformation at long-term followup seems very little, with only one case reported in the literature of unsuspected adrenocortical carcinoma discovered at followup. Although a slight increase in size of adrenal masses or the appearance of another mass in the contralateral adrenal gland may be suggestive of malignancy, these features also have been frequently observed in benign masses (Table 5). Reduction and even disappearance of the adrenal mass have also been reported (Table 5).

By analyzing risk factors for adrenal mass enlargement or hyperfunction (i.e., sex, age, obesity, hypertension, diabetes, abnormal endocrine tests at diagnosis, mass size, mass location, and scintigraphic uptake pattern), we demonstrated that the presence of endocrine test abnormalities at diagnosis had predictive value for mass enlargement, whereas mass size of 3 cm or more at diagnosis and exclusive radiocholesterol uptake by the mass with no visualization of the contralateral adrenal gland at scintigraphy had relevance for the occurrence of adrenal hyperfunction. Long-term perspective studies are needed to assess the risk of tumor progression and to identify reliable markers of malignancy.

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Recent Update of Histopathology of Adrenocortical Incidentaloma—Changes in the Concept

Hironobu Sasano, M.D., Ph.D.

Diagnosis of adrenal incidentaloma has recently increased because of the advancement of radiological diagnostic means. The histopathological diagnosis and clinical management of the resected adrenal mass has therefore become increasingly important. In an analysis of 1,014 hospitals in Japan, 2,106 cases of adrenal incidentalomas (male 1,095—52 percent and female 1,011—48 percent) were detected in 1999. More than 50 percent of these cases were hormonally inactive adrenocortical adenoma. Malignant tumors were also detected in 1.6 percent for adrenocortical carcinoma and 4 percent in metastatic primary carcinoma from the lung, kidney, and liver.

When evaluating the resected adrenal mass in patients with adrenal incidentaloma, it is very important to evaluate the following aspects: (1) Is the mass functional? (2) Is the mass malignant? and (3) Is the mass of adrenocortical origin?

1. Functional?

Morphologically, most adrenocortical incidentalomas cannot be differentiated from adrenocortical adenomas associated with Cushing's syndrome or primary aldosteronism. All of these tumors expressed steroidogenic enzymes with the exception of adrenocortical oncocytoma. The only morphological differences between hormonally active cortical tumors and inactive adrenocortical incidentalomas may be the presence or absence and the degree of cortical atrophy of attached non-neoplastic adrenal glands. The degree of cortical atrophy is to some extent correlated with the degree of suppression of serum cortisol by dexamethasone suppression test and diminished expression of steroidogenic enzymes, especially dehydroepiandrosterone sulfotransferase (DHEA-ST) in the attached non-neoplastic adrenal gland. In attached adrenals of adrenocortical neoplasms, especially adrenocortical incidentalomas, the degree of DHEA-ST expression in the zona reticularis of the attached non-neoplastic glands correlated well with that of dexamethasone suppressibility and serum DHEA-S levels, an important evaluation of autonomous function of adrenocortical neoplasms. Therefore, it is very important to study not only the presence or absence and/or the degree of cortical atrophy in the attached non-neoplastic adrenal but also DHEA-ST expression in these adrenals, which can contribute to the more precise evaluation of the patients' preoperative status of the hypothalamo-pituitary-adrenal axis. From a practical standpoint, when confirming that the resected adrenocortical mass is grossly considered as adrenocortical in origin, based on the color of the lesion at the cut surface and others, and its attached adrenal shows macroscopic adrenocortical atrophy, prophylactic postoperative glucocorticoid replacement therapy is advised for the patients to avoid postoperative adrenocortical insufficiency.

2. Malignancy?

In our review of 2,106 Japanese cases of adrenal incidentaloma, 34 cases, or 1.6 percent of the cases, had adrenocortical carcinoma. When evaluating these resected tumors, gross examination is very important. When grossing, the weight of the neoplasm should be determined as carefully as possible. Among 66 cases of adrenocortical neoplasms with full-blown Cushing's syndrome operated on between 1954 and 1985 at Tohoku University Hospital in Sendai, Japan, tumors weighing more than 100 gm comprised 93 percent of carcinomas but only 6 percent of adenomas. However, it is also very important to note that small adrenocortical tumors can metastasize and some large tumors do not. The presence of necrosis and hemorrhage are strongly suspect in the diagnosis of adrenocortical carcinoma. However, many adrenocortical carcinomas are not associated with the foci of necrosis and hemorrhage. In addition, it is important to sample the specimens from the areas adjacent to the foci of necrosis and hemorrhage when grossing the specimens.

The majority of adrenocortical carcinomas are associated with characteristic gross features described above, including large size, necrosis, and hemorrhage, and do not usually pose diagnostic problems for surgical pathologists. However, adrenocortical carcinomas not associated with these ominous macroscopic features have recently increased in number. The distinction of "well-differentiated" adrenocortical carcinoma from adenoma is perhaps one of the most difficult diagnoses in the surgical pathology practice. There is no single histological criterion that can reasonably well differentiate adrenocortical carcinoma from adenoma as there is for capsular and vascular invasion of thyroid follicular carcinoma. Only the systems that evaluated multiple histological and/or nonhistological criteria of the resected cases can provide reliable histological diagnosis.

3. Adrenocortical Origin?

In our recent study of 2,106 Japanese cases of adrenal incidentaloma, more than 4 percent of the study subjects had metastasis to the adrenal glands. The primary lesions were subsequently detected by the analysis of adrenal metastasis in a number of the cases. In our experience with patients who do not manifest any clinical hormonal abnormalities, the malignancies that may be associated with histopathologic differential diagnosis of adrenocortical carcinoma at both primary and metastatic sites are renal cell carcinoma, hepatocellular carcinoma, clear-cell carcinoma of the ovary and uterus, malignant melanoma, and large-cell carcinoma of the lung and pheochromocytoma. The two most important primary neoplasms in the differential diagnosis of primary adrenocortical carcinoma are renal cell and hepatocellular carcinoma, especially when the lesions are large. In addition, the differential diagnosis of adrenocortical carcinoma or metastatic tumor, such as malignant melanoma or large-cell carcinoma of the lung or clear-cell carcinoma of the ovary or uterus, can be difficult. The presence or absence of steroidogenic enzymes and/or specific cell organelles involved in adrenocortical steroidogenesis is very important in the differential diagnosis above but by no means specific.

Adrenal 4 binding protein or Ad4BP is a transcription factor for all steroidogenesis. We have shown that Ad4BP immunoreactivity was demonstrated in almost all the tumor cells of adrenocortical carcinoma, both histological sections and cytology specimens, but not in renal cell

carcinoma, hepatocellular carcinoma, malignant melanoma, ovarian and uterine clear-cell carcinoma, large-cell carcinoma of the lung, and pheochromocytoma. Ad4BP expression is reported in gonadal sex cord-stromal tumors, including steroid cell tumors, but application of Ad4BP immunohistochemistry can greatly contribute to the differential diagnosis of adrenocortical carcinoma from other malignancies both at primary and metastasis sites, even in the evaluation of needle biopsy specimens.

Test Performance for Evaluating Incidentaloma

Ethan M. Balk, M.D., M.P.H.

Background

An incidentally discovered adrenal mass may represent adrenal or metastatic cancer, a chemically active benign tumor, an inactive benign mass, or other processes. The appropriate diagnostic evaluation of incidentalomas has yet to be elucidated. Currently there are multiple modalities being advocated for the diagnostic evaluation of incidentalomas. We sought to evaluate the published evidence of the diagnostic performance of diagnostic modalities used to differentiate adrenal masses in patients with either truly incidentally discovered adrenal masses (with no prior expectation of adrenal disease) or with adrenal masses found during work-up for extra-adrenal cancer (and thus suspected to be metastatic disease).

Methods

We performed a systematic review of the literature. We searched Medline for relevant articles published in English. We included studies with at least 10 patients. We included articles that examined the test performance of any test to diagnose incidental adrenal masses. We excluded studies that included mostly subjects with symptomatic adrenal disease. When multiple articles included the same series of subjects, we included only the study with the most complete series.

Results

Twenty-three articles met our inclusion criteria. The studies examined the use of computed tomography (CT), magnetic resonance imaging (MRI), scintigraphy, fine needle aspiration (FNA), biochemical markers, ultrasonography (US), and positron emission tomography (PET). See Table.

Computed Tomography (CT). We found 10 studies that evaluated the diagnostic performance of CT to diagnose adrenal masses. Three studies included subjects with adrenal masses found incidentally, two included subjects with adrenal masses found in extra-adrenal cancer work-up, and five stated only that subjects had adrenal masses. Seven studies evaluated unenhanced CT, one evaluated immediate enhanced CT, one evaluated combined unenhanced and immediate enhanced CT, and two evaluated delayed enhanced CT. Various definitions of abnormal tests and thresholds were used. To differentiate malignant from benign adrenal disease, the nine studies found a wide range of both sensitivity and specificity for CT.

Category	Study	N	CT		MRI		Scintigraphy		FNA		Biochemistry		US		PET	
			Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp	Sn	Sp
Total	23		10		5		4		5		3		1		1	
"True" Incidentaloma			3				4				2		1			
	Gross, 1994	229					71%	100%								
	Fontana, 1999	150	92%	54%									67%	52%		
	Terzolo, 2000	84	100%	80%							100%*	38%*				
	Nakajo, 1993	39					100%	74%								
	Bondanelli, 1997	38	100%	86%			100%	88%			100%**	51%**				
	Gross, 1995	29					100%	50%								
Cancer Work-up			2		2										1	
	Hussain, 1986	57	44%	100%												
	Schwartz, 1997	54	33%	100%			100%	94%								
	Krestin, 1991	44	61%	50%			79%	63%								
	Boland, 1995	20					93%	83%								100% 100%
Combined Incidentaloma and Cancer Workup									4							
	Welch, 1994	270							81%	99%						
	Silverman, 1993	97							89%	77%						
	Bernardino, 1985	53							Acc: 91%							
	Berkman, 1984	16							100%	91%						
Adrenal Mass			5		2											
	Szolar, 1997	72	83%– 100%	61%– 100%												
	Lee, 1991	55	79%	96%												
	Korobkin, 1996	39	100%	95%												
	McNicholas, 1995	33	100% 68%	72% 100%	95% 84%	83% 89%										
	Chezmar, 1988	28			92% 92%	91% 85%										
	Singer, 1994	23	58%	92%												
Incidental Benign Adenomas											1					
	Valli, 2001	31									100%***	67%***				
Include Clinically Suspected Mass					1				1							
	Bilbey, 1995	38			100%	89%										
	Katz, 1984	22							85%	78%						

Footnotes:

N = study size; CT = computed tomography; MRI = magnetic resonance imaging; FNA = fine needle aspiration; US = ultrasonography; PET = positron emission tomography; Sn = sensitivity; Sp = specificity.

* High or normal DHEA-S to detect malignancy.

** Low DHEA-S to detect pheochromocytoma.

*** Unsuppressed overnight 1 mg dexamethasone suppression test to predict unilateral uptake on scintigraphy (associated with functional autonomy).

Magnetic Resonance Imaging (MRI). We found five studies that evaluated the performance of MRI to diagnose adrenal masses. Two studies included subjects with adrenal masses found in extra-adrenal cancer work-up, two stated only that subjects had adrenal masses, and one included only subjects with incidentally discovered benign adenomas. All studies evaluated chemical shift MRI; one also evaluated dynamic contrast-enhanced MRI. Various definitions of abnormal tests and thresholds were used. Four studies found that MRI had high sensitivity and moderate to high specificity to differentiate benign from malignant disease. One study found high sensitivity and moderate specificity to differentiate adenomas from non-adenomas (including other benign processes).

Scintigraphy. We found four studies that evaluated the diagnostic performance of ¹³¹I-6β-iodomethyl-norcholesterol (NP-59) scintigraphy to evaluate adrenal masses. All included subjects with incidentally discovered adrenal masses. Various descriptions were used to categorize test results. Depending on how a positive test result was defined, studies found either

perfect sensitivity with low to moderate specificity or perfect specificity with low to moderate sensitivity to differentiate malignant from benign tumors.

Fine Needle Aspiration (FNA). We found five studies that evaluated the diagnostic performance of CT- or US-guided fine needle aspiration to evaluate adrenal masses. Four included subjects with adrenal masses discovered either incidentally or during extra-adrenal cancer work-up; one study included some subjects with clinically suspected masses. All used fine and large-bore needles. In general, the accuracy of FNA to diagnose adrenal masses was high, but varied across studies.

Biochemical Markers. We found three studies that evaluated the diagnostic performance of various biochemical markers to evaluate adrenal masses. Two included subjects with incidentally discovered adrenal masses; one included only subjects with incidentally discovered benign adenomas. One found high sensitivity and low specificity for dehydroepiandrosterone sulfate (DHEA-S) to detect malignancy; one found high sensitivity and low specificity for DHEA-S to detect pheochromocytoma; one found high sensitivity and moderate specificity for overnight dexamethasone suppression to predict unilateral uptake on scintigraphy (which is associated with functional autonomy).

Ultrasonography (US). We found only one study that evaluated the diagnostic performance of US in subjects with incidentally discovered adrenal masses. Sensitivity and specificity were poor to differentiate benign from malignant disease.

Positron Emission Tomography (PET). We found only one study that evaluated the diagnostic performance of PET in subjects with adrenal masses found during extra-adrenal cancer work-up. This study had perfect sensitivity and specificity to differentiate benign from malignant disease.

Conclusions and Future Directions

With few exceptions, the overall methodological quality of the studies we examined was poor to fair. The evaluated studies examined multiple tests, used multiple variations of tests (such as enhanced and unenhanced CT), used different definitions and thresholds for test results, and included a variety of sample populations. Study size ranged from 16 to 270. The heterogeneity of the studies limits the ability to estimate the overall diagnostic performance of each of the evaluated tests. Although some studies reported that CT, MRI, scintigraphy, FNA, and PET have good to excellent test performance to differentiate benign from malignant disease, others found only moderate to poor performance (except for PET, for which there was only one small study). US had poor performance in a single study. DHEA-S and overnight dexamethasone suppression had high sensitivity, but poor to moderate specificity to detect clinically important adrenal diseases. Further high-quality studies of well-defined diagnostic tests in well-defined populations (such as those with truly incidentally discovered adrenal masses) are required.

Endocrine and Biochemical Evaluation of Adrenal Incidentaloma

William F. Young, Jr., M.D.

Although the optimal diagnostic approach to a patient with an adrenal incidentaloma is debated, evidence supports evaluating the patient for the following forms of adrenal hyperfunction or autonomous function: autonomous cortisol secretion, pheochromocytoma, and primary aldosteronism.

Subclinical Cushing Syndrome

Patients with subclinical Cushing's syndrome (SCS) lack the usual obvious stigmata of Cushing's syndrome, but they may have the side effects of continuous endogenous cortisol secretion (Reincke, 2000). SCS is the most frequent (5–8 percent) hormonal abnormality detected in patients with adrenal incidentalomas (Reincke, 2000; Young, 2000). Therefore, some measurement of adrenal cortical autonomy is essential in all patients with adrenal incidentalomas. Because of a lack of sensitivity of most adrenocorticotropic hormone (ACTH) assays at the lower range of normal, most centers rely on an alternate measure of adrenal autonomy with the overnight dexamethasone suppression test (DST). Some centers use a higher dose of dexamethasone (e.g., 3 mg rather than the standard 1 mg) to reduce false positive results (Reincke, 2000), and others use a lower cortisol cutoff (e.g., $> 2.2 \mu\text{g/dL}$ [$> 60 \text{ nmol/L}$] rather than $> 5 \mu\text{g/dL}$ [$> 138 \text{ nmol/L}$]) to reduce false negative results (Valli et al., 2001). If the post-overnight DST 8 a.m. serum cortisol concentration is abnormal, then baseline serum ACTH, as well as blood and 24-hour urinary cortisol measurements, should be obtained and a formal two-day low- or high-dose DST is indicated to confirm the autonomy.

However, it is becoming clear that most adrenal cortical adenomas have some degree of functional autonomy. With a formal two-day low-dose DST, Tsagarakis et al. (1998) showed a gradation between autonomy and complete suppression of serum cortisol concentrations in 57 patients with adrenal incidentalomas (21 percent had undetectable serum levels of cortisol, 67 percent had values between 1 and $5 \mu\text{g/dL}$, and 12 percent had values between 5 and $7.8 \mu\text{g/dL}$).

Should all patients with SCS undergo unilateral adrenalectomy? In the absence of a prospective randomized study, it is reasonable to consider that younger patients and those who have disorders potentially attributable to autonomous glucocorticoid secretion (e.g., recent onset of hypertension, diabetes, obesity, and low bone mass) and have lack of suppression to both an overnight DST (8 a.m. serum cortisol $> 2.2\text{--}5 \mu\text{g/dL}$) and a formal two-day low- or high-dose DST (24-hour urinary-free cortisol $> 20 \mu\text{g}$) are candidates for adrenalectomy. Patients with SCS should be treated with perioperative glucocorticoid coverage because of the risk adrenal insufficiency, hemodynamic crisis, and death. Weight loss, improvement in hypertension and/or glycemic control, and normalization of markers of bone turnover are frequently found following unilateral adrenalectomy in patients with SCS (Mantero and Arnaldi, 1999).

Clinically Silent Pheochromocytoma

Of all patients with adrenal incidentalomas, approximately 5.1 percent prove to have pheochromocytomas (Young, 2000). At the Mayo Clinic, 10 percent of all patients with adrenal pheochromocytomas present as adrenal incidentalomas (Young, 2000). The optimal type of screening test is debated and is institution/laboratory-dependent. At least 21 different laboratory tests have been used to screen for pheochromocytoma. For patients in whom the pretest probability of pheochromocytoma is high (e.g., patients with a vascular or inhomogeneous adrenal mass), it is reasonable to screen with both fractionated plasma metanephrine measurements and 24-hour urinary measurements of total metanephrines and catecholamines. However, when the clinical suspicion of pheochromocytoma is low, fractionated plasma metanephrine measurements have inferior specificity and positive predictive value compared with urinary total metanephrines and catecholamines (Pacak et al., 2001). False positive results of plasma metanephrines may result in needless further endocrine testing, imaging, and possibly surgery, particularly in the elderly. Thus, if based on the image phenotype, the clinical suspicion is relatively low and the diagnosis of pheochromocytoma is merely to be ruled out, 24-hour urinary measurements of total metanephrines and catecholamines are preferred. It is important to resect these tumors because (1) the associated hypertension is curable with surgical removal of the tumor, (2) there is risk of a lethal paroxysm, and (3) 10 percent of the tumors are malignant.

Primary Aldosteronism

Of all patients with adrenal incidentalomas, approximately 1 percent prove to have primary aldosteronism (Young, 2000). Because the majority of patients with primary aldosteronism are not hypokalemic, all hypertensive adrenal incidentaloma patients should be evaluated with the ambulatory morning plasma aldosterone concentration (PAC)-to-plasma renin activity (PRA) ratio (PAC/PRA ratio). The mean value for the ratio in normal subjects and patients with essential hypertension ranges from 4 to 10 versus more than 30 to 50 in most patients with primary aldosteronism (PAC in ng/dL; PRA in ng/mL per hour). The PRA is low in a minority of patients with essential hypertension but a high PAC (typically >15 ng/dL [416 pmol/L]) and a truly abnormal ratio are uncommon. The combination of a PAC above 20 ng/dL (555 pmol/L) and a PAC/PRA ratio above 30 had a sensitivity and specificity of 90 percent for the diagnosis of aldosterone-producing adenoma (Weinberger et al., 1993). The cutoff for a “high” PAC/PRA ratio is laboratory-dependent. The PAC/PRA ratio can be obtained while the patient is treated with any antihypertensive drug except spironolactone. If the PAC/PRA ratio is positive, the diagnosis of primary aldosteronism should be confirmed with an additional measure of mineralocorticoid secretory autonomy (e.g., saline infusion test or 24-hour urinary aldosterone excretion on a high salt diet). Hypertension improves in 99 percent and resolves in at least 33 percent of patients following adrenalectomy (Sawka et al., 2001).

Screening for Other Hormonally Active Processes

Sex hormone-secreting adrenal cortical tumors are rare; patients with these tumors usually have symptoms and, thus, do not present with adrenal incidentalomas. Routine screening for sex hormone excess in patients with an adrenal incidentaloma is not warranted. Nonclassic

congenital adrenal hyperplasia (CAH) can cause unilateral or bilateral adrenal masses, and some investigators have suggested routine cosyntropin stimulation testing in all patients with adrenal incidentalomas. However, this recommendation cannot be supported in view of the relative infrequency of CAH and the finding that subtle disturbances in steroid secretion in the adenomas may lead to increased levels of 17-OH progesterone and an exaggerated response to cosyntropin stimulation. Cosyntropin stimulation testing should be reserved for patients in whom CAH is suspected on clinical grounds and patients who have bilateral adrenal masses.

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Imaging of Adrenal Incidentaloma

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Adrenal cortical adenomas are commonly found at autopsy and are commonly detected on computed tomographic (CT) scans. Unfortunately they cannot be differentiated from most adrenal nonadenomas by standard morphologic features. Until very recently, serial CT scanning for one or two years was typically performed in nononcology patients with small (≤ 3 cm) adrenal masses to ensure stability in size and exclude a small adrenal cortical carcinoma. Similarly, percutaneous biopsy was typically performed in oncology patients with an adrenal mass if there were no other sites of suspected metastatic disease. During the past 10 years, there has been extensive research to determine if noninvasive imaging studies could be used to characterize adrenal masses in order to reduce the number of percutaneous biopsies and serial CT scans.

Evidence has accumulated that unenhanced CT densitometry can be used to accurately differentiate benign adenomas from nonadenomatous masses, especially metastases. Most adenomas have unenhanced CT attenuation values lower than those of malignant masses, and the scatterplot data from such studies can be used to assign threshold values for the calculation of sensitivity and specificity for the diagnosis of adenoma. Unlike unenhanced attenuation values, intravenous contrast-enhanced CT values show too much overlap between the two groups to allow an accurate differentiation between adenomas and nonadenomas. It has been shown that the most optimal sensitivity (71 percent) and specificity (98 percent) for the diagnosis of adrenal adenoma results from choosing a threshold value of 10 Hounsfield units on unenhanced CT.

During the same period of time, evidence was accumulating that chemical shift MR (CSI) can be used to characterize many adrenal masses as adenomas. Taking advantage of the different resonance frequency peaks for the hydrogen atom in water and triglyceride (lipid) molecules, this technique results in a decrease in the signal intensity of tissue containing both lipid and water compared with tissue containing no lipid. Using the breath-hold opposed-phase gradient echo technique, CSI can detect the significant amount of lipid often found in adrenal adenomas and typically absent in most metastases and other nonadenomatous masses. Assessment of the chemical shift change can be made using simple visual assessment or by quantitative methods using region of interest measurements of the signal intensity of the adrenal mass and of a reference tissue on both in-phase and opposed-phase images. Several studies have shown a nearly identical accuracy for detecting intratumoral lipid using visual analysis and quantitative methods. Using visual analysis in two large studies, researchers found sensitivity for the detection of lipid in adrenal adenomas was 78 percent and 81 percent, with corresponding specificities of 87 percent and 100 percent, respectively.

Evidence that both CSI and unenhanced CT detect the presence and the amount of lipid in adrenal adenomas comes from two studies. In one study of 47 adrenal masses evaluated with both techniques, the results were highly correlated, and six of the eight adenomas that were indeterminate using one technique were also indeterminate with the other. In the other study of surgically resected adenomas, there was good linear correlation between the percentage of lipid-rich cortical cells and decreasing unenhanced CT attenuation value and increasing CSI change.

Although adrenal adenomas and nonadenomas have a similar attenuation value on routine enhanced CT, adenomas have a much more rapid loss of attenuation on delayed images. Specific threshold attenuation values for differentiating adenomas from nonadenomas on delayed enhanced CT have been reported, but even more emphasis has been placed on the percentage enhancement washout. In our own study, analysis of the scatterplots showed that an optimal threshold of 60 percent enhancement washout for the diagnosis of adenoma on 15-minute delayed enhanced CT resulted in a sensitivity of 88 percent and a specificity of 96 percent. A subsequent study showed that lipid-poor adenomas, those which cannot be differentiated from nonadenomas on unenhanced CT, have enhancement washout features nearly identical to lipid-rich adenomas.

A recent prospective study assessed the accuracy of combined unenhanced and delayed enhanced CT for characterization of adrenal masses. One-hundred sixty-six adrenal masses underwent unenhanced CT, and for those with attenuation values > 10 HU, delayed enhanced CT. The sensitivity and specificity for the diagnosis of adenoma was 98 percent and 92 percent, respectively. This protocol correctly characterized 160 of 166 (96 percent) masses. When the five nonadenomas that were not metastases were excluded, the sensitivity and specificity for characterizing an adrenal mass as adenoma versus metastasis was 98 percent (124/127) and 97 percent (33/34), respectively.

Two radionuclide studies can also be used to characterize adrenal masses. Radioiodocholesterol scanning using NP-59 is a highly accurate technique for detecting or excluding an adrenal adenoma as the cause of a unilateral adrenal mass, especially for lesions larger than 2 cm. Unfortunately, this technique is not approved by the FDA and lack of commercial availability has limited its widespread use. Position emission tomography (PET) using fluorodeoxyglucose (FDG) shows abnormal tracer uptake in malignant adrenal masses. Although initial reports are promising, FDG-PET is more expensive and much less widely available than CT and MR, and there is too little published data on its accuracy to predict its future role in the evaluation of incidental adrenal masses.

In summary, most adrenal masses are benign cortical adenomas, and most adenomas contain sufficient intratumoral lipid to allow characterization by unenhanced CT densitometry or clinical shift MR. Delayed enhanced CT densitometry can characterize the majority of lipid-poor adenomas. The use of percutaneous adrenal biopsy in oncology patients and serial CT scanning in nononcology patients with small (< 3 cm) adrenal masses can be limited to those masses whose imaging studies do not indicate a likely adenoma.

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Pathologic Evaluation of Adrenal Incidentaloma

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Evaluation of the nodular adrenal gland can be a challenge for pathologists. Adrenal cortical nodules are seen with increased frequency in the elderly population, in patients with diabetes, and in patients with hypertension (Dobbie, 1969), but cortical nodules can occur in the adult population without any known association. Cortical nodules can be bilateral and multiple, and vary considerably in size. In most cases this represents nodular hyperplasia, but it is typically not associated with endocrinologic or clinical evidence of hypercorticalism. Some have arbitrarily divided nodular hyperplasia into micronodular (< 1 cm nodules) and macronodular (>1 cm) hyperplasia. Nodular hyperplasia with one or more dominant nodules can simulate an adrenal cortical neoplasm. Indeed, a macronodule 2 to 5 cm in diameter is commonly designated as an adenoma, but it may coexist with some degree of diffuse and/or micronodular hyperplasia in the ipsilateral or contralateral adrenal. A solitary lesion with evidence of autonomous growth favors a diagnosis of neoplasia. Investigations into the functional status of these silent adenomas suggest that many are nonhyperfunctional. An important but small subset of incidentalomas includes examples of preclinical or subclinical Cushing's syndrome (McLeod et al., 1990; Reincke et al., 1992).

Surgical pathologists typically become involved with an incidentaloma when a patient is found to have an unexpected adrenal mass during abdominal imaging (e.g., CT scan) or rarely during surgery for unrelated reasons. The abdominal imaging is often done for staging of a malignant tumor in another site (e.g., breast or lung), or it may be performed for other reasons in a nononcologic setting. Fine needle aspiration biopsy (FNAB) may be a valuable procedure in diagnosis. The pathologist can get additional information at the time of FNAB, including location, size, and imaging characteristics of the incidentaloma. Size alone may emerge as the pivotal factor in management if the FNAB shows an adrenal cortical adenoma (ACA). An incidental adrenal cortical carcinoma (ACC) is very unusual for tumors 3 to 5 cm in diameter (Herrera et al., 1991). An ACA on FNAB is characterized by relatively uniform cells with round to oval nuclei and a small dot-like nucleolus. Cytoplasm may be pale staining and contain small vacuoles representing lipid. There may be marked nuclear enlargement and hyperchromasia but this feature alone is not diagnostic for malignancy. A cell block preparation of the aspirated material or a small core biopsy specimen may provide additional material as well as the opportunity to do special stains or immunohistochemistry. There is no pathognomnic immunoprofile for ACA or ACC, but the following are often seen: positive immunoreactivity for vimentin, cytokeratin, EMA, and negative results for chromogranin. An important caveat here is that both ACA and ACC may show strong immunoreactivity for the neuroendocrine markers synaptophysin and neuron-specific enolase. This immunoreaction may result in a mistaken diagnosis of a neuroendocrine tumor such as pheochromocytoma.

In the event of surgical resection of the incidentaloma, pathologic features useful in diagnosing ACC include large size (> 6 cm), necrosis, broad fibrous bands, vascular invasion, mitotic rate of 6 or more per 50 high-power fields, and atypical mitoses (Lack, 1997). The differential diagnosis of an incidentaloma preoperatively will include other primary tumors such as pheochromocytoma and myelolipoma and tumefactive lesions such as adrenal cysts. In

patients with a known malignancy elsewhere, a metastasis also has to be considered. Cytologic features may be typical for metastatic carcinoma such as malignant cells with glandular or signet-ring configuration in the case of metastatic adenocarcinoma, malignant cells with clear cytoplasm (e.g., renal cell carcinoma), and cells with cytoplasmic pigment (metastatic malignant melanoma). Availability of a cell block preparation or needle core biopsy will permit additional study if needed.

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When Should an Adrenal Incidentaloma Be Operated On— Survey From the Italian Study Group

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Although in most cases, clinically “silent” tumors (adrenal incidentaloma) are benign, adrenocortical adenomas, malignancy and/or subtle forms of Cushing’s syndrome, pheochromocytoma, hyperaldosteronism, and hyperandrogenism are not a rare occurrence. The optimal diagnostic procedure for adrenal incidentaloma is still controversial, and the clinician is called upon to devise a cost-effective approach taking into account the extensive endocrine work-up and radiological or other investigations that may be necessary to determine the cases that should undergo surgery.

Evaluation of Malignancy

Adrenocortical carcinoma is an uncommon neoplasm with an estimated annual incidence of 0.5–2 cases per million of population (Kloos et al., 1995; Bornstein et al., 1999); in most cases they are nonhypersecretory masses. Presently, a significant number of primary adrenal carcinomas are found incidentally, and this finding may modify their epidemiology. It is possible that the poor prognosis characteristic for this carcinoma may change into a better one because of an earlier detectability. In the largest series in literature, comprising more than 1,000 adrenal incidentaloma, that we collected in Italy, 47 patients had a clinically silent primary adrenal carcinoma (4.6 percent) (Mantero et al., 2000). Abdominal pain was the most common reason leading to discovery of carcinomas as a likely consequence of local infiltration, intratumoral hemorrhage, and necrosis. Only five of these patients were producing slight amount of steroids (cortisol and androgens); in four cases distant metastases were found at the time of the discovery of the adrenal enlargement. In the differential diagnosis, the lesion size is an important parameter of malignancy; the risk correlates with diameter even though malignant tumors as small as 2.5 cm in diameter have also been described. The cut-off size for suspicion of malignancy is between 3 and 6 cm. Based on the receiver operating characteristic (ROC) curve for the diameter, we have calculated a cut-off value of 4 cm (Mantero et al., 2000). Among the 47 cases of adrenal carcinoma found at surgery within the 387 patients who underwent adrenalectomy, only two had a diameter smaller than 4 cm; the mean diameter was 7.5 cm, and the range 2.6 to 25 cm. Although tumor size is highly predictive of malignancy, additional information comes from other radiological features; however, unfortunately benign and malignant masses cannot be completely discriminated on the basis of radiological features alone (Pender et al., 1998). On CT scans, adrenocortical adenomas usually appear as small, homogeneous round masses with smooth margins, with relatively low density and without enhancement after intravenous contrast. By contrast, malignancies exhibit irregular margins and nonhomogeneous density with marked enhancement after intravenous contrast. At MRI, malignancies usually show low signal intensity on T1-weighted images and high signal intensity on T2-weighted images, while most benign tumors have isointense or low signal intensity on both T1- and T2-weighted images. However, in our experience, almost 30 percent of the masses cannot reliably be distinguished on T2-weighted images, and again, there is overlap between benign and malignant tumor appearance. Metastases

are a common cause of incidental adrenal mass, especially in oncological patients for whom the prevalence ranges from 32 percent to 73 percent. Obviously, in these patients, distinguishing between metastases and other causes of adrenal enlargement may be critical in the management of primary cancer. Although the majority of metastases to the adrenal glands occur in the presence of metastases situated elsewhere, they may be the only site of tumor spread. Adrenal metastases have been documented at autopsy in up to 38 percent of patients with cancer. (Kloos et al., 1995). Usually, metastatic lesions, often bilateral, have irregular margins, are not very homogeneous, and show a thick, irregular enhancing rim after contrast. If metastases are suspected, the US- or CT-guided fine needle aspiration (FNA) biopsy may be, in our experience, a useful diagnostic tool in the evaluation of adrenal lesions (sensitivity 80–95 percent, specificity 99 percent, accuracy 75–85 percent) (Welch et al., 1994). FNA biopsy should be reserved for patients in whom the presence of adrenal metastasis may alter its therapy or prognosis. FNA biopsy really has no proved efficacy in patients with adrenal incidentaloma and no history of malignancy and is seldom successful in distinguishing cortical adenoma from carcinoma. Molecular markers of malignancy (p53 mutations, LOH on locus 11p15, hyperexpression of IGF-II and hypoexpression of TGF- β , lack of ACTH receptor expression) have not yet been studied on cytological samples. The potential hormonal activity of an adrenal incidentaloma must always be ascertained before performing an adrenal biopsy as this activity could precipitate a potentially lethal hypertensive crisis in patients with pheochromocytoma. Adrenal scintigraphy, using a radiocholesterol such as ^{131}I -6 β -iodomethyl-19-norcholesterol (NP-59) or ^{75}Se -selenomethylnorcholesterol, has proved useful in discriminating between benign and malignant lesions. A “discordant” scintigraphic pattern (i.e., demonstrating decreased or absent radiocholesterol uptake by the affected adrenal gland) is compatible with malignancy (primary and secondary) and other nonfunctioning space-occupying or destructive adrenal lesions. None the less, well-differentiated carcinomas with radiotracer uptake have sometimes been described (1/5 in our series). A recent and more promising technique is positron emission tomography (PET) with ^{18}F -fluorodeoxyglucose (FDG). Indeed, FDG PET scanning correctly differentiated adenomas from adrenal metastases in 27 patients with bronchogenic carcinoma (Erasmus et al., 1997). However, this noninvasive technique showed a nonoptimal specificity for malignancy.

Endocrine Evaluation

Although the majority of adrenal incidentaloma are nonhypersecretory cortical adenomas (67–94 percent), in many cases they can secrete glucocorticoids, mineralocorticoids, androgens, or catecholamines. Adrenal masses may be also cortical functioning carcinomas; an hormonal screening evaluation can reveal a significant number of cases of clinically unsuspected hormone-secreting adrenal tumors. The recognition of such tumors is important because they are good candidates for surgical removal. The most common incidental secreting mass appears to be the cortisol-secreting tumor (5–15 percent). Indeed, a good proportion of patients with adrenal incidentaloma (50 percent) may have isolated or multiple slight abnormalities of the hypothalamo-pituitary-adrenal (HPA) axis. A subclinical Cushing’s syndrome (SCS) may be a common finding in patients with incidental adrenal adenomas that needs to be recognized in order to detect the possible appearance of an overt Cushing’s syndrome (Ambrosi et al., 1997). The prevalence of SCS we found in our large cross-sectional study was 9.2 percent. We base our definition of SCS on at least two abnormal tests of HPA function in patients with adrenal incidentaloma and, by definition, without overt clinical stigmata of hypercortisolism. The

spectrum of cortisol excess in these patients may be wide: most have UFC at a different degree; half may show an incomplete cortisol suppression ($>5\mu\text{g}/\text{dl}$) after 1 mg of dexamethasone overnight. The other hormonal abnormalities observed in these patients are loss of the normal diurnal rhythm of cortisol (~80 percent), low ACTH levels (50 percent), impaired ACTH response to CRH test (~60 percent). The most frequent combinations encountered in our collaborative study were cortisol unsuppressibility after overnight dexamethasone and above normal UFC excretion. Furthermore, isolated abnormal tests of HPA axis are present in almost half of patients with incidentally discovered cortical adenoma. A long-term followup of patients with adrenal incidentaloma should be performed in order to evaluate the real significance of the mild endocrine alterations observed. Patients classified as SCS have been found to have an unchanged endocrine function at 12 months followup. However, in a recent study, 75 adrenal incidentalomas were followed for at least two years after diagnosis. The percentage of patients who developed hypercortisolism and had an enlargement of the mass was higher than that reported in previous studies (Barzon et al., 1999). Subtle disturbances of steroid secretion are thus probably present in subjects with adrenal incidentaloma in spite of our inability to detect them. We are currently measuring UFC with HPLC to improve specificity and precision. Furthermore, a reduction of osteocalcin (BGP), a marker of osteoblastic activity as well as IGT and insulin resistance in patients with adrenal incidentaloma, could be an early marker of subtle hypercortisolism. Sex hormone-secreting tumors are rare as incidentalomas. Most androgen-secreting neoplasms are adrenocortical carcinomas rather than benign adenomas. The majority of these tumors secrete DHEA, its sulfate, and androstenedione, whereas few are pure testosterone-secreting tumors. Serum DHEAS levels are frequently elevated in patients with clinically manifest adrenocortical cancer, and DHEAS determination could contribute to the differential diagnosis of malignant masses. On the other hand, low basal plasma of DHEAS was frequently observed in patients with SCS and cortical adenomas (Ambrosi et al., 1997). However, this parameter has low sensitivity with a sub-optimal positive predictive value. An exaggerated response of ^{17}OH -Progesterone is seldom a marker of CAH; this response was present in about 50 percent of the patients in our adrenal incidentaloma SIE study, was independent of the nature of the mass, and disappeared after surgery. Primary aldosteronism is an uncommon but important cause of secondary hypertension. Recent data suggest that this pathology may be significantly more frequent than previously reported (up to 5–15 percent of the hypertensive population) and may become the most common form of curable hypertension. In our study, aldosterone-producing adenomas had only a 1.6 percent prevalence. The low prevalence was probably due to the exclusion of cases with severe hypertension and hypokalemia. All patients with aldosteronomas had moderate hypertension and suppressed PRA levels. An apparently normal plasma aldosterone level was found in 30 percent of cases but the aldosterone/PRA ratio was greater than 40 in all cases. The aldosteronism was normokalemic in 40 percent of cases while potassium levels were between 3.5 and 3.8 mEq/l in the remainder. A low level of aldosterone (and a high level of aldosterone precursors) may be indicative of malignancy. Although pheochromocytoma is rare (0.01–0.1 percent of hypertensive patients), we strongly recommend that a hormonal screening evaluation be done in all patients to exclude the presence of this potentially lethal condition. Clinically silent pheochromocytomas are not so rare, and their prevalence in patients with adrenal incidentaloma ranges from 1.5 percent to 13 percent. In our study, incidental pheochromocytomas were the second most prevalent form of hyperfunctioning tumors, occurring in 4.2 percent of all masses. About half of these patients were normotensive, the other half had mild to moderate hypertension, and none had paroxysmal symptoms of

adrenergic discharge (Aron, 1998). ¹²³I-MIBG scintigraphy and MRI are the imaging techniques of choice in the suspicion of pheochromocytoma. At MRI, these tumors usually tend to have brighter signal intensity with T2-weighted images. However, adrenal carcinoma and metastases may present similar hyperintensity on T2-weighted images. In conclusion, from our experience, surgery should be performed when an adrenal mass is greater than 4 cm in diameter, or presents radiological aspects compatible with malignancy; FNAB should be performed in selected cases. The hormonal screening for detecting a hypersecretory mass should include UFC, overnight dexametasone suppression test, DHEAS, aldosterone/PRA ratio (in hypertensives), and urinary catecholamines or metanephrines. Age and psychological attitude of the patients should also be taken in account. The wide diffusion of laparoscopic adrenalectomy could also somewhat influence the decision to operate. Negative cases should be monitored yearly. The data from hormonal and radiological five-year followup of about 300 cases will be presented at the meeting to corroborate or modify these guidelines.

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Criteria for Surgery

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Our experience concerning incidentally detected adrenal tumors is based on observation of 655 cases referred with such diagnosis to the Department of Endocrinology (Centre for Postgraduate Medical Education, Warsaw, Poland) or diagnosed accidentally by our department during the past 16 years.

The material included 469 women and 186 men, age 11 to 87 years. Tumor diameter ranged from 0.5 to 23.0 cm.

The methods included imaging studies (ultrasound scanning, computed tomography [CT] and magnetic resonance imaging [MRI]), hormonal investigations, and histological examinations of the cases submitted to surgery.

Most of the adrenal tumors were found by ultrasound scan and all were confirmed by CT. Ultrasound scanning was also used in the long-term monitoring of tumor size. MRI was used mainly for differentiating adrenocortical carcinoma and adrenal adenomas.

Endocrine investigations performed on all the patients included serum cortisol and dehydroepiandrosterone sulphate (DHEA-S) level determination as screening methods for subclinical Cushing's syndrome and adrenal carcinoma detection. Other hormonal measurements included serum androstendione, testosterone, and 17-hydroxy-progesterone (17OH-P) levels, plasma ACTH concentration, and 24-hour urinary excretion of 17-hydroxycorticosteroid (17-OHCS) and 17-ketosteroids (17-KS); urinary metanephrines excretion was measured in hypertensive patients and in the patients with paroxysmal arrhythmias. Additionally, in 54 nonselected patients plasma metanephrines were determined (Graeme Eisenhofer, NIH, Bethesda). Dexamethasone suppression and CRH stimulation tests were performed when necessary. Aldosterone and ARO assays were conducted in some hypertensive patients with low normal kalium values.

Two-hundred thirty patients were treated by surgery. Microscopic and immunohistochemic investigations of the removed adrenal tumors were done in all the cases.

Analysis of the clinical data and the results of the above-mentioned studies allowed us to divide the material into three groups: (1) Nonmalignant tumors—571 patients = 87 percent

(432 women, 139 men, ages 16–87 years; F/M ratio = 3.1), (2) Malignant tumors—54 patients = 8 percent (32 women, 22 men, ages 11–76 years; F/M ratio = 1.45): adrenal carcinoma—48 cases, malignant pheochromocytoma—2 cases, lymphoma—3 cases, ganglioneuroblastoma—1 case, and (3) Metastatic tumors—30 patients = 5 percent (9 women, 21 men, ages 45–74 years; F/M ratio = 0.4).

In the first group of patients (those with nonmalignant masses) tumors exceeding 6.0 cm in diameter were sometimes found. Adenomas were the most frequent tumors in this group, followed by pheochromocytomas and myelolipomas.

Among 28 patients with pheochromocytoma (which is frequently clinically silent), only about half experienced increased urinary metanephrines excretion. The size of adrenal carcinomas ranged from 5.4 to 23.0 cm; however, in four patients it was less than 4.0 cm. In all the patients with adrenal carcinoma, mitotane was administered following surgery. The treatment results depended on the stage of the disease and were better when mitotane was given immediately after the operation. The patients with nonmalignant tumors, who did not undergo surgery, have been carefully observed and ultrasound scan monitoring is performed every three to six months.

The main indications for surgical treatment were (1) suspicion of malignancy (tumor diameter = 4.0 cm or larger, high-density values in CT exceeding 20 HU, irregular shape, poor content of lipids detected in MRI, elevated DHEA-S or other androgen, and rapid growth of adrenal tumor in serial ultrasound scans), (2) subclinical Cushing's syndrome, (3) suspicion of pheochromocytoma (high-density values in CT, multiple cystic regions in the tumor, elevated urinary metanephrines), and (4) acute hemorrhage into the tumor. Extraordinary indications were taken into account in patients with symptomatic cholelithiasis coexisting with right-sided adrenal incidentaloma. In the past four years, many adrenal incidentalomas sized 3.0 to 5.0 cm have been removed by laparoscopy.

Followup revealed good results of the surgical treatment in majority of the patients, apart from patients with adrenal cancer with large regional infiltration or multiple metastatic lesions. Subclinical Cushing's syndrome was diagnosed in 18 patients before surgery. Following adrenal tumor removal in 17 additional patients, a transitory secondary adrenal hypofunction appeared. Interestingly, this finding occurred not only in patients with adrenal adenomas, but also in some patients with myelolipoma, ganglioneuroma, and adrenal cysts. Thus, the traditional indications for surgery may be changed in the future.

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Considerations in the Management of Adrenal Incidentalomas: A Practical Algorithm

David E. Schteingart, M.D.

Adrenal masses are discovered in 1-3 percent of patients undergoing abdominal imaging (CT, MR imaging, or ultrasound). They include benign or malignant adrenal cortical tumors, pheochromocytomas, adrenal myelolipomas, and adrenal cysts and hematomas. Para-adrenal masses (retroperitoneal sarcomas, hematomas, ectopic lung) are occasionally confused with an adrenal mass. Prevalence increases with age above 50.

Evaluation of Hormone Secretion

Although most incidentally discovered masses are clinically silent, 10 percent are hormone-secreting and associated with subtle symptoms of hormone excess. Approximately 7 percent secrete cortisol and are clinically or subclinically apparent; 1 percent secrete aldosterone. Occasionally these masses occur in patients with nonclassic congenital adrenal hyperplasia (CAH). Specific hormonal evaluation determines the functional character of the mass. Pheochromocytomas, the second most common type of hormone-secreting incidentally found adrenal mass, may present without a history of hypertension or typical symptoms of catecholamine excess.

Evaluation of the Benign or Malignant Character of an Adrenal Mass

The major concern in the management is the possibility that the mass is malignant. However, the probability of malignancy is low. A review of all reported series of incidentally found adrenal masses shows that adrenal cortical adenomas are 60 times more common than primary adrenal cortical carcinomas, that primary adrenal cortical carcinomas are rare, and that many of the lesions that are malignant are metastatic from extra-adrenal neoplasms. Other reports suggest a higher incidence of adrenal cortical carcinoma. This discrepancy emphasizes the need of larger collaborative prospective studies to determine the true prevalence of primary adrenal cortical carcinoma.

Importance of Size in the Evaluation of Adrenal Masses

Size is a significant factor in determining the probability that a lesion is benign or malignant. There is consensus that most benign lesions are < 3 cm, whereas most malignant lesions are > 6 cm. There is uncertainty regarding masses measuring 3 to 6 cm, and these masses need to be further investigated. It is difficult to rely solely on size as a determinant of malignancy. Primary adrenal cortical carcinomas are assumed to be small before they qualify for suspicion of malignancy based solely on size. This is important because an early diagnosis and treatment can determine better prognosis for patients with these lesions.

Risk for Primary Adrenal Cortical Carcinoma in Patients With an Incidentally Found, Silent Adrenal Cortical Mass

The overall risk for primary adrenal carcinoma in patients with an incidentally found, nonfunctioning adrenal mass is 0.026 percent based on available retrospective data. Prospective studies should confirm this estimation of risk.

Evaluation Beyond Size

Information obtained from other diagnostic techniques should be added to size. These data include the imaging characteristics on CT, MR imaging, or ultrasound; adrenal scintigraphy with ¹³¹I-6β-iodomethylnorcholesterol; and the results of CT- or ultrasound-guided fine needle biopsy. CT and MR imaging of the adrenal mass may help determine whether the mass is lipid-rich or lipid-poor. Lipid-rich masses have a high probability of being benign, whereas lipid-poor masses have a higher probability of being malignant. Occasionally, benign adrenal cortical adenomas are lipid-poor and may be confused with a malignant lesion. With unenhanced CT, an attenuation of less than +10 Hounsfield units (HU) is consistent with an adenoma, whereas nonadenomas have unenhanced attenuation of greater than +30 HU. With contrast enhancement, a major distinguishing characteristic is the different retention of contrast by benign and malignant lesions. Benign lesions exhibit greater than 70 percent washout of contrast in 15 minutes, whereas malignant lesions wash out only 20 percent of the contrast in that time. Using chemical shift MR imaging, lipid-rich adenomas show a decrease in relative signal intensity of 34 percent, whereas nonadenomas show no significant change in relative signal intensity ($P < 0.001$). These techniques have high sensitivity and specificity. Benign tumors homogeneously enhance, whereas malignant tumors are inhomogeneous because of areas of necrosis. Ultrasound scanning of an adrenal mass may help distinguish cystic from solid masses. A homogeneous mass with a thin noncomplex wall is consistent with a benign adenoma.

¹³¹I-6β-iodomethylnorcholesterol scintigraphy has been combined with CT to evaluate adrenal masses smaller than 4 cm. Concordant images (increased uptake on the side of the mass) were 100 percent benign, whereas 19 of 26 discordant images (uptake contralateral to the mass) were associated with malignant lesions. MIBG scintigraphy is highly specific for detecting pheochromocytomas.

Fine needle biopsy of adrenal masses may be helpful in the detection of metastatic disease to the adrenal, most commonly from the lung. Occasionally, the primary tumor is unknown, but the adrenal metastasis is found incidentally and can direct attention to the site of the primary neoplasm. A potentially serious complication of fine needle biopsy in patients with a suspected primary adrenal cortical carcinoma is tracking and seeding neoplastic cells along the path of the needle with consequent dissemination of the tumor. If based on its size or imaging characteristics, a mass is suspected to be malignant, a fine needle biopsy should not be performed.

Conclusion

Incidentally found adrenal masses are discovered in as many as 2 percent of patients undergoing an abdominal CT scan for nonadrenal-related symptoms. The dilemma is to identify functioning or malignant tumors requiring resection. The recommended algorithm for managing these masses is as follows:

1. Hormone-secreting or large (>6 cm) masses should be surgically removed. When there is a suspicion of malignancy, the resection should be by transabdominal approach.
2. Silent masses smaller than 3 cm should be imaged further. No further followup is needed if the mass is lipid-rich based on unenhanced and enhanced CT or chemical shift MR imaging. No further followup is needed if a concordant image with CT is obtained with NP-59 nuclear scan. If the mass is lipid-poor, it could still be an adenoma; in this case, followup CT scans should be performed to evaluate for change in size at 6, 12, and 18 months. A malignant tumor is likely to grow, whereas a benign tumor will remain stable.

Masses between 3 and 6 cm should be evaluated by radiographic and scintigraphic techniques to ascertain whether they are potentially benign or malignant. If the imaging features are consistent with a benign adenoma, the patient should be observed if 50 years of age or older. Surgical resection should be considered if the patient is younger than 50 years.

Fine needle biopsy should be reserved only for confirmation of metastatic disease.

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Adrenal Incidentaloma: Surgical Progress or Status Quo?

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Laparoscopic surgery has revolutionized adrenal surgery by decreasing morbidity and accelerating return to full activity after surgery. The first open adrenalectomies were performed by Roux and Mayo via the anterior transabdominal approach in 1927. The posterior approach was described by Young in 1936; however, it was not until the late 1970s that the procedure was popularized. Since then, the posterior approach has been the procedure of choice for the vast majority of adrenal lesions including aldosterone secreting tumors, benign adenomas measuring less than 6 cm, and relatively small pheochromocytomas. The transabdominal approach was commonly selected for patients with pheochromocytomas, for children and for some patients with adrenal carcinomas. The other conventional approaches include the flank and thoracoabdominal approaches. The flank approach is a variant of the posterior approach with the retroperitoneal space being entered after the eleventh rib is resected. The thoracoabdominal approach which was utilized for large adenomas, for some large adrenal carcinomas and pheochromocytomas. The posterior or the flank approach avoids the peritoneal and thoracic cavities and minimizes the risk of mechanical ileus and pulmonary problems. The use of these direct approaches, however, was generally limited to the removal of smaller glands. These techniques precluded the intraabdominal exploration and bilateral incisions required in patients with bilateral disease.

Although the transabdominal approach provided access to the entire peritoneal cavity for exploration of the contralateral adrenal gland as well, it was associated with the morbidity of a major laparotomy. Although, the thoracoabdominal approach provided the widest exposure to the adrenal gland, it was accompanied with the morbidity of a thoracotomy. The morbidity associated with conventional techniques has been as high as 40% and mortality 2% to 4%. The morbidity after open adrenalectomy includes wound pain, intercostal neuralgia, pneumonia, wound infection, pulmonary atelectasis, and incisional hernia.

In the past decade, however, there have been dramatic changes in adrenal surgery with the introduction of laparoscopic adrenalectomy techniques by Gagner in 1992 and by Mercan in 1993. The small size of the adrenal gland, the benign nature of most adrenal tumors, and the difficulty of exposure with open means have made this gland particularly amenable to laparoscopic surgery. The development of an animal model, and the availability of many instructional courses have promoted the popularity of laparoscopic adrenalectomy. Through late 1997, nearly 600 cases had been reported in the literature. These studies have established the safety, efficacy, and cost-effectiveness of laparoscopic adrenalectomy. Laparoscopic adrenal surgery decreases estimated blood loss and wound complications, produces less postoperative pain, shortens hospital stays, and enables rapid return to normal activity. Laparoscopic surgery has become the gold standard for the removal of benign adrenal lesions.

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Laparoscopic Adrenalectomy¹

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There are multiple surgical approaches to the adrenal gland, including anterior transabdominal, flank, thoraco-abdominal, supracostal, posterior, and the newer laparoscopic techniques that use a transperitoneal or retroperitoneal approach. The traditional techniques of adrenalectomy are well described.⁽²⁻⁴⁾ Laparoscopic adrenalectomy has already had a major impact on the management of adrenal neoplasms.

The successful application of laparoscopic adrenalectomy was reported by Gagner and colleagues in 1992.⁽⁵⁾ They described an anterior transabdominal approach in patients with Cushing's syndrome and pheochromocytoma. Since that time, the techniques and indications have been refined and, in many institutions, it has become the standard technique used for adrenalectomy. The indications for laparoscopic adrenalectomy have expanded and in skilled hands it is appropriate for virtually all nonmalignant adrenal tumors. Most, but not all, endocrine surgeons agree that large tumors and clearly malignant tumors should be excised using an open technique.⁽⁶⁻⁹⁾

Laparoscopic adrenalectomy appears to have distinct advantages compared to traditional open techniques. Avoidance of large incisions and decreased tissue trauma appear to decrease morbidity and mortality.^(6, 10-12) Interestingly, even pheochromocytomas have been successfully managed with this technique.^(6, 12-15)

Several investigations have compared various anatomic approaches with laparoscopic adrenalectomy.^(6, 16-20) It is now clear that in skilled hands laparoscopic adrenalectomy can be performed safely, and this procedure results in decreased hospital stays, increased patient comfort, and a shorter interval until the resumption of normal activity.^(18,19) The result obtained in a recent study by Shell et al. compared the results of laparoscopic and open transabdominal adrenalectomy.⁽⁶⁾ The results demonstrated a marked improvement in length of stay and time until resumption of normal diet and activity. In addition, when the length of stay was compared to statewide data, the improvement was even more pronounced. The decreased length of stay resulted in significant cost savings when the results of laparoscopic adrenalectomy were compared to statewide data.⁽⁶⁾

There are no randomized prospective trials comparing the results of laparoscopic and open adrenalectomy. The results obtained in several retrospective case-controlled studies are presented below. These data demonstrate that laparoscopic adrenalectomy is consistently associated with marked decreases in the postoperative length of stay and the interval until resumption of normal diet and activity.

Most surgeons have adopted the transperitoneal flank approach when performing laparoscopic adrenalectomy. A posterior retroperitoneal approach has also been successfully employed.⁽²¹⁾ This technique may have select advantages in patients who have had previous intra-abdominal surgery.

Laparoscopic adrenalectomy has already become the standard of care in several institutions.^(6, 14, 20, 22) This technique is technically demanding and requires special equipment, experienced surgeons, and mature judgment.

Laparoscopic Versus Open Adrenalectomy¹

Study		Laparoscopic	Open Anterior	Data Class*
Prinz, 1995 ⁽¹⁶⁾	N:	10	11	II
OR Time (min):		212	174	
Postoperative Stay (days):		2.1	6.4	
Guazzoni, 1995 ⁽²³⁾	N:	20	20	II
OR Time (min):		170	145	
Postoperative Stay (days):		3.4	9	
Return to Work Activity (days):		9.7	16	
Brunt, 1996 ⁽⁹⁾	N:	24	25	II
OR Time (min):		183	142	
Postoperative Stay (days):		3.2	8.7	
Resumption of Regular Diet (days)		1.6	6.0	
MacGillivray, 1996 ⁽²⁴⁾	N:	14	9	II
OR Time (min):		289	201	
Postoperative Stay (days):		3.0	7.9	
Resumption of Regular Activity (days)		8.9	14.6	
Vargas, 1997 ⁽²⁵⁾	N:	20	20	II
OR Time (min):		193	178	
Postoperative Stay (days):		3.1	7.2	
Convalescence (weeks):		3	7	
Korman, 1997 ⁽²⁶⁾	N:	10	10	II
OR Time (min):		164	124	
Postoperative Stay (days):		4.1	5.9	
Hospital Charges:		\$3,645	\$5,752	
Linos, 1997 ⁽²⁷⁾	N:	18	86	II
OR Time (min):		116	155	
Postoperative Stay (days):		2.2	8	
Winfield, 1998 ⁽²⁸⁾	N:	21	17	II
OR Time (min):		309	233	
Postoperative Stay (days):		2.7	6.2	
Resumption of Regular Diet (days):		1.7	4.6	
Shell, 1998 ⁽⁶⁾	N:	22	17	II
OR Time (min):		267	257	
Postoperative Stay (days):		1.7	7.8	
Resumption of Regular Diet (days):		1.6	6.1	
Resumption of Independent Activity (days):		1.6	7.9	
Hospital Charges:		\$8,698	\$12,610	

* Clinical studies are classified according to the design of study and the quality of the resulting data: Class I= prospective randomized studies. Class II= prospective, nonrandomized or case-controlled retrospective studies. Class III= retrospective analyses without case controls.

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Risk and Complication Rate of Different Surgical Techniques

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Background

Over the past 20 years, adrenalectomy has evolved from abdominal surgery requiring a prolonged hospital stay and recovery period to retroperitoneal, laparoscopic, and finally needlescopic surgery, offering the possibility of outpatient adrenalectomy. This article outlines the risks and complications of the various techniques.

Adrenal tumors cover a broad range of lesions, from small benign adenomas to pheochromocytomas, metastases, and large adrenal carcinomas. Surgical complications of adrenalectomy depend not only on the approach, but also on the size and type of tumor. In general, pheochromocytomas involve higher intra-operative risk than other tumors due to extreme fluctuations in blood pressure that may occur during and immediately after removal. Adrenal carcinomas, which tend to be large and invasive, require wide excision, making them challenging to remove using laparoscopy.

Methods

We performed a systematic review of the literature. We searched Medline for relevant articles published in English. We included all studies that enrolled at least 10 patients, and excluded articles that did not explicitly state the surgical approach. Seventy articles met our inclusion criteria.

Results

Open Adrenalectomy. We found one published series of the abdominal approach (55 patients), eight series of the retroperitoneal approach (470 patients), and four studies comparing the two approaches (514 patients). The most common complications of the abdominal approach were accidental injuries to the spleen that required splenectomy, wound infection, pneumonia, hemorrhage, and pleural effusion. Complications of the retroperitoneal approach included pleural tear, wound infection, bleeding, and urinary tract infection. Mean length of hospital stay in the United States ranged from 9.3 to 9.8 days for the abdominal approach, and from 4.3 to 6.1 days for the retroperitoneal approach.

Endoscopic Adrenalectomy. We found 14 published series of laparoscopy involving 509 patients, nine series of retroperitoneoscopy involving 308 patients, and five series comparing the two approaches (486 patients). Complications of laparoscopic surgery included bleeding, conversion to open surgery, hypotension/hypertension, and wound infection. Complications of retroperitoneoscopy included retroperitoneal hematoma, subcutaneous emphysema, conversion

to open or laparoscopic surgery, and pancreatic or splenic injury. Mean length of stay in the United States ranged from 2.0 to 3.9 days for laparoscopy and 1.0 day for retroperitoneoscopy.

Comparative Studies

The overall methodological quality of the comparative studies is poor. None is randomized. The studies used historical controls, often unmatched for tumor size or type, making them susceptible to selection bias as patients referred for open surgery were more likely to have pheochromocytomas and cancers, as well as have a larger mean tumor size. In addition, many series excluded laparoscopic patients with complications who were converted to open surgery or included those patients in the open surgery results, thereby introducing a reporting bias.

In open surgery, the retroperitoneal approach had a shorter mean operating time (85–101 versus 95–160 minutes), shorter length of stay (5.3–6.1 versus 9.3–9.8 days), and fewer major complications (4–10 percent versus 15–47 percent) than the transabdominal approach. Compared to the open retroperitoneal approach (381 patients), laparoscopy had a longer mean operating time (150–212 versus 60–139 minutes), shorter length of stay (2.1–3.1 versus 5.5–6.2 days), and a similar rate of major complications (0–22 percent versus 3–12 percent). Laparoscopy and retroperitoneoscopy had similar operating times (89–226 versus 105–202 minutes), lengths of stay (2.2–3.0 versus 1.5–2.8 days), and rates of major complications (0–8 percent versus 0–24 percent). A single study of needlescopic surgery found that compared to retroperitoneoscopy, needlescopy resulted in a shorter operating time (169 versus 220 minutes), shorter hospital stay (1.1 versus 2.7 days), and fewer complications (0 percent versus 20 percent).

Conclusions and Future Directions

The overall methodological quality of the studies we examined is poor. The evidence suggests that for adenomas, laparoscopy or retroperitoneoscopy is superior to open surgery because it decreases morbidity and complications. The optimal approach for pheochromocytomas and adrenal cancers remains uncertain. Randomized controlled trials would be appropriate in these settings. Needlescopic surgery holds the promise of outpatient adrenalectomy, but high-quality evidence from large studies is needed.

Evidence for Followup Strategies

Joseph Lau, M.D.

Background

The natural history of incidentally discovered, small, biochemically inactive, and asymptomatic adrenal masses is not well understood. Most of these lesions are not removed, and there are many proposed strategies to follow these masses. The question addressed in this presentation is: What evidence is there to support the use of periodic biochemical and imaging studies to follow untreated adrenal masses?

Methods

Potentially relevant studies addressing this question were identified in our rapid screening of about 5,000 abstracts obtained from a general overall adrenal incidentaloma literature search using the PubMed database. We looked for studies that prospectively applied pre-specified imaging or biochemical testing protocols to a population of patients with untreated incidentally discovered adrenal masses as part of their followup strategies. To supplement the few studies that we came across with pre-specified protocols, we also accepted studies that reported analyses of patients followed with unspecified protocols. A total of nine studies were included in this report.

Results

Four studies reported the use of pre-defined imaging and biochemical testing protocols as part of their followup strategy. Two of these were prospective studies, one study reported the results of patients acquired both retrospectively and prospectively, and the fourth study did not clearly report this information. The studies included 12 to 75 patients and complete followup data was available on 109 subjects. The age of the patients ranged from 19 to 80 years. The average tumor size was 2.5 cm and varied between 0.8 cm and 5.6 cm. All studies performed followup CT or MRI and three studies combined imaging tests with biochemical tests as part of the followup strategy. Protocols were dissimilar across studies. The duration of patient followup ranged from 11 months to 18 years with a median of about 4.6 years. Three of the four studies reported adrenal outcomes.

The largest study of 75 patients performed CT or MRI combined with biochemical testing at six months, 12 months, and yearly thereafter. A total of 17 patients were found to have changes during followup periods that lasted from two to 10 years (median 4.6 years). Fourteen of 17 patients had changes in the mass size, and six of 17 patients developed endocrine abnormalities. One case of pheochromocytoma was found in a 62-year-old patient after five years of followup. The adrenal mass increased in size from 1.5 cm to 2.8 cm, and the catecholamines level was found to be elevated. Two deaths due to lung and colon cancers occurred in patients without adrenal changes.

Five studies reported data on patients who were followed with unspecified protocols of imaging or biochemical studies. These studies followed patients acquired both retrospectively and prospectively. There were many variations in the inclusion and exclusion criteria of the study population, and the information about the followup testing was poorly described. A subset of 142 patients from these studies who had untreated adrenal incidentaloma is the subject of this analysis. These patients were followed for one month to 11.7 years. All studies used CT for imaging, although MRI was also used in one study. CT was combined with biochemical studies in only one study.

The largest study of 91 subjects had a mean followup duration of seven years (range one month to 11.7 years), and it reported increases in tumor size in four patients. The tumors in these four patients were excised and were found to be either adenoma (three) or hemorrhagic cyst (one). There was no followup biochemical report from this study. Three small studies with fewer than 20 patients each reported no change in the size of the adrenal mass with repeated CT. The CT interval was not defined.

Conclusions and Future Directions

There is very little good evidence to guide the management of untreated incidentally discovered adrenal masses. Most of the existing studies are either too small to give meaningful results or suffer from methodological problems. Results from studies that did not pre-specify their followup protocols are difficult to interpret. This is further complicated by the lack of specificity in the definition of incidentaloma.

Future studies should be based on prospective application of pre-specified protocols to well-defined populations. The rarity of adrenocortical carcinoma and pheochromocytoma will obviously require a large number of subjects be evaluated to assess the utility of a followup protocol. If the recent studies of subclinical biochemically active adrenal mass are confirmed to be clinically important, followup strategies that include biochemical evaluations may have great utility.

Obviously, well-designed clinical trials will provide the most reliable evidence to the management of incidentaloma patients, but these trials will take many years and may be infeasible. An international registry of patients with incidentaloma with clearly defined entry criteria, carefully collected data, and well-documented followup methods could form the basis of an alternative solution.

The Long-Term Complications of Incidentally Discovered Adrenal Mass (Adrenal Incidentaloma)

Alberto Angeli, M.D., G. Osella, and M. Terzolo

In the era of evidence-based medicine, the long-term complications of incidentally discovered adrenal tumors (adrenal incidentalomas) remain surrounded by many uncertainties and, consequently, the management of such tumors is largely empirical.⁽¹⁾ There are several factors compounding our understanding of whether and when an adrenal incidentaloma puts the patient at increased risk for an adverse outcome. First, experience with adrenal incidentaloma is limited to fewer than two decades and prospective studies are virtually lacking.⁽²⁾ Second, there is not general agreement on the definition of incidentaloma, and some series may have been biased by the inclusion of hypersecreting tumors causing an unrecognized clinical syndrome, as clinician skillfulness and experience with adrenal disease are prerequisites for correctly outlining adrenal incidentaloma.⁽³⁾ Third, adrenal incidentaloma is an umbrella definition encompassing many different types of adrenal masses.^(2, 3)

There is no doubt on the potential hazard associated with adrenal cancer and pheochromocytoma; however, it is presently unclear if cortical adenoma, the most frequent incidental tumor, can significantly affect patients' health.^(2, 3) A significant number of such adenomas display functional autonomy and may produce cortisol in slight excess, thus causing the so-called subclinical Cushing's syndrome.⁽⁴⁾ Hypercortisolism in patients bearing these adenomas may vary greatly, even in the same individual, as a function of time.⁽⁵⁾ It is reasonable to anticipate that subclinical Cushing's syndrome may predispose patients to arterial hypertension, obesity, impaired glucose tolerance (IGT), and dyslipidemia. These features are shared by the metabolic syndrome and overt Cushing's syndrome.

We recently found a high prevalence of IGT (36 percent), or previously undiagnosed diabetes mellitus (5 percent), in 41 patients with incidental adrenal adenoma compared with sex-, age-, and BMI-matched patients with euthyroid multinodular goiter, who served as controls. In this group, 14 percent of the subjects qualified for IGT ($p=0.01$ versus incidentaloma patients). For both patients and controls, exclusion criteria were age equal to 70 years or greater, previous history of fasting hyperglycemia or IGT, severe hypertension, current use of medication or concomitant relevant illnesses, and BMI equal to 30 kg/m^2 or greater. Family history of diabetes was superimposable in patients and controls (32 percent versus 33 percent, $p=\text{NS}$). Fasting glucose and fasting insulin levels did not differ between the two groups ($89.3 \pm 11.0 \text{ mg/dL}$ versus $88.0 \pm 10.5 \text{ mg/dL}$, $p=\text{NS}$; $9.3 \pm 4.7 \text{ } \mu\text{U/mL}$ versus $8.3 \pm 4.5 \text{ } \mu\text{U/mL}$, $p=\text{NS}$). Conversely, the two-hour postchallenge glucose was significantly higher in patients than in controls ($134 \pm 45 \text{ mg/dL}$ versus $110 \pm 26 \text{ mg/dL}$, $p=0.01$) parallel to UFC ($103.7 \pm 76.8 \text{ } \mu\text{g/24h}$ versus $67.2 \pm 29.3 \text{ } \mu\text{g/24h}$, $p=0.005$) and midnight cortisol levels ($5.5 \pm 3.4 \text{ } \mu\text{g/dL}$ versus $3.2 \pm 0.9 \text{ } \mu\text{g/dL}$, $p<0.0001$). No difference in the standard lipid pattern was seen between the two groups, although either systolic or diastolic blood pressure was higher in patients ($135.4 \pm 15.5 \text{ mmHg}$ versus $125.0 \pm 15.6 \text{ mmHg}$, $p=0.003$; $82.9 \pm 9.1 \text{ mmHg}$ versus $75.3 \pm 6.6 \text{ mmHg}$, $p<0.0001$). We calculated the whole-body insulin sensitivity index (ISI)

derived from the OGTT, which was significantly reduced in patients (4.3 ± 1.7 versus 5.7 ± 2.5 , $p=0.01$), and correlated with midnight cortisol ($r=-0.66$, $p=0.005$). In a multiple regression analysis, two-hour glucose was associated with BMI and midnight cortisol values ($r^2=0.36$, $p=0.002$). Twelve patients qualified for subclinical Cushing's syndrome according to the criteria previously developed by us.⁽⁶⁾ These patients displayed elevated UFC (165.8 ± 98.4 $\mu\text{g}/24\text{h}$ versus 83.2 ± 51.4 $\mu\text{g}/24\text{h}$, $p=0.001$) and midnight cortisol (8.3 ± 4.0 $\mu\text{g}/\text{dL}$ versus 3.7 ± 1.0 $\mu\text{g}/\text{dL}$, $p<0.0001$) compared with those with nonfunctioning adenoma ($n=29$). In parallel, they had increased two-hour postchallenge glucose (157.2 ± 57.1 mg/dL versus 126.6 ± 31.8 mg/dL , $p=0.03$) and higher triglyceride levels (153.6 ± 84.8 mg/dL versus 94.4 ± 35.6 mg/dL , $p=0.002$), while the ISI was conversely reduced (2.9 ± 1.2 versus 5.2 ± 1.4 , $p<0.0001$).

These data suggest that some features of the metabolic syndrome, namely altered glucose tolerance, reduced insulin sensitivity, and arterial hypertension, are observed in many non-obese patients with incidental adrenal adenoma. The slight hypercortisolism caused by such tumors, even if insufficient to give the Cushing's phenotype, may significantly contribute to this state of insulin resistance.

Because osteoporosis is a well-known complication of endogenous and exogenous glucocorticoid excess, it is likely to assume that patients with incidentaloma lose bone as a consequence of subclinical hypercortisolism. Studies on the issue have provided conflicting results, plausibly due to small series of patients, different criteria to categorize cases, and different techniques for bone mineral density (BMD) measurement (and comparison to reference values as well). We measured BMD at the lumbar spine and hip using dual energy x-ray absorptiometry (DEXA) in 27 patients and 54 healthy subjects carefully matched for age, sex, BMI, and menstrual status for a 1:2 case-control analysis and did not find significant differences among groups.⁽⁷⁾ Our data vary from those of other studies;⁽⁸⁾ there is no doubt that longitudinal studies in larger series of patients with or without other risk factors for osteoporosis are needed to assess the risk for future fracturing as a function of the actual diagnosis of subclinical hypercortisolism. Needless to say, according to WHO criteria, about 15 percent of menopausal women are osteoporotic and 40–50 percent have BMD values in the range of osteopenia.⁽⁹⁾ We believe that in the majority of cases, subclinical glucocorticoid excess does not reach the pathogenetic threshold for diminishing osteoblast population, as it occurs in overt Cushing's syndrome. As in the case of insulin resistance and its associated complications clustering in the metabolic syndrome, it is likely that subtle detrimental effects of subclinical hypercortisolism complement (and possibly enhance) those of other risk factors while advancing age.

In conclusion, there is increasing awareness that aside from obvious, yet rare, progression to clinically apparent Cushing's syndrome, long-term complications of incidentally discovered adrenocortical adenomas reside in non-endocrine morbidity. Management of such tumors should consider and properly weigh concomitant risk factors and/or signs of the metabolic syndrome and relevant impact on the cardiovascular system. Prospective studies are needed to evaluate the role of subclinical hypercortisolism as a risk factor for osteoporosis, sexual dysfunction, depression, and neurovegetative disease.

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The Adrenal Incidentaloma: Public Health Dimensions and Followup

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The discovery of an adrenal mass in the course of abdominal roentgenography performed for other reasons is a common clinical occurrence (adrenal incidentaloma) and it presents a diagnostic challenge: to distinguish the vast majority of benign adrenal incidentalomas from other malignant or hormone-secreting lesions that require further therapy. Our approach should be guided by the answers to the following a series of questions:

1. **Does an adrenal incidentaloma put the patient at increased risk for an adverse outcome?** A patient with an incidental adrenal mass is susceptible to three types of adverse outcomes: endocrinologic or oncologic morbidity, mortality, and anxiety from knowing about a tumor that might cause problems in the future. Hypersecretion of glucocorticoids, mineralocorticoids, sex steroids, and catecholamines produces clinical syndromes, each associated with morbidity and premature mortality. Clinically diagnosed cases of hormone-secreting adrenal tumors and adrenal cancer are uncommon: pheochromocytoma $\sim 13/10^4$, aldosterone-producing adenoma $\sim 14/10^4$, glucocorticoid-producing adenoma $\sim 7/10^6$, and adrenal cancer $\sim 12/10^6$. Thus, mass population screening is impractical. However, these studies rely on clinically diagnosed cases; the frequency of these and other disorders in patients with adrenal incidentalomas is much higher. Caution must be taken in trying to generalize the results from series based on referrals rather than unselected cases. Anxiety for both patient and physician from knowing about the presence of a mass is also not a trivial concern. These findings suggest a benefit of pre-symptomatic diagnosis, but the risk to an individual of excess morbidity or mortality resulting from an adrenal incidentaloma, though real, is small.
2. **Can individuals with treatable syndromes be accurately diagnosed?** Established algorithms exist for the diagnosis of hormonally active adrenal lesions. When patients present with signs or symptoms of these disorders, diagnostic evaluation can proceed apace. However, when patients have few or no signs of a particular disorder, the evaluation is more challenging. Diagnostic test performance characteristics in such patients in actual practice is not known, but they will be less accurate than in patients with clinically apparent disease. Test sensitivity is likely to be lower than in the study population from which the original characteristics were derived. Test specificity is also likely to be lower. Finally, predictive value depends on the prevalence of disease. Even a test with high sensitivity and specificity will, when used to detect a rare condition, falsely identify many non-affected individuals as having the disease. Fine needle aspiration is not accurate in differentiating primary adrenal adenomas from adrenal carcinomas; we must await the development of better molecular markers of malignancy. Despite much work to determine diagnostic “imaging phenotypes” based on CT and MRI findings, discrimination between benign and malignant masses cannot be reliably made on the basis of radiological features alone.

3. **Is treatment of these syndromes more effective in pre-symptomatic patients?** Effective treatment for benign hormone-secreting tumors is available. Little is known about whether early treatment is beneficial for these conditions before they cause significant symptoms. Analogous studies in lung cancer have yielded disappointing results.⁽²⁾ Although it seems intuitive that early diagnosis would be associated with better outcomes, studies of screening chest x-rays, and sputum cytology examinations have not found this to be the case. In addition to the impact of the biases noted above, another concern involves the morbidity and mortality of managing false positive results. This controversy is currently being played out in the recommendations for screening chest CTs. Earlier diagnosis is being made, but many more patients are being subjected to surgery with its attendant risks.

4. **Do the beneficial effects of pre-symptomatic detection and treatment of these patients justify the costs incurred?** Recognizing the probabilistic nature of outcomes, cost-effectiveness/cost-benefit analyses can inform both policy-making at the population level and clinical decision-making for the patient. Cost per quality-adjusted life year (QALY) is a typical measure in such studies. However, in the reality of clinical practice, choices are not taken only on the basis of expected QALY gains, but are determined by various psychological or social factors, including the degree of preference for certainty and aversion to risk and the fear of liability. These factors may be more difficult to take into account in the QALY measure. Both patients and doctors tend to be more aggressive in their pursuit of diagnosis and treatment than a strict cost per QALY-based approach would advise. In part, this results from the difficulty of understanding, interpreting, and communicating information about risk. While cost-effectiveness analyses make explicit their assumptions and provide another perspective, the process of clinical decision-making does not end with them. The recommendations of most experts involve more testing and lower size thresholds for surgical extirpation than those suggested by one cost-effectiveness analysis.

One of the most controversial issues in the management of a patient with adrenal incidentaloma is the frequency and duration of followup evaluations. Evaluation of several reports that included a total of >250 patients with adrenal incidentalomas who were followed for an average of >4 years indicates that a conservative approach is justified. What the best protocol for radiologic re-evaluation is also remains unclear and recommendations vary widely. The possibility of evolving adrenal autonomy suggests the utility of followup hormonal evaluation, but the questions remain: when and how often? Whether more extended followup of hormonal function is needed will be determined by future studies. Most agree that surgery is indicated for lesions that grow significantly in diameter in the course of followup. In fact, laparoscopic adrenalectomy when performed by an experienced surgeon has relatively little morbidity compared with open procedures, and it allows the extension of the surgical indication to the removal of relatively small lesions when even minimal doubt exists about their nature. Again, however, experience with laparoscopic cholecystectomy should serve as a caution; experience is important and performing surgery on more people, even using a safer procedure, has the potential to cause considerable morbidity.

There are many unanswered questions. The optimal strategy for evaluation of a patient with an incidentally discovered adrenal mass is unclear and remains controversial. A prospective multicenter randomized trial would go a long way toward resolving the controversies, but there are many obstacles to performing such a study—ethical, methodological, and practical. For example, a major issue in interpretation of the results of a screening test trial is the choice of the outcome measure. Survival from the time of diagnosis of a disease can be misleading because of lead-time bias, length-time bias, and overdiagnosis bias. More appropriate outcome measures would be disease-specific or all-cause mortality. However, these outcome measures may be impractical when dealing with a rare disorder and/or a disorder with low disease-specific mortality. Even the development of a registry so that population-based observations can be made would be a great advance. Meanwhile, our ability to accurately determine *clinically* those at increased risk among the vast majority who are not at increased risk is poor. We therefore rely on biochemical and radiological diagnostic tests, which have their own limitations. Subjecting patients to unnecessary testing and treatment carries its own set of risks. The harm that occurs as false positive results are pursued has been termed the “cascade effect.” We must avoid the pitfall of overestimating disease prevalence and the benefits of therapy resulting from advances in diagnostic imaging by using our best clinical judgement based on the best available evidence and by carrying out studies that address the pertinent issues.

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Cost-Effectiveness Analysis of Diagnosis and Treatment of Adrenal Incidentaloma

Job Kievit, M.D., Ph.D.

Introduction

Most adrenal incidentalomas are either benign adenomas or other “insignificant” disorders that neither affect a patient’s health nor warrant the costs and risks of diagnostic or therapeutic interventions, and should thus be left untreated. However, some are “significant” disorders—such as cancer or pheochromocytoma—that pose a serious health risk and therefore deserve treatment. Differentiating between these two categories and choosing the right strategy is a diagnostic-therapeutic challenge that must be resolved following detection of an adrenal incidentaloma.⁽¹⁾ The choice to either ignore or investigate and treat should be based on a careful weighing of costs, risks, and benefits and supported by the best available evidence.

Methods

Methods of meta-analysis, decision analysis, and cost-effectiveness analysis were applied to solve the adrenal incidentaloma dilemma.⁽²⁾ The various events and outcomes in the diagnostic-therapeutic approach to adrenal incidentaloma were modeled using a decision tree. In the model, eight different tests were used to differentiate between significant and insignificant disorders: (1) computer tomography (CT), (2) magnetic resonance imaging (MRI), (3) I¹³¹-metiodobenzylguanidine-scanning (MIBG) or (4) I¹³¹-iodomethyl-norcholesterol-scanning (NP59), hormonal analysis of (5) adrenocortical function only, of (6) adrenomedullary function only, and of (7) both adrenocortical and adrenomedullary function, and finally (8) fine needle aspiration cytology (FNAC). Treatment was assumed to consist of surgical removal of the affected adrenal gland, using either a laparoscopic or an open approach.

A 20-year Medline search on adrenal incidentaloma was performed to quantify the variables needed for the model. Additional information was obtained using cross-references between articles leading to a 380-article database. Abstracts from this database were screened and articles were only used if they (1) reported original data (2) used unambiguous variable definitions, (3) contained quantitative data from which on one or more of the required variables could be calculated, and (4) contained a minimum number of 10 observations per variable.

Two reference situations were used to assess the merits of various strategies. The “no incidentaloma” situation (a patient with similar age, sex, and clinical characteristics but without adrenal incidentaloma) was used to assess the potential negative impact of adrenal incidentaloma on a patient’s health. The “ignore” strategy was used as the reference strategy against which the costs, risks, and benefits of diagnosis and treatment of a patient with adrenal incidentaloma were measured. A total of 68 diagnostic-therapeutic strategies were analyzed with respect to their cost-effectiveness in accordance with the guidelines of the panel on cost-effectiveness analysis.⁽³⁾

Results

In a population of 2,681 patients reported in 15 articles, adrenal incidentalomas are inactive benign cortical adenomas in 84 percent of cases, primary adrenocortical cancers (PACC) in 5 percent, pheochromocytomas in 3 percent, hormonally active benign cortical adenomas in 6 percent, and metastases from extra-adrenal cancers in 2 percent. If left untreated, an average 3 cm adrenal incidentaloma decreases quality-adjusted life expectancy by a mean of one quality-adjusted life year (QALY). The main threats to health come from the potential presence of cancer (a 7 percent risk of losing 15 QALYs) or pheochromocytoma (a 3 percent risk of losing 4 QALYs). The approach to adrenal incidentaloma should primarily be directed at eliminating or reducing the health risks that these particular disorders pose. Of these, pheochromocytoma can be treated most effectively (treatment eliminating 65 percent or more of potential life loss, depending on its benign or malignant character), whereas treatment of adrenocortical cancer and metastasis from extra-adrenal cancer is less successful (eliminating 8 percent in the case of adrenocortical cancer and, effectively, none in the case of metastasis).

In general, analysis of adrenomedullary hormonal function (by urinary metanephrines, at sensitivity of 95 percent and specificity of 96 percent for pheochromocytoma in 1,647 patients from 15 articles) followed by surgery if positive, has the most favorable marginal cost-effectiveness ratio (MCER) of \$22,000 per QALY. Full hormonal testing or imaging may be more effective in patients with higher risk of adrenocortical cancer (through larger incidentaloma size [≥ 6 cm] or malignant aspect on primary imaging test), at an MCER of \$35,000 or lower. Full hormonal analysis is likewise justified in patients in whom the combination of hypertension and hypokalemia suggests Conn's syndrome, at an MCER of \$20,000 per QALY. From the perspective of optimizing life expectancy, small or medium-sized adrenal incidentalomas (< 4 to 5 cm) may be ignored in the elderly (> 70 to 80 years) and/or in patients who may not be fit enough to undergo surgery.

Conclusions

The approach to adrenal incidentaloma should be guided by the aim of improving (quality-adjusted) life expectancy at acceptable cost and not by “fear of missing something.” This is best achieved by identifying and curing primary adrenocortical cancer, pheochromocytoma or Conn's syndrome. Pheochromocytoma screening by urinary metanephrines is warranted in all patients except the most elderly or unfit. Screening for adrenocortical cancer by analysis of adrenocortical hormonal function, imaging and/or fine needle aspiration, is cost-effective in patients with large incidentalomas. Full hormonal analysis is likewise warranted when Conn's syndrome is suspected on the basis of hypertension and hypokalemia. Small or medium-sized non-suspect lesions may be ignored in elderly and/or unfit patients.

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Novel Tumor Markers in the Adrenal Gland

Sandra Ann Murray, Ph.D.

The differentiation between malignant and benign adrenocortical tumors is an important but often difficult distinction in the early diagnosis and treatment of adrenal diseases. Although tumor size is widely used as a preoperative indicator of malignant potential for adrenal tumors, better diagnostic markers are needed. The preponderance of available markers are based on the assumption that errant metabolic processes will either alter the quantity of a normal metabolic marker or induce the production of proteins not normally associated with a given cell type. In this context, high levels of circulation protein are used to monitor neoplastic growth in a variety of cancers.

In contrast to methodologies that seek to identify abnormal or excessive protein production, measurements of decreased protein amounts may serve as reliable assessments of tumor development. Major histocompatibility complex (MHC) Class II antigens, for example, are absent in adrenocortical carcinomas, whereas normal adrenal glands and the majority of adenomas express these proteins.⁽¹⁾ Thus, absence of MHC Class II expression has been used to assess adrenocortical tumors. Our work has centered on the concept that a decrease in the protein connexin, required for normal cell-cell communication, might signal a loss of normal regulation of cell proliferation and also be used as an adrenal tumor marker. Loss of intercellular communication is thought to be involved in the metastatic events characteristic of carcinogenesis in many tissues.^(2,3) There is extensive evidence that cancer cells exhibit uncontrolled growth as a result of a diminished ability to communicate with surrounding cells.⁽⁴⁾ A major route for such cell-cell communication is through gap junction pores, which are composed of integral membrane proteins termed connexin.⁽⁵⁾ Connexins are a multifamily of related proteins, identified by their relative molecular mass, of which at least 15 species have been isolated.⁽⁶⁾ Thus, alterations in the amount of regulatory molecules and/or alterations in cell-cell communication through gap junctions may be one mechanism contributing to tumor development. Determining the type, distribution, and quantity of gap junctions in normal versus diseased adrenal tissues should provide insight into the role of gap junctions in adrenal carcinogenesis as well as suggest methods for improved diagnosis and treatment of adrenal diseases.

Using immunocytochemical techniques, we have characterized and compared α_1 -connexin 43 gap junction protein levels in normal adrenal glands with those found in benign and malignant adrenocortical human tumors.⁽⁷⁾ In addition, gap junction protein levels have been studied in a human adrenal cancer cell line (H295). In both normal and neoplastic adrenal tissues, only α_1 -connexin 43 could be detected, while β_1 -connexin 32 and β_2 -connexin 26 were not found. In the normal adrenal gland, the zona fasciculata was determined to have the highest incidence of gap junctions per cell (13.78 ± 1.93 SEM). In comparison with these findings in the normal zona fasciculata, the number of gap junctions per cell was significantly reduced in benign adrenocortical adenomas (4.6 ± 1.17 SEM $P \leq 0.05$) and the lowest number was found in malignant adrenocortical tumors (1.42 ± 0.58 SEM $P \leq 0.05$). As anticipated from our results in adrenal tissue samples, there were few or no α_1 -connexin 43 gap junctions in the H295

population. In summary there was a progressive decrease in gap junction plaques in adrenocortical cancer cell populations compared with normal cell populations. Therefore, analysis of gap junction protein along with other markers such as MHC Class II may be helpful for the differential diagnosis of benign and malignant adrenal tumors, and it appears that the induction of gap junctions in malignant cells might provide a novel therapeutic strategy for the treatment of adrenal cancer.

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Novel Biochemical Markers and Imaging Techniques for Diagnosis of Pheochromocytoma in Patients with an Incidentally Discovered Adrenal Mass

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Introduction

The increasing use of radiologic imaging modalities as standard procedures in modern medicine has led to recognition of incidentally discovered adrenal masses as a relatively common clinical problem, with a prevalence in the general population of up to 5 percent.^(1, 2) Although the majority of adrenal incidentalomas are benign nonhypersecretory cortical adenomas, an important minority represent pheochromocytomas, aldosteromas, or cases of cortical cancer or Cushing's syndrome. These tumors are pathologic and require appropriate diagnosis and treatment. Pheochromocytomas are particularly life-threatening, appearing in about 4.2 percent of adrenal incidentalomas.⁽¹⁾ Pheochromocytomas found as incidentalomas often do not secrete large amounts of catecholamines and may be present without hypertension or symptoms. Also often not considered is the fact that many adrenal masses found during testing for pheochromocytoma simply reflect incidentally discovered benign adenomas. Differentiation of pheochromocytoma from other adrenal tumors is therefore essential for appropriate treatment and it requires highly sensitive and specific biochemical tests and imaging modalities.

Biochemical Tests

Biochemical tests of catecholamine excess commonly used for diagnosis of pheochromocytoma include measurements of urinary and plasma catecholamines, urinary metanephrines, and urinary vanillylmandelic acid. More recently developed tests include measurements of plasma concentrations of free normetanephrine and metanephrine, or of deconjugated (free plus sulfate-conjugated) normetanephrine and metanephrine.^(3, 4)

Plasma-free metanephrines (either normetanephrine or metanephrine or both) are constantly produced by the actions of catechol-O-methyltransferase on catecholamines leaking from storage vesicles within tumors. Therefore, these measurements show larger and more consistent increases above normal than plasma catecholamines and appear to reliably exclude the presence of all but the smallest of pheochromocytomas (> 99 percent sensitivity, > 90 percent specificity). Where excluded, no other tests are necessary. This means that measurements of plasma-free metanephrines avoid a missed diagnosis and minimize the need to run multiple diagnostic tests to differentiate a pheochromocytoma from other adrenal tumors.

However, as with all biochemical tests used in the diagnosis of pheochromocytoma, an elevated plasma normetanephrine or metanephrine does not necessarily prove that an adrenal tumor is a pheochromocytoma. Since increases in plasma normetanephrine or metanephrine in

patients with pheochromocytoma are positively related to tumor mass, a nomogram relating adrenal tumor diameter to plasma concentrations of metanephrines can provide additional assistance in differentiating pheochromocytoma from other adrenal tumors. Use of the clonidine suppression test, coupled with measurements of both plasma norepinephrine and normetanephrine, can also be helpful.

Imaging Techniques

Standard radiological procedures, such as CT or MRI, do not have sufficient specificity to reliably distinguish a pheochromocytoma from other adrenal tumors. The high specificity of metaiodobenzylguanidine (MIBG) scintigraphy has made this imaging modality particularly useful for identifying an adrenal mass as a pheochromocytoma. However, limited sensitivity of this imaging modality, particularly when involving ^{131}I -labeled rather than ^{123}I -labeled MIBG, presents a problem in many cases of pheochromocytoma. Positron emission tomographic scanning provides an alternative imaging modality that allows for the use of large doses of short-lived positron-emitting radionuclides, resulting in superior resolution compared to single photon emitters.

6- ^{18}F Fluorodopamine, a positron-emitting analog of dopamine, is transported actively and avidly by both the plasma membrane norepinephrine and intracellular vesicular monoamine transporters. Since pheochromocytoma cells express the plasma membrane and vesicular catecholamine transporters, 6- ^{18}F fluorodopamine was hypothesized to be a good radiolabelled compound for the diagnostic localization of pheochromocytoma.⁽⁵⁾ In our series of 32 patients who presented with either solitary or metastatic pheochromocytoma, 6- ^{18}F fluorodopamine positron emission tomographic scanning was found to detect and localize pheochromocytomas in 30 patients.⁽⁶⁾ Based on the present results, we suggested that 6- ^{18}F fluorodopamine positron emission tomographic scanning may be particularly useful for discriminating pheochromocytoma from other adrenal tumors.

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Subclinical Endocrine Activity and Adrenal Biopsy

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Subclinical Disease

By definition, no clinical signs or symptoms of adrenal disease should be present at the time of diagnosis in patients with incidentally detected adrenal masses. However, lack of symptoms does not exclude the presence of a significant endocrine activity of the adrenal lesion. While it is important to limit costs and risks for the patient by avoiding all unnecessary diagnostic interventions, careful diagnostic evaluation holds the potential of early detection of possibly harmful diseases and can lead to a curative therapy (e.g., in secondary hypertension due to Cushing's syndrome and pheochromocytoma).

Approximately 80 percent of incidentally detected adrenal masses are clinically and biochemically nonfunctional. The percentage of incidentalomas with significant endocrine activity increases with tumor size. For lesions larger than 1 cm, up to 20 percent show significant hormonal activity.⁽¹⁻⁴⁾ The percentage of hyperfunctioning lesions increases to > 50 percent in tumors with a diameter of > 6 cm.⁽⁵⁾ Approximately 10 percent of initially nonfunctional masses will develop an endocrine hypersecretion during the next two to 10 years.⁽⁶⁾ Hormonal activity can be divided into subclinical Cushing's syndrome, pheochromocytoma, and primary hyperaldosteronism.

Subclinical Cushing's Syndrome (SCS). Autonomous cortisol secretion by adrenal incidentaloma is reported, depending on the definition and the screening procedure, in 5 to 20 percent of the patients.^(1,2,7-14) For this entity the term subclinical Cushing's syndrome has been established. Depending on the amount of glucocorticoids secreted by the tumor, the clinical significance ranges from only slight attenuated diurnal cortisol rhythm to complete atrophy of the contralateral gland with long-lasting adrenocortical insufficiency after adrenalectomy.^(12,15) Thus, subclinical Cushing's syndrome must be excluded in every patient scheduled for surgery to avoid postoperative adrenal crisis.^(15,16) The best means to uncover autonomous cortisol secretion is the short (overnight) dexamethasone suppression test, which rarely fails to detect subclinical Cushing's syndrome.⁽¹⁷⁾ To reduce false positive results some centers prefer a higher dexamethasone dose (3 mg instead of 1 or 2 mg). A suppressed serum cortisol concentration (< 3 µg/dl or 80 nmol/l) excludes significant cortisol secretion by the tumor. In a second step, serum cortisol concentrations of > 3 µg/dl require a confirmatory high-dose dexamethasone suppression test (8 mg). If serum cortisol concentrations are again not suppressible, subclinical Cushing's syndrome is diagnosed. Increased values of urinary-free cortisol are a late finding usually associated with emerging clinical signs of Cushing's syndrome.⁽¹⁶⁾ Thus, diagnosis of SCS should not exclusively be established by urinalysis.⁽¹²⁾

Pheochromocytoma. The proportion of pheochromocytoma among adrenal incidentaloma patients has been reported in a range from 0 to 11 percent.^(1,2,7,11,13,18-21) As many of these individuals have no typical clinical symptoms such as hypertension or tachycardia, a careful biochemical evaluation is necessary.⁽¹⁾ Diagnosis should be confirmed or excluded in all

incidentally detected adrenal masses by determination of 24-hour urinary catecholamines or metanephrines, which have the highest sensitivity (96 percent).⁽²²⁾ Measurement of plasma catecholamines is inferior and a suppression test (clonidine test) is rarely required. In patients with elevated catecholamine excretion, ¹³¹I-metaiodobenzylguanidine (MIBG) scintigraphy is advocated for preoperative detection of metastasis or multilocular pheochromocytoma/paraganglioma.⁽²³⁾ Adequate preoperative alpha and beta receptor blockade is mandatory to minimize life-threatening hypertensive crisis.⁽²³⁾

Primary Hyperaldosteronism (PHA). The classic manifestation of PHA is hypertension and hypokalemic alkalosis. Recently, a normokalemic variant of PHA, which is frequently found in nonselected series of hypertensive individuals, was reported by means of an elevated plasma aldosterone to renin ratio (ARR).^(24–27) Using this ratio as a screening tool, we can detect PHA in a significant percentage (1.6–5 percent) of patients with incidentally detected adrenal incidentalomas.^(1,6, RD Gordon, personal communication) In the recently published multicenter Italian incidentaloma study, 60 percent of patients with adrenal incidentaloma and PHA had potassium levels below 3.8 mmol/L, and the remainder were normokalemic.⁽¹⁾ Because of the normokalemic variant, screening for PHA by determination of the ARR is recommended in all hypertensive subjects with an adrenal incidentaloma independent of the potassium concentration. In subjects with elevated ARR and a high-normal or elevated plasma aldosterone concentration, PHA should be confirmed by additional tests (fludrocortisone suppression, saline suppression).^(26, 28)

DHEAS Secretion. Measurement of DHEAS has been recommended to exclude adrenocortical carcinoma in incidentaloma patients. In a recently published retrospective study in incidentaloma patients, DHEAS values were elevated in 17 percent of all patients who turned out to have cortical carcinoma (28 percent in younger individuals, age < 50 years). The sensitivity and specificity were 17 percent and 93 percent, respectively; negative and positive predictive values were 95 percent and 10 percent, respectively.⁽¹⁾

Authors recommendation for screening of subclinical endocrine activity include

1. SCS: Serum cortisol after dexamethasone suppression (3 mg at 11 PM orally)
2. Pheochromocytoma: 24-hour urinary catecholamine excretion
3. PHA: Serum potassium and repeated blood pressure measurements in case of spontaneous hypokalemia or arterial hypertension measurement of serum aldosterone and plasma renin activity.

Therapeutic Consideration. To prevent serious morbidity, all hormonally active incidentalomas have to be surgically removed.^(1,14,16) This strategy is undisputed for Conn's syndrome adenomas and pheochromocytoma. However, it remains doubtful whether all patients with subclinical Cushing's syndrome benefit from adrenal surgery, as progress from subclinical disease to overt Cushing's syndrome occurs only in a minority of cases.^(6,12) As autonomous cortisol secretion by the tumor can range from a small percentage of the daily requirements to borderline hypersecretion with suppression of the contralateral adrenal, it is likely that the metabolic benefits of surgery will vary accordingly. In patients with subclinical Cushing's

syndrome undergoing unilateral adrenalectomy, a permanent weight loss in obese individuals, a reduction of hypertension, and an improvement of glycemic control in diabetics are frequent findings.^(3,4,12) Moreover, recently a reduced bone mineral density and altered bone metabolism in patients with SCS (diagnosed by elevated urinary-free cortisol) was shown, which indicates that these individuals are at higher risk of osteoporosis.⁽²⁹⁻³¹⁾ Although these results were not obtained from large prospective studies, they indicate that surgical therapy should be advocated in more patients.

Adrenal Biopsy (FNA) in Adrenal Incidentaloma

It is generally accepted that in patients with adrenal incidentaloma and no history of malignancy, fine needle aspiration cytology and adrenal cut biopsy have no proved efficacy, as histological differentiation between benign and malignant primary adrenal tumors is difficult.⁽³²⁾ Adrenal biopsy is not free of side effects; it may lead to pneumothorax, frank retroperitoneal bleeding, or needle track metastasis in the case of adrenocortical carcinoma.^(33,34) Because of recent improvements in imaging techniques leading to a better characterization of the dignity of adrenal masses (e.g., chemical shift MRI) adrenal biopsy can be currently restricted to few indications. Adrenal biopsy is undisputed in patients with a known extra-adrenal malignancy and a suspicious adrenal lesion. In this group of patients, adrenal biopsy is a good tool (sensitivity and specificity approximately 90 percent), and it should be performed if the presence of adrenal metastasis may alter the therapy or prognosis.⁽³⁵⁾ Importantly, pheochromocytoma must always be excluded prior to adrenal biopsy as biopsy may cause hypertensive crisis and even death.^(36,37)

Recently, in a prospective German multicenter trial, the diagnostic accuracy of adrenal biopsy was re-evaluated by an ex-vivo puncture approach using modern histopathological tools.⁽³⁸⁾ Two-hundred thirty-one consecutive tumorous adrenal samples (87 adenomas, 56 pheochromocytomas, 21 adrenocortical carcinomas, 13 metastases, 45 others) were investigated using conventional histology and immunohistochemistry (keratin KL1, vimentin, S100 protein, chromogranin A, synaptophysin, neuron-specific enolase, D11, Ki-67, and p53). Compared with the diagnosis from surgical specimens, bioptic diagnosis was absolutely correct in 75 percent of cases, nearly exact in 13 percent, and incorrect in 8 percent. Pheochromocytoma was correctly diagnosed in 95 percent of cases, cortical adenomas in 94 percent, cortical carcinoma in 76 percent, and metastases in 92 percent. The overall sensitivity for malignancy was 99 percent, the specificity 96 percent. From these data, it appears that under optimized conditions (e.g., experienced pathologist, sufficient biopsy specimens) adrenal biopsy may be a more valuable method for identifying and classifying adrenal tumorous lesions than assumed up to now.

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