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The Clinically Inapparent Adrenal Mass: Update in Diagnosis and Management

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Clinically inapparent adrenal masses are incidentally detected after imaging studies conducted for reasons other than the evaluation of the adrenal glands. They have frequently been referred to as adrenal incidentalomas. In preparation for a National Institutes of Health State-of-the-Science Conference on this topic, extensive literature research, including Medline, BIOSIS, and Embase between 1966 and July 2002, as well as references of published metaanalyses and selected review articles identified more than 5400 citations. Based on 699 articles that were retrieved for further examination, we provide a comprehensive update of the diagnostic and therapeutic approaches focusing on endocrine and radiological features as well as surgical options. In addition, we present recent developments in the discovery of tumor markers, endocrine testing for subclinical disease including autonomous glucocorticoid hypersecretion and silent pheochromocytoma, novel imaging techniques, and minimally invasive surgery. Based on the statements of the conference, the available literature, and ongoing studies, our aim is to provide practical recommendations for the management of this common entity and to highlight areas for future studies and research. (*Endocrine Reviews* 25: 309–340, 2004)

Abbreviations: AA, Anterior open adrenalectomy; ALD, aldosterone concentration; CT, computed tomography; DHEAS, dehydroepiandrosterone sulfate; FDG, ^{18}F-2-fluoro-D-deoxyglucose; FNA, fine-needle aspiration; HPA, hypothalamic-pituitary-adrenal; HU, Hounsfield units; LOH, loss of heterozygosity; MEN, multiple endocrine neoplasia; MHC, major histocompatibility complex; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; NP-59, ^{131}I-6-β-iodomethyl-norcholesterol; PA, posterior open adrenalectomy; PET, positron emission tomography; PRA, plasma renin activity; RLA, retroperitoneal laparoscopic adrenalectomy; SAGH, subclinical autonomous glucocorticoid hypersecretion; SDHD, succinate dehydrogenase subunit D; TLA, transperitoneal laparoscopic adrenalectomy; US, ultrasonography; VHL, von-Hippel Lindau syndrome; VMA, vanillylmandelic acid.

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I. Introduction

CLINICALLY INAPPARENT ADRENAL masses detected through imaging for nonadrenal disease, often referred to as adrenal incidentalomas, were first described about 20 yr ago (1, 2). However, their impact on health outcomes is now better appreciated and gaining broader attention (3, 4). Despite the rarity of primary endocrine cancers of the adrenal, adrenal masses are one of the most prevalent of all human tumors. The prevalence of adrenal incidentaloma approaches 3% in middle age, and increases to as much as 10% in the elderly (5). Consequently, as our population ages, the management of clinically inapparent adrenal masses is becoming an increasingly important aspect of health care. Moreover, advances in imaging and the availability of imaging technology may reveal an even higher incidence, making the management of incidentaloma a challenge for modern medicine.

Algorithms for endocrine testing and imaging procedures are currently available for investigating the underlying causes of adrenal masses, including primary hyperaldosteronism, pheochromocytoma, and Cushing's syndrome (6–10). Because even subclinical hormone overproduction by incidentalomas left untreated may be associated with increased morbidity, the threshold for treating this condition has been lowered during the last decade. Differentiating between malignant and benign masses is an essential part of diagnosis because metastases in the adrenals are common. Adrenal cortical carcinoma, on the other hand, is a rare condition, but remains a focus of clinical concern due to its high mortality rate (11, 12).

Improved computed tomography (CT), magnetic resonance imaging (MRI), scintigraphy techniques, and selective

catheterization studies are proving useful in localizing adrenal tumors and distinguishing between benign and malignant lesions or functional and nonfunctional masses. 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 times.

Several of the molecular and cellular mechanisms involved in adrenal cell regulation and tumorigenesis have begun to be unraveled in recent years (11–18). As a result, alterations in intercellular communication through gap junctions, local production of growth factors and cytokines, and aberrant expression of ectopic receptors on adrenal tumor cells have all been implicated in adrenal cell growth, hyperplasia, tumor formation, and autonomous hormone production (13, 17, 18). In addition to genetic and chromosomal abnormalities involving several chromosomal loci and the genes encoding the p53 tumor suppressor family, other chromosomal markers have been associated with a number of familial syndromes associated with adrenal tumors such as menin [responsible for multiple endocrine neoplasia (MEN) type I] and the hybrid gene that causes glucocorticoid remediable hyperaldosteronism (11–16).

In the present review, we provide a comprehensive overview and update on the management of clinically inapparent adrenal masses. This overview is based partly on an evidence report prepared for the National Institutes of Health (NIH) State-of-the-Science Conference, the conclusions of the Conference, and also recent research findings (19, 20).

Studies for the evidence report were identified by a literature search of English-language communications published between 1966 and 2001. References of published metaanalyses and selected review articles were also included to identify additional studies. Searches on the following databases were conducted in March 2001: Medline, PreMedline, BIOSIS, and Embase. An updated search for surgical series was conducted in October 2001. A combination of search terms was used to map to the subject heading, publication title, or publication abstract, yielding a total of 5427 independent citations. The abstracts were screened manually, and 602 articles were retrieved for further assessment. The literature search was updated in September 2003, and an additional 97 articles were used for a supplementary examination. Reports that had only been published as letters or abstracts in proceedings were excluded. In general, all studies with at least 10 human subjects were included. The methodological quality of the studies summarized in the evidence report was graded using study design, conduct, and reporting of the clinical study as a basis (20).

II. Causes and Prevalence

Clinically inapparent adrenal masses are not a single pathological entity; they may be benign or malignant. The prevalence of adrenal masses varies according to the inclusion criteria of the study and the circumstances under which patient data are collected. Varying definitions in the literature could lead to different interpretations of the data, depending on the criteria for patient selection. So will studies including patients with symptoms or signs retrospectively attributable to an adrenal tumor increase the proportion of large masses, which are more likely to be cancerous. Conversely, studies that exclude patients with signs or symptoms will find a greater proportion of small masses and biochemically silent tumors. A detailed review on the etiological classification of adrenal masses and their relative frequency has been published (5).

In autopsy series, the prevalence of previously undiagnosed adrenal masses ranges between 1.4 and 2.9% (5, 21–24). Hedeland *et al.* (25) found adrenal masses in 8.7% of all autopsies in a study that included nodules above 2 mm. Of over 40,000 healthy subjects screened by routine transabdominal ultrasonography (US) during a general health examination, only 43 patients (0.1%) had abnormal findings in the adrenal gland or retroperitoneal space (26). Of 28 of these patients who had CT, the diagnosis of an adrenal mass was confirmed in 12. In 1,500 hypertensive patients screened with ultrasound, a higher prevalence of 0.5% was reported with detection of adrenal masses, most of which were hormonally inactive (27). Because of their technical superiority, CT and MRI identify clinically inapparent adrenal masses more often than US. In large CT studies, the prevalence of unexpected adrenal masses ranges from 0.6–1.9% (2, 21, 28–30). Other estimates range from 0.42% among non-cancer patients evaluated for nonendocrine complaints to 4.4% among patients with a previous diagnosis of cancer (31, 32). In lung cancer patients, adrenal masses were detected in 4.0%; a quarter of these corresponded to benign adenomas, whereas the rest were metastases (33).

There are over 44 reports from various countries describing the causes and prevalence of pathologies found in adrenal incidentalomas (21, 26, 30, 31, 33–69). Table 1 gives an overview of studies including 20 patients or more (31, 33, 34, 36–38, 40, 42–45, 48–58, 60–68, 70, 71). Combining the studies that used the broadest definitions of incidentaloma and those that reported descriptions of individual cases (35, 40, 41, 47, 53, 55, 72–74), the etiology of incidentalomas was as follows: adenoma 41%, metastases 19%, adrenocortical carcinoma 10%, myelolipoma 9%, pheochromocytoma 8%, with other, mostly benign lesions such as adrenal cysts comprising the remainder (Fig. 1A). This distribution is similar to that reported in the largest study published so far, which included 1004 patients (60), except that this study found more adenomas and fewer metastases (Fig. 1B). Rather than being a function of size, the prevalence of metastases depends primarily on the incidentaloma definition. Accordingly, studies excluding patients with known malignancies revealed a much lower rate of metastases than others.

In contrast, the prevalence of primary adrenal carcinoma in clinically inapparent adrenal masses is clearly related to mass size (75). Adrenocortical carcinomas represent 2% of all tumors less than or equal to 4 cm in diameter; 6% of those tumors range from 4.1–6 cm, with 25% of the tumors greater than 6 cm. Adenomas comprise 65% of masses 4 cm or less, and 18% of masses above 6 cm. The distribution of mass pathologies derived from surgical series overestimates the prevalence of adrenocortical carcinoma because suspicion of carcinoma is an

TABLE 1. Prevalence and characteristics of clinically inapparent adrenal mass pathologies

Author Year (Ref.)	Country	N	Cancer included	Age (yr)[a]	Tumor size (cm)[a]	% Adenoma[b]	% Pheo[b]	% Carcinoma[b]
Pagani 1982 (34)	United States	37	●	nd	nd	0	6	6
Bernardino 1985 (36)	United States	53	●	nd	(1.5–9)	nd	0	0
Hussain 1986 (37)	United States	33	●	nd	3.6	21	0	0
Francis 1988 (38)	United States	28	●	(54–75)	(1.2–10)	57	0	0
Virkkala 1989 (40)	Finland	20		59	2.3	70	0	0
Caplan 1991 (42)	United States	23		56	nd	54	0	6
Chapuis 1991 (43)	France	34		58	4.0	50	3	6
Herrera 1991 (31)	United States	342		61 ± 13	94% <5.0	96	1.5	1
Aso 1992 (44)	Japan	210	●	53	~4.7	33	23	4
Gillams 1992 (33)	United Kingdom	22	●	66	2.6	23	0	0
Jockenhovel 1992 (45)	Germany	36	nd	56	3.1	78	0	0
Kobayashi 1993 (48)	Japan	23	nd	57	2.5 ± 1.1	55	0	0
Nakajo 1993 (49)	Japan	33		nd	nd	3	6	9
Burt 1994 (50)	United States	27	●	58	2.2	81	0	0
Boland 1995 (51)	United States	20	●	65	2.8	nd	0	0
Flecchia 1995 (52)	Italy	32	●	57	3.7	69	0	6
Ambrosi 1995 (53)	Italy	32		67	2–6.3	57	0	14
Bencsik 1995 (54)	Hungary	63		(27–85)	(2–21)	22	0	1.5
Terzolo 1995 (55)	Italy	45		58	3.7	18	4	7
Aydintug 1996 (56)	Turkey	20	nd	50	3.7	85	0	10
Seppel 1996 (70)	Germany	85		54 ± 13	3.6 ± 2.5	62	1	2
Bastounis 1997 (57)	Greece	86		61	4.1	67	7	3
Bondanelli 1997 (58)	Italy	38	●	58 ± 2.3	(2–12)	33	13	7
Mantero 2000 (60)	Italy	1004		56 ± 12.9	3.0	82	4	5
Kasperlik-Zeluska 1997 (61)	Poland	208	nd	52	(0.8–21)	82	6	9
Barzon 1998 (62)	Italy	202		55	3.6	21	5	11
Barry 1998 (63)[c]	United States	231	nd	64	2.0	97	0	0
Xiao 1998 (64)	China	78	●	39	nd	12	22	12
Tütüncü 1999 (65)	Turkey	33		51	5.2 ± 4.0	21	18	6
Fontana 1999 (66)	Italy	208		55 ± 14	(0.5–25)	51	9	13
Rossi 2000 (67)	Italy	65	●	54	(1–6.5)	77	8	3
Luton 2000 (68)	France	88		53 ± 14	5.0 ± 3.0	41	11	2
Bülow 2002 (71)	Sweden	318	nd	64	3.0	44	17	12

N, Number of subjects; nd, no data; Pheo, pheochromocytoma; ●, studies including cancer patients.
[a] Mean ± SD (range).
[b] Percentage might not add up to 100 because of either multiple diagnoses or other pathologies not listed in the table.
[c] Subgroup of patients from a previously reported study (31).

indication for surgery. Moreover, the reported frequency of adrenocortical carcinoma is derived from highly selected patient populations and does not reflect the prevalence rates seen in population-based studies. Sixty percent of adrenal incidentalomas occur between the sixth and eighth decade at a mean age of 56 ± 12.9 yr (60). Thus, although approximately 64% of the adenomas and 70% of the adrenal carcinomas were found in females, age and sex do not appear to be helpful in predicting the presence of adrenocortical carcinoma.

A. Benign adrenocortical masses

Adenomas comprise the vast majority of incidental asymptomatic adrenal masses. Adenomas are benign; there is no evidence that they degenerate into malignant lesions (76). The true incidence of adrenal adenomas is difficult to determine. Several large autopsy series reports have found adrenal adenomas greater than 2–5 mm in 1.5 to 5.7% of the population, and the incidence appears to increase with age (22–24, 77, 78). Because most masses are small, a distinction between true adenomas (Figs. 2C and 3B), focal hyperplasia (Fig. 2B), and accessory cortical nodules is difficult (5). Among patients with congenital adrenal hyperplasia, a high incidence of adrenal adenomas has been found: 82% in homozygous and 45% in heterozygous patients (79). In patients with suspected adrenal disease, the size of adenomas ranged from 1.4–9 cm with a mean of 3.3 cm (80). These data correspond to results of the Italian Study Group, which found a median diameter of 3.5 cm (range, 1.0–15.0 cm) in clinically inapparent adenomas (60). In populations with no prior history of cancer, two thirds of all clinically inapparent adrenal masses are labeled as benign tumors corresponding mostly to adenomas, irrespective of changes in their endocrine output (60). Although most adrenocortical masses are nonhypersecretory adenomas, 5–47% secrete cortisol and 1.6–3.3% mineralocorticoids (29, 44, 60, 62, 81–85). Benign masses secreting androgens or estrogens are extremely rare.

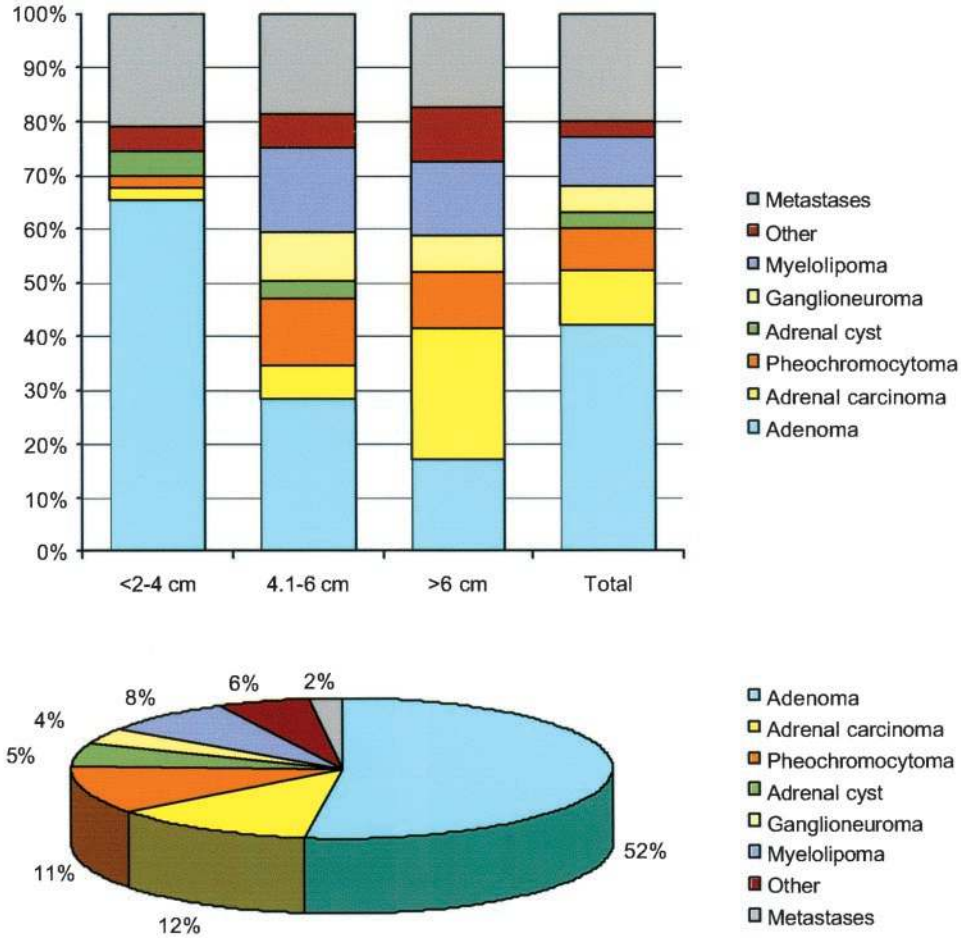

FIG. 1. *Top*, Distribution of diagnosis by tumor size. Data from eight studies with 103 diagnoses determined by histology (35, 40, 41, 47, 53, 55, 72, 73). *Bottom*, Distribution of 380 clinically inapparent adrenal masses by histological confirmed diagnosis. [Reproduced with permission from F. Mantero *et al.*: *J Clin Endocrinol Metab* 85:637–644, 2000 (60). © The Endocrine Society.]

B. Pheochromocytoma

Pheochromocytoma, a catecholamine-producing tumor, can lead to significant morbidity and mortality (86, 87). It is among the most life-threatening endocrine diseases, particularly if it remains undiagnosed. Pheochromocytoma is a frequent cause of clinically inapparent adrenal masses, accounting for 1.5–23% of these masses (Table 1). In a review of 40,078 autopsies at the Mayo Clinic between 1928 and 1977, pheochromocytoma was found in 0.13% and had not been diagnosed in 76% of the patients while alive (88). The prevalence of secondary hypertension due to pheochromocytoma, which may be sustained or paroxysmal, is estimated at 0.1–0.5% (89, 90). The most frequent clinical features are headache, palpitations, diaphoresis, and anxiety. Severe hypertension occasionally shows malignant features of encephalopathy, retinopathy, and proteinuria. However, because none of the symptoms are either specific or necessarily apparent, the diagnosis of pheochromocytoma is frequently delayed, with a mean interval of 42 months between initial symptoms and diagnosis reaching 30 yr in one large Italian study (91).

Histologically, pheochromocytoma is composed of large pleiomorphic chromaffin cells (Fig. 3C). Between 10 and 13% of pheochromocytomas are malignant (88, 92), but no widely accepted pathological criteria exist for differentiating between benign and malignant pheochromocytomas. Thus, metastatic disease remains the only irrefutable proof of malignancy. Ninety percent of pheochromocytomas are located in the adrenal glands, and the remaining 10% are located in the paraaortic sympathetic chain, aortic bifurcation, and urinary bladder (93). Bilateral tumors occur in approximately 10% of patients, and are much more common in familial pheochromocytoma often found in association with the familial MEN syndromes (MEN IIA and IIB). These autosomally inherited disorders are associated with mutations of the RET protooncogene, which encodes a tyrosine kinase receptor involved in the regulation of cell growth and differentiation (94). The neuroectodermal disorders von-Hippel Lindau syndrome (VHL) and neurofibromatosis type 1 are associated with pheochromocytoma to a much lesser extent.

C. Adrenocortical carcinoma

Adrenocortical carcinoma (Figs. 2D and 3H) is rare, with an estimated incidence ranging from 0.6 to 2 cases per million in the normal population (11, 12, 95–99). Overall, this neo-

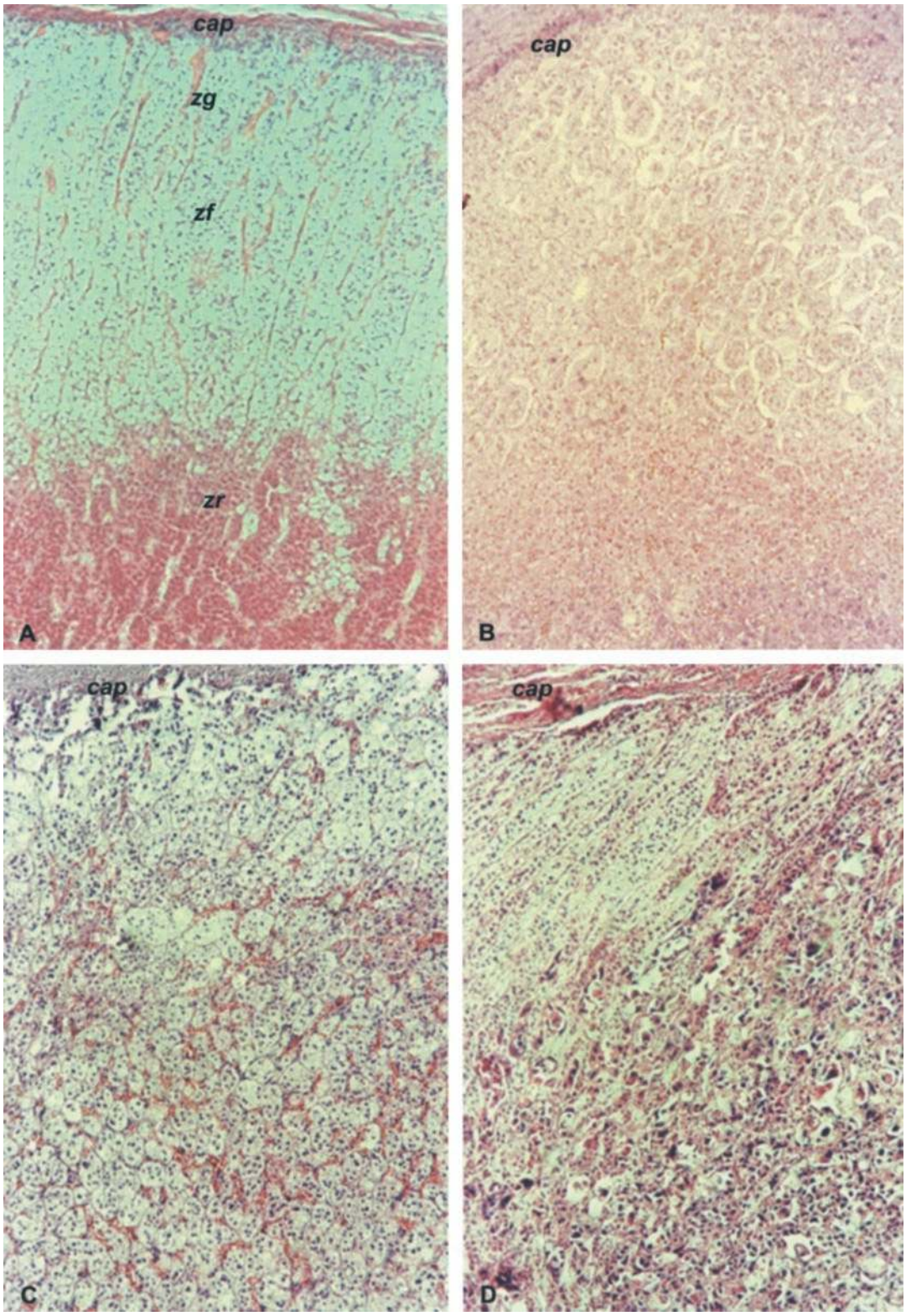

FIG. 2. Histological panel. Hematoxylin-eosin staining of normal human adrenal (A), adrenocortical hyperplasia (B), adrenocortical adenoma (C), and adrenocortical carcinoma (D). Magnification, ×60. cap, Capsule; zg, zona glomerulosa; zf, zona fasciculata; zr, zona reticularis.

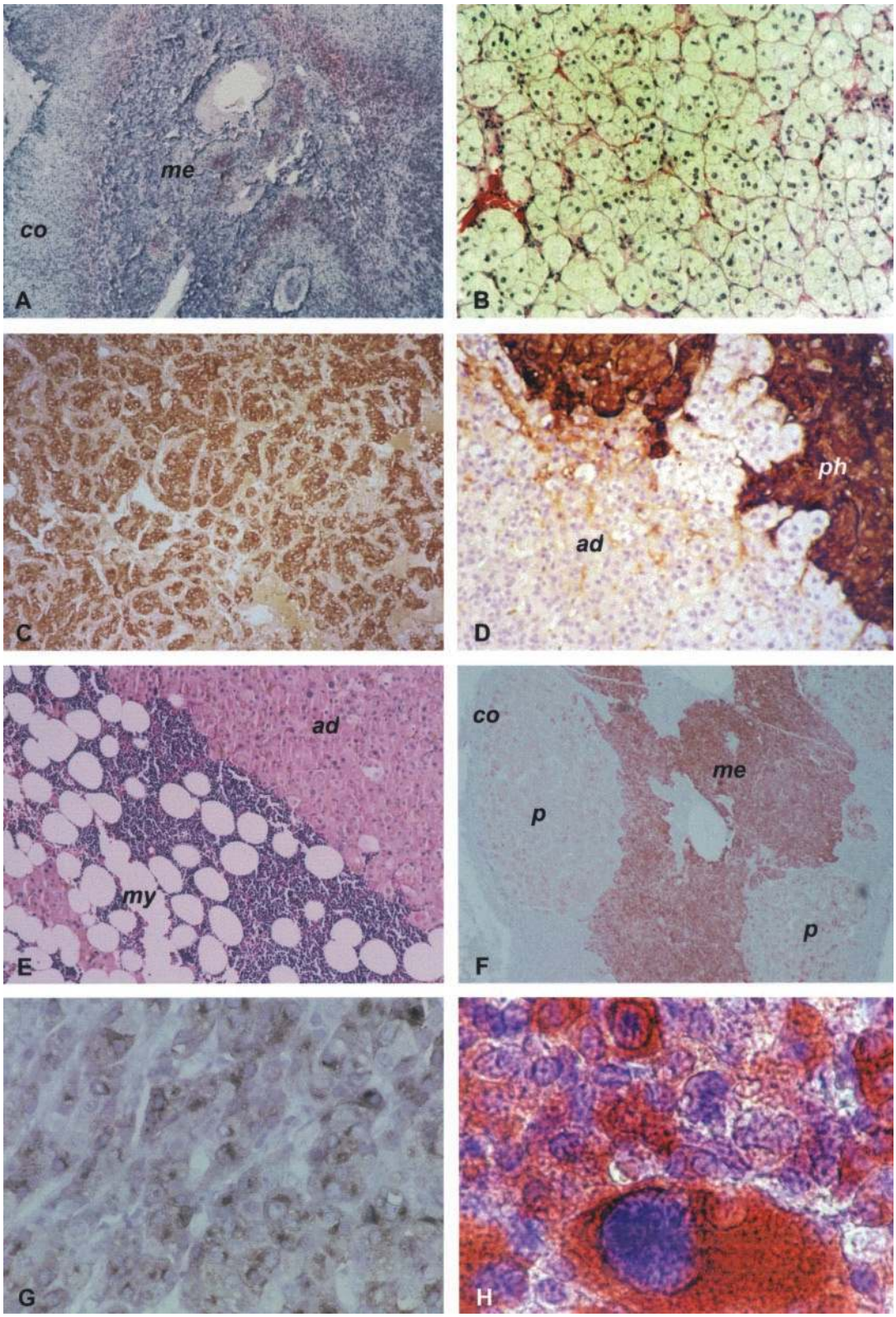

FIG. 3. Histological panel. A, Normal adrenal with cortex (co) and medulla (me), staining with antibodies to MHC class II antigens (304). B, Adenoma, hematoxylin-eosin staining. C, Pheochromocytoma, staining with antichromogranin A monoclonal antibody. D, Mixed adenoma-pheochromocytoma (ad, ph), staining with anti-chromogranin A monoclonal antibody. E, Hematoxylin-eosin stained mixed myelolipoma-adenoma (my, ad). F, Synaptophysin immunoreactivity in primary pigmented nodular adrenocortical disease (PPNAD). Staining of normal adrenal cortex (co), medulla (me), and adrenocortical nodules caused by PPNAD (p) (137). G, Adenoma, synaptophysin immunoreactivity. H, Adrenocortical carcinoma, immunostaining with an antibody against 17 α-hydroxylase cytochrome P450 enzyme (473, 474).

plasia accounts for 0.02 to 0.2% of all cancer-related deaths. There is a bimodal age distribution with peak incidence in the first and fifth decades of life (100). In some reports investigating clinically inapparent adrenal masses, the high prevalence of adrenocortical carcinoma is certainly an effect of overreporting due to admission and inclusion criteria and selection for surgery (Table 1).

Adrenocortical carcinoma can be functional or nonfunctional with regard to hormone synthesis and clinical features. Some authors require a clinically apparent endocrine syndrome to classify a tumor as functional, whereas others accept biochemical activity alone as demonstrated by excessive amounts of hormones or hormonal precursors. Using the clinical definition, functional tumors accounted for 26–94% of adrenocortical carcinomas (100–102). Although virilization by androgen-secreting tumors is a common phenomenon in children, its rate is much lower in adults (102–104). Estrogen-secreting tumors, which can cause feminization, are rare. Hypercortisolism, which can lead to Cushing's syndrome or a mixed Cushing-virilizing syndrome, is more common. Isolated primary mineralocortisolism has rarely been described (105). The female predominance among adrenocortical cancer patients that has been noted in many studies could be related to a higher prevalence of nonfunctioning tumors in males (97, 98, 100, 102, 106–116).

The prognosis of adrenocortical carcinoma is generally poor, with a median survival of 18 months. Survival is clearly related to the extent of disease (12, 101, 102). The majority of authors agree that neither sex nor functional status are predictors of survival (102, 110, 112, 114, 116–120). Besides hypertension, a common feature in adrenocortical carcinomas, symptoms include weight loss, weakness, anorexia, nausea, vomiting, severe abdominal gas, and myalgia (96, 102, 112). Abdominal pain accompanied by a palpable tumor often indicates advanced disease. Fever may signify tumor necrosis, hemorrhage, or opportunistic infection.

D. Metastases

The adrenal glands are frequent sites for metastases from many cancers. Virtually any primary malignancy can spread to the adrenals (121). Lymphoma and carcinoma of the lung and breast account for a large proportion of adrenal metastases. Other primary cancers include melanoma, leukemia, and kidney and ovarian carcinoma. In a review of 1000 consecutive autopsies of patients with carcinoma, the adrenal glands were involved in 27% of the cases (122). The incidence of adrenal metastases in patients with breast and lung cancer is approximately 39 and 35%, respectively (122, 123). Among cancer patients, 50–75% of clinically inapparent adrenal masses are metastases (28, 33, 124). Usually, either a primary site is obvious, or widespread disease is apparent. Occasionally, an adrenal mass may present as a metastatic cancer of unknown primary. These tumors generally do not respond to surgical removal and should be treated with systemic therapy based on the origin of the primary cancer.

E. Other entities

Adrenal myelolipoma (Fig. 3E) is a benign neoplasm of the adrenal cortex composed of mature fat and hematopoietic tissue in varying proportions (125, 126). Most myelolipomas are functionally inactive and are detected incidentally. Patients are usually asymptomatic, although larger lesions can cause pain or may manifest themselves with retroperitoneal hemorrhaging. Myelolipomas are slow growing, usually not exceeding 5 cm in size, but giant forms weighing over 5.5 kg have been reported. Generally, myelolipomas and adrenal cysts are benign lesions that require no therapy. Larger, symptomatic or rapidly growing tumors are treated with surgery, which is usually curative.

Other pathologies for incidentally detected adrenal masses comprise ganglioneuromas, adrenal hyperplasia, hematomas, and rare entities such as angiomyelolipoma, malignant epithelial carcinoma, epithelioid angiosarcoma, and neurinoma (5, 127–129). Rarely, extraadrenal pathologies, *e.g.*, regenerative hepatic nodule or angiomyolipoma of the kidney, might feign an adrenal mass. Fewer than 80 cases of primary adrenal lymphoma have been reported in the medical literature (130, 131). Nevertheless, recognition of this uncommon entity is important, because lymphoma is a potentially curable disease. Infections, especially tuberculosis and histoplasmosis, can also manifest themselves as an adrenal mass (132, 133). Composite adrenal tumors are rare, consisting of coexisting histological variant tumors of the same embryological origin and mixed adrenal tumors, typically mixtures of pheochromocytoma, spindle-cell sarcoma, and adrenocortical carcinoma (134). Contrasting findings between the clinical presentation that suggested adrenocortical tumor and the pathology that revealed an adrenomedullary tumor (as well as vice versa) led to the discovery of hybrid tumors (135, 136). This rare entity consists of hybrid corticochromaffin cells. Interestingly, even normal adrenocortical cells can exhibit properties of neuroendocrine cells, whereas various adrenocortical tumors aberrantly express neuroendocrine markers or receptors, neuropeptides, and cytokines (136, 137). Single cases of extremely uncommon causes of adrenal masses such as extramedullary hematopoiesis have been reported (138).

III. Diagnostic Strategies

A. Endocrine evaluation

Recent evidence demonstrates that the presence of an inapparent adrenal mass does not mean absence of endocrine activity. The patient with an adrenal mass requires a complete history and physical examination, biochemical evaluation of all pertinent hormones, and possibly additional radiological studies.

Special attention should be given to a history or episodes of high blood pressure, tachycardia, profuse sweating, and to findings such as hirsutism, striae, central obesity, or gynecomastia. Diagnostic testing should exclude clinically silent pheochromocytoma, hypercortisolism, and primary aldosteronism. If the diagnosis of overt endocrine disease such as Cushing's syndrome, Conn's syndrome, pheochromocytoma, and congenital adrenal hyperplasia are each suspected during an adrenal mass evaluation, the established diagnostic algorithm for the confirmation and differential diagnosis of these hypersecretory states applies. Excellent overviews

have been published for these adrenal disorders and will not be discussed in detail in this review (13, 86, 94, 139–149). The following focuses on the diagnostic approach for incidentalomas to exclude manifest or subclinical endocrine disease.

1. Cortisol-secreting masses. The prevalence of hypercortisolism in clinically inapparent adrenal masses has been reported to range from 5 to 47% across different studies with varying study protocols and diagnostic criteria (53, 58, 60, 67, 70, 74, 81–84, 150–153). Cushing's syndrome does occur in these patients, for example when complications such as abdominal sepsis of a previously undiagnosed disease lead to detection of an adrenal mass (21). Because most of these patients do not show a clinical pattern of manifest hypercortisolism but only an abnormal regulation of the hypothalamic-pituitary-adrenal (HPA) axis, the term subclinical Cushing's syndrome has been widely used. There is a further differentiation between subclinical Cushing's syndrome, which refers to a biochemical abnormality that never becomes clinically manifest, and preclinical Cushing's syndrome, which refers to an early stage in the development of patent Cushing's syndrome (154). This distinction can be made only retrospectively after long-term follow-up and does not appear to be helpful regarding clinically inapparent adrenal masses. Furthermore, it has been concluded as unlikely that subclinical hypercortisolism is a preclinical state of a patent glucocorticoid excess, because the prevalence data of Cushing's syndrome caused by adrenal adenoma (1.4 per million, with a mean preclinical phase of 5 yr) and disturbed HPA axis in clinically inapparent adrenal masses (0.028%) greatly differ (154).

A recently proposed term is subclinical autonomous glucocorticoid hypersecretion (SAGH) to define an autonomous cortisol secretion by an adrenal adenoma in patients without symptoms of Cushing's syndrome. Many symptoms of hypercortisolism, especially hypertension, obesity, and diabetes, are not specific; the degree of its clinical appearance varies with the extent of hormone overproduction. Therefore, the prevalence of SAGH depends largely on its definition, the testing methods used, and the selection criteria for patients with clinically inapparent adrenal masses.

The overnight 1-mg dexamethasone suppression test has been widely used as a screening test with asymptomatic adrenal incidentalomas, but whether its specificity and sensitivity are superior to a 2- or 3-mg suppression test is still unclear. The low-dose sensitivity of the dexamethasone suppression test has been reported as 98.1% for overt Cushing's disease, whereas its specificity ranges between 80.5 and 98.9%, depending on subject selection criteria (155). False-positive results may occur in patients receiving drugs that accelerate dexamethasone metabolism or increase corticosteroid-binding globulin, or in patients with endogenous depression (156). To prevent false-positive results, some authors have reported preferring a higher dexamethasone dose using 3 mg for the suppression test in clinically inapparent adrenal masses (153). To provide a standard, the NIH State-of-Science Conference panel recommended the 1-mg dexamethasone suppression test in all patients with incidentally detected adrenal masses (19). Generally, a serum or plasma cortisol at 0800 h of less than 5 μg/dl (<138 nmol/liter) is considered negative. Values greater than 10 μg/dl are suggestive of Cushing's syndrome, whereas levels in between are equivocal and can be found in SAGH. Salivary cortisol has not yet been adopted into routine clinical practice, although salivary cortisol levels reflect plasma free cortisol levels better than total plasma cortisol levels (142, 157).

A positive suppression test should be confirmed by other tests, but the appropriate biochemical evaluation of SAGH is controversial (158). There is little evidence regarding biochemical tests in this setting, and the definition of a gold standard for diagnosis of SAGH is still a major problem. High-dose dexamethasone suppression test (8 mg), 24-h urinary free cortisol, and dynamic testing with CRH have all been proposed, but the biochemical findings in SAGH vary with a broad spectrum (29, 60, 152, 159). The circadian rhythm of cortisol may be altered, which would result in high midnight cortisol levels. Morning ACTH levels may be normal or suppressed (82) but should only be measured at the same time as cortisol levels. The urinary free cortisol excretion may be normal or slightly elevated, and the response to CRH administration blunted with lower peak levels of ACTH.

Unfortunately, SAGH has not been adequately characterized, and the natural course of this syndrome is unknown. Rarely, SAGH may progress to overt Cushing's syndrome (151). It is unclear whether or not SAGH patients are prone to the classic long-term complications of full-blown Cushing's syndrome (152, 160). An increased prevalence of hypertension, central obesity, diabetes, and metabolic conditions such as hyperlipoproteinemia and impaired glucose tolerance has been reported in patients with SAGH (67, 69, 75, 152, 158, 161, 162). A recently published study found an increased cardiovascular profile risk, determined by the presence of atherosclerotic plaques and the metabolic syndrome, in patients with incidentally detected adrenal masses and SAGH in comparison to an age-, gender-, and body mass index-matched control group (163). Interestingly, a high prevalence of disturbed glucose tolerance (61%) has also been found in patients with nonfunctional adrenal incidentaloma, that is, patients without abnormal low-dose suppression test (164). The authors speculated that compensatory hyperinsulinemia after development of insulin resistance would lead to an overstimulation of the adrenal cortex via a constantly or intermittently increased circulating ACTH, and then to adrenal adenomas. Conflicting data have been published in regard to bone mass in clinically inapparent adrenal masses and SAGH. Most studies suggest that patients with SAGH might have an increased risk of osteoporosis (165–171), although one group rejected an increased risk, because no difference in lumbar and femoral bone mineral density compared with healthy controls had been determined (172).

Little in the way of data have been published concerning a benefit of surgery in SAGH, so hypertension, obesity, non-insulin-dependent diabetes mellitus, and other risk factors for cardiovascular events were irregularly improved in some patients (67, 70, 81, 163, 173). With regard to the inconsistent data, it is not yet established whether patients with an adrenal mass and SAGH do actually profit from adrenalectomy. Therefore, further studies are clearly needed to define

the role of SAGH in morbidity and mortality. Finally, it has to be mentioned that hypercortisolism to any extent, including SAGH, might be caused by adrenocortical carcinoma (58).

2. Mineralocorticoid-secreting masses. The prevalence of aldosteronoma in clinically inapparent masses has been reported as approximately 1.6–3.8% (29, 44, 60, 62, 174). Apart from aldosterone-producing adenoma, other forms of primary aldosteronism exist as idiopathic hyperaldosteronism and primary adrenal hyperplasia. Additional mineralocorticoid excess syndromes include inherited enzyme deficiencies, licorice ingestion, use of chewing tobacco, and glucocorticoid-remediable hyperaldosteronism, an autosomal dominant form of hyperaldosteronism in which aldosterone synthesis is regulated by ACTH (175, 176). In general, no adrenal mass is present in these causes of hyperaldosteronism. Historically, spontaneous hypokalemia (≤3.5 mmol/liter) was considered to be the hallmark of primary aldosteronism in hypertensive patients, but normokalemic primary aldosteronism appears at a frequency that is 7–38% higher than previously thought (141, 177, 178). Of 90 normokalemic patients with clinically inapparent adrenal masses and hypertension, at least 5.5% were found to suffer from primary aldosteronism (85), so screening all hypertensive patients with an adrenal mass for primary hyperaldosteronism is advisable.

The plasma aldosterone concentration (ALD)/plasma renin activity (PRA) ratio was found to be a sensitive and specific tool for diagnosis of disorders of the renin-angiotensin-aldosterone system (149, 179, 180). A ratio greater than 30 (ALD expressed in nanograms per deciliter, PRA in nanograms per milliliter per hour) is highly suggestive of autonomous aldosterone production, and additional testing for further evaluation is also recommended (141). A cut-off ratio of 50 was found to clearly distinguish primary aldosteronism from other forms of essential hypertension. However, a low renin level can result in an elevated ratio, even when aldosterone is in the low normal range, so use of the ALD/PRA ratio should be discouraged in this setting. Special attention should be given to kidney failure and concomitant medications such as beta-blockers and antisympathetic agents that may lead to false-positive test results by reducing PRA values. Calcium-channel blockers may increase PRA and reduce ALD to normal values in patients with primary hyperaldosteronism.

Additional testing using the 25-mg captopril test, salt-loading tests, or fludrocortisone suppression test can confirm the diagnosis of primary aldosteronism by demonstrating the presence of insuppressible aldosterone. In addition, the urinary excretion of methyloxygenated cortisol metabolites, *i.e.*, 18-hydroxycortisol and 18-oxo-cortisol, will usually be elevated. If the diagnosis of primary hyperaldosteronism has been made, an adrenal vein sampling or a scintigraphy with ^{131}I-iodocholesterol can be helpful in confirming lateralization of aldosterone production that is consistent with the presence of a mineralocorticoid-secreting adrenal mass. Here, the major concern is to differentiate aldosterone-producing adenoma from bilateral adrenal hyperplasia, because the detection of an adrenal mass does not necessarily prove its functional status (181). Although rare, the possibility of a malignant mineralocorticoid-secreting tumor has to be considered, especially when the tumor is large or radiological signs suggest malignancy (105).

3. Pheochromocytoma. Endocrine testing should exclude pheochromocytoma in all patients, including normotensive patients, with clinically inapparent adrenal masses because this is a frequent cause of clinically silent adrenal masses. Adequate biochemical testing will identify most pheochromocytomas. The diagnosis of pheochromocytoma is established by the demonstration of elevated 24-h urinary excretion of free catecholamines (norepinephrine and epinephrine) or catecholamine metabolites [vanillylmandelic acid (VMA) and total metanephrines]. The measurement of plasma catecholamines is not recommended, because this method has poor sensitivity and specificity often leading to false-positive results. Plasma free metanephrines, normetanephrine and metanephrine, have been reported to be more sensitive than other tests, including measurement of catecholamines in 24-h urine for diagnosis of sporadic pheochromocytoma (Table 2) (182–185). Although urine metanephrines and VMA have a higher specificity, receiver operating characteristic curves revealed a better test performance for plasma metanephrines than other biochemical tests (185). Special attention should be given to acetaminophen use, which interferes with assays of plasma free metanephrines and is a source of false-positive testing.

Pharmacological testing with agents such as glucagon or clonidine may be useful in diagnosis (94, 140, 186), although the glucagon test has been considered problematic because it may provoke hypertensive crisis. It should only be performed in patients with infrequent episodes without any severe symptoms during spontaneous hypertensive attacks. A continuous measurement of the blood pressure is highly recommended. Administration of a calcium-channel blocker before testing is to our experience appropriate to prevent pressure crisis, whereas others favor the administration of phentolamine in case of severe hypertension (187).

Although chromogranin A is not specific for pheochromocytoma and might be elevated in other neuroendocrine

TABLE 2. Sensitivities and specifities of biochemical tests for diagnosis of sporadic pheochromocytoma

	Upper reference limit	Sensitivity (%)	Specificity (%)
Plasma (nmol/d)			
Free metanephrines	0.3 (0.6)[a]	99	82
Catecholamines	0.5 (2.9)[b]	92	72
Urine (μmol/d)			
Fractionated metanephrines		97	45
Female	0.7 (1.7)[a]		
Male	1.2 (3.0)[a]		
Catecholamines	0.1 (0.5)[b]	91	75
Total metanephrines	6	88	89
VMA	40	77	86

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[a] Metanephrine (Normetanephrine).

[b] Epinephrine (Norepinephrine).

tumors, its evaluation can be useful. The level of chromogranin A correlates with tumor mass. Thus, small masses can go undetected by chromogranin A (188). However, postoperative levels have been reported to be a good index for a successful outcome of surgery or relapse, and levels within the normal range are highly predictive of negative findings in metaiodobenzylguanidine (MIBG) scintigraphy. Moreover, chromogranin A is poorly influenced by drugs commonly used in the diagnosis or treatment of pheochromocytoma such as phentolamine and clonidine (189). The production of calcitonin, opioid peptides, somatostatin, ACTH, and vasoactive intestinal peptide has been also described in pheochromocytoma. Another possible pheochromocytoma indicator is hyperglycemia, which occurs in about one third of all patients with clinically suspected pheochromocytoma, but is infrequently found in clinically inapparent adrenal masses.

4. Sex hormone-secreting masses. Most commonly, androgen- or other sex hormone-secreting masses represent adrenocortical carcinomas. If clinically inapparent at first diagnosis, signs of virilization or feminization may appear over time. Benign adenomas only rarely secrete sex hormones, so routine evaluation of testosterone and estradiol is not recommended in patients with adrenal masses (190). An exception should be made in patients with clinically suspected virilizing or feminizing tumor or if adrenocortical carcinoma is supposed on the basis of radiological studies and the patient's history.

Standard evaluation of dehydroepiandrosterone sulfate (DHEAS), a marker of adrenal androgen excess, has been suggested (5), but there is still controversy over its value. Based on age- and gender-specific thresholds, Terzolo *et al.* (191) assessed the performance of 0800 h DHEAS levels to differentiate malignant from benign adrenal masses. DHEAS was significantly higher in patients with primary adrenal carcinoma. However, at 100% sensitivity and 41% specificity, the diagnostic accuracy of low DHEAS levels in identifying a benign lesion was only 47% among the subjects analyzed. Other studies found no convincing data that DHEAS is helpful in discriminating malignant from benign masses (52, 59, 192, 193). In fact, results of a multivariate analysis indicate that DHEAS might be a function of tumor size (191). So, low to below-normal DHEAS levels in patients with (smaller) benign masses are explained by a negative feedback of autonomously cortisol-producing adenomas on the ACTH axis with suppressed DHEAS expression in the adjacent adrenal cortex (58, 74, 194). In conclusion, DHEAS does not appear to offer relevant information regarding the dignity of a mass.

B. Imaging studies

1. CT. CT is an accurate tool for detecting the presence of adrenal masses. Using a fast scanner and 1-m scanning intervals, both adrenals can be identified in 97–99% of patients. Numerous comprehensive reviews on the topic of radioimaging have been published describing the most common adrenal gland pathologies (195–200).

Using CT, adrenal adenomas are generally small, homogeneous, well-defined lesions with clear margins. Most adenomas remain constant in size on serial CT scans (37, 57, 63, 201, 202). Calcification, necrosis, and hemorrhage are uncommon. However, these features are nonspecific.

Most lesions smaller than 4 cm appear to be benign, but malignancy cannot be excluded by small size alone. Smaller size thresholds corresponded to higher sensitivity to diagnose malignancy and lower specificity, and vice versa (37, 203–207). No size threshold has yielded both high sensitivity and specificity. With the exception of one study finding attenuation values on unenhanced CT and mass size to be equally useful in diagnosing adrenal malignancy (205), attenuation thresholds have shown a better performance to diagnose adrenal malignancy and nonadenomas than size or subjective criteria (203, 206–208).

Frequently, adrenal adenomas contain a large amount of intracytoplasmic lipid, which allows a quantitative evaluation by measurement of the attenuation value of the lesions, conventionally expressed in Hounsfield units (HU) (203, 204, 208–213). Adenomas usually have attenuation values less than 18 HU on unenhanced CT. Perfect specificity with moderate sensitivity (68 and 89%) was achieved at higher density thresholds (20 and 21 HU) on unenhanced CT (203, 204, 206–208). Thresholds of 16.5 and 18 HU attained both high sensitivity and specificity (85–95% and 93–100%, respectively). Accordingly, it was concluded that further work-up is unnecessary when the lesion has an attenuation of less than 10 HU suggesting lipid-rich adrenal adenoma (203, 204, 208, 210–213). However, lipid-poor adenomas represent 10–40% of all adenomas (214, 215). These masses have a substantially higher mean attenuation value than lipid-rich adenomas. Thus, not all adenomas can be characterized using unenhanced CT alone.

On the other hand, adenomas are generally characterized by rapid washout of iv contrast. Although CT scans immediately after iv contrast have poor specificity to diagnose malignancy (66, 205, 210), enhanced CT test performance is excellent if the CT scan is delayed for 30–75 min and a threshold of 30–40 HU is used (204, 210). A 3-min delayed enhanced CT yielded good to excellent test performance using thresholds between 64 and 70 HU to differentiate nonadenomas from adenomas (204). Another advantage to delayed enhanced CT is the fact that lipid-poor adenomas show enhancement and washout features similar to lipid-rich adenomas, allowing a distinction from metastasis (214–216). Using a 10- to 15-min delayed enhanced CT, a threshold value of 50–60% of the initial enhancement is used to distinguish adenoma from nonadenoma (198, 211, 217). Without performing unenhanced CT beforehand, the relative enhancement washout is calculated as demonstrated in Fig. 4, A and B. Using this method, a relative washout of more than 40–50% is highly suggestive of a benign mass with a sensitivity of 96% and a specificity of 100%, whereas lower relative washout percentages strongly suggest a metastasis (196, 215, 218).

Studies that evaluated various subjective criteria for reading CT scans including homogeneity, distinctness and smoothness of margins, and irregular shape generally delivered poor test performance (37, 66, 203, 219).

Adrenocortical carcinomas are usually large, dense, irregular, heterogeneous, enhancing lesions that may invade

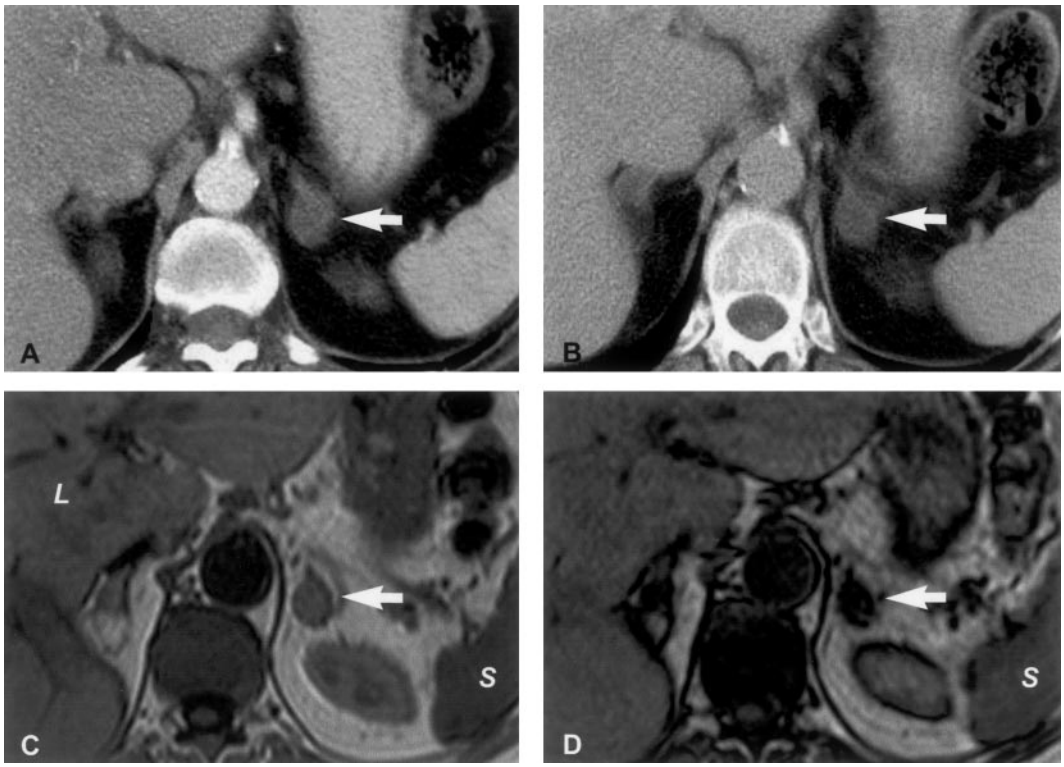

FIG. 4. Radiological panel of an adrenal cortical adenoma. Findings in a 66-yr-old woman with a history of breast cancer. Panels A and B demonstrate the use of CT for calculation of the relative enhancement washout. A, The contrast-enhanced CT shows a left-sided 1.5-cm adrenal mass (*arrow*) with a mean attenuation of 32.9 HU. B, On the 12-min delayed image, the attenuation of the left adrenal (*arrow*) is 12.9 HU. The relative enhancement washout is calculated using the following equation: percentage of relative enhancement washout = (1 − delayed enhanced HU value/initial enhanced HU value) × 100. With a relative washout of (1 − 12.9 /32.9) × 100 = 61%, the delayed enhanced CT is indicative of an adrenal adenoma (196, 215). Panels C and D depict the decrease in signal intensity in adrenal cortical adenoma using chemical-shift MRI. C, In the T1-weighted in-phase image, the signal intensity (SI) of the adrenal mass (*arrow*, SI = 131) is relatively isointense to the liver (L) and of slightly higher intensity than the spleen (S; SI = 93). D, The T1-weighted opposed-phase MRI shows a signal drop in the adrenal mass (*arrow*, SI = 39) relative to the spleen (S; SI = 110). The adrenal-spleen-ratio (ASR) is calculated by the following formula (Refs. 238 and 239): ASR = $[(\text{SI adrenal mass/SI spleen})_{\text{opposed-phase}}/(\text{SI adrenal mass /SI spleen})_{\text{in-phase}}] \times 100$. The diagnosis of an adenoma is confirmed by an ASR of [(39 /110)/(131 /93)] × 100 = 25.2.

other structures (37, 213, 220). Calcification and necrosis are common. Malignant tumors less than 6 cm in maximum diameter are often homogeneous and may resemble adenomas, so that in small masses morphological criteria are a poor predictor of diagnosis (201, 220, 221).

The morphological CT imaging features of metastases are nonspecific. Size varies from microscopic disease undetectable on imaging studies to extensively large masses. Small deposits tend to be homogeneous, but less well-defined than adenomas. Larger lesions may have irregular cystic areas as a result of hemorrhage or central necrosis. Calcification is rarely seen, suggesting previous hemorrhaging. Attenuation values on unenhanced CT images are generally higher than those measured in patients with adenomas, although a certain overlap has been observed in daily clinical practice (204, 211). Contrast enhancement can be homogeneous in smaller lesions and inhomogeneous in larger lesions. More recently, several studies have demonstrated a significantly delayed contrast material washout in metastases compared with adenomas (204, 210–212, 217).

Pheochromocytomas usually appear as rounded or oval masses with a similar density to the liver on unenhanced CT. Larger lesions may show a cystic component due to central necrosis or hemorrhage. Calcification is present in approximately 10% of cases. Owing to their hypervascularization, pheochromocytomas usually exhibit intense enhancement. With reported sensitivities ranging from 93–100%, CT is very accurate in the detection of adrenal pheochromocytomas (211, 213, 222–224). However, nearly one third of all cases show a nonspecific appearance that may overlap with the appearance of adrenocortical carcinoma.

The diagnosis of myelolipoma is made by demonstrating the presence of fat within an adrenal mass and can be easily accomplished with either CT or MRI (225–227). The mass typically has an attenuation ranging from −30 to −120 HU (228). Even if the tumor consists of small amounts of fat, it can be detected with narrow collimation. Diagnosis may be complicated by hemorrhage, with imaging findings of acute, subacute, or chronic hemorrhage that are superimposed over the lesion.

2. MRI. Both T1 and T2 relaxation times have been studied in MRI to differentiate between adenomas, metastases, and pheochromocytomas. In general, malignant masses are denser than benign masses, due to their higher fluid content, and therefore appear brighter on T2-weighted images (132,

229, 230). Metastases are usually hypointense compared with liver on T1-weighted images and hyperintense on T2-weighted images. After injection of paramagnetic contrast, metastases typically demonstrate strong contrast enhancement with delayed washout. Hyperintense signal on T2-weighted images and avid enhancement with delayed washout are features often shared by adrenocortical carcinomas, which usually contain less lipid than adenomas. However, multiple exceptions to these general rules have been described (such as fat-containing metastases from carcinomas and lipid-poor adenomas) (196, 209, 231).

MRI is also a useful tool in staging adrenal carcinomas. Sagittal and coronal magnetic resonance sequences allow a better identification of invasion into adjacent organs than do axial CT scans. In particular, the extent of infiltration into the inferior vena cava is best determined with MRI.

Pheochromocytomas are generally characterized by low T1 and bright T2 signal intensities, but exceptions to this rule have been published (232). Central necrosis is frequently observed. Because pheochromocytomas do not contain intracellular lipids, there are no signal changes from out-of-phase to in-phase images.

Fat-containing areas in myelolipoma are indistinguishable in signal intensity from sc and retroperitoneal fat in all sequences, but fat-saturated MRI can be performed to test for fatty content and facilitate diagnosis (226, 227).

Which MRI technique for accurate diagnosis of adrenal masses works best is still a matter of controversy. Chemical-shift MRI, based on the principle of different resonance frequency rates of protons in fat and water, has been proposed to differentiate between adenomas and metastases (198). Like the low attenuation seen with adenomas on unenhanced CT, the presence of lipids in many adenomas causes a loss in signal intensity on chemical-shift MRI (209, 233). In contrast, adrenal masses lacking cytoplasmic lipids do not have a significant loss of signal intensity on out-of-phase images, and appear brighter than lipid-rich adenomas. Generally, the ratio between the signal drop-off from T1-weighted in-phase to opposed-phase images of the adrenal mass and various organs including spleen, fat, liver, and muscle has been tested to distinguish between benign and malignant masses (50, 206, 207, 229, 232, 234–237). If the adrenal mass-reference organ-ratio, the ratio between signal intensities of the adrenal mass and the internal standard (such as the spleen) is less than 70, the lesion is regarded as benign (238, 239). An example is given in Fig. 4, C and D. When the mass-to-spleen ratio was used, masses were differentiated with a sensitivity of 84–100% and a specificity of 78–94% (206, 234–236).

Two studies found similar results with mass-to-liver and mass-to-fat ratios where high sensitivity was only achieved with poorer specificity, and vice versa (207, 229). Because of frequent intrinsic liver disease such as steatosis causing variable signal intensity, it has been discussed that liver might be a less reliable internal standard. Nevertheless, other authors have found better test performance using liver as the standard (232, 237, 240). With an overall accuracy of 94% (89% sensitivity and 99% specificity), MRI findings have been found to correlate closely with histopathological results using liver in T1- and T2-weighted images for unenhanced chemical-shift MRI and enhanced gadolinium series for washout characterization of 229 adrenal masses (232). These results were confirmed by a second study, with an analogous approach revealing a 100% sensitivity and specificity (240).

Trials comparing unenhanced MRI to combined unenhanced and enhanced CT found superior, similar, and inferior MRI test performance, depending on just which technique was used (206, 207, 219, 241). From qualitative comparison of test accuracy, the conclusion was that combined unenhanced and enhanced MRI was superior to both combined unenhanced and enhanced CT and unenhanced MRI alone (219). The combination of unenhanced CT with a threshold density of 0 HU and MRI with a mass-to-spleen signal intensity ratio of 0.70 resulted in perfect sensitivity and 94% specificity to diagnose metastases in cancer work-up patients (206). T2-spin measurements on MRI were an inferior parameter in diagnosing nonadenomas compared with attenuation values on CT (207). None of these studies was performed before the development of delayed enhanced CT for characterizing lipid-poor adenomas. In addition, there are no reported studies that compare unenhanced CT, delayed enhanced CT, and chemical-shift MRI for characterizing adrenal masses as adenomas *vs.* metastasis.

Preliminary data indicate that the use of double-echo chemical-shift gradient-echo MR imaging with a fast low-angle shot (FLASH) sequence can characterize adrenal adenomas without overlap in signal intensity with other masses (242, 243). Because an internal standard with a reference tissue is not needed for double-echo FLASH MRI, a better performance of MR imaging might be demonstrated in the future.

3. US. US depends to a large extent on operator skills. Furthermore, obesity and overlying gas are obstacles for the visualization of the adrenal glands (Fig. 5) (244). Not surprisingly, US does not detect adrenal masses with the same sensitivity as CT or MRI (245, 246). In a series of 61 patients with adrenal masses, US correctly identified all adrenal tumors over 3 cm in diameter, whereas only 65% of masses less than 3 cm were detected compared with 100% using CT or MRI (245). US (66, 247), color Doppler US, and power-flow imaging (248) each showed poor test performance for dis-

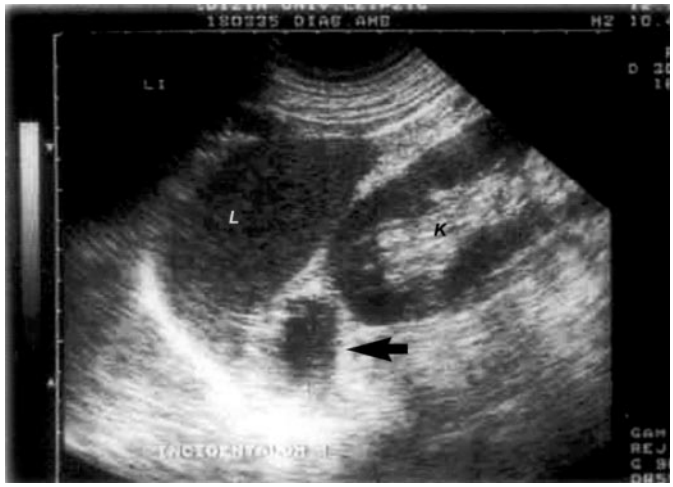

FIG. 5. Abdominal ultrasound. Incidentally discovered adrenal mass (*arrow*) in a 55-yr-old female. L, Liver; K, kidney.

tinguishing between benign and malignant masses, so their use is not recommended for this purpose. However, US can be a simple and effective follow-up method with benign lesions. The diameter of adrenal masses as measured by US correlates highly with mass diameter measured by CT (66, 249). Endoscopic US of the adrenal is a novel technique that has been recently performed in a few centers with promising results (250). Even small lesions of 1–2 cm could be detected reliably using this technique.

4. Scintigraphy. For adrenal cortical morphology and function imaging, two radiocholesterol derivatives have been mainly studied: ^{131}I-6-β-iodomethyl-norcholesterol (NP-59) and ^{75}Se-selenomethyl-19-norcholesterol (251, 252). One disadvantage with the radiotracers for adrenocortical scintigraphy is their inherent high radiation dose on the adrenal glands (253). The value of scintigraphy to diagnose adrenocortical masses has been analyzed by imaging patterns, relative uptake of marker, and concordance with CT. A concordant scintigraphic pattern, defined as a unilateral adrenal visualization or increased radiotracer uptake at the side of the detected mass, has been proposed as a typical pattern of benign cortical adenoma or nodular hyperplasia. In contrast, a discordant pattern with absent, decreased, or distorted uptake by the adrenal mass may indicate adrenocortical carcinoma, metastasis, or other nonfunctioning, space-occupying or destructive adrenal lesions. In patients with lesions larger than 2 cm, a nonlateralizing pattern with normal symmetrical adrenal uptake may be consistent with a pseudoadrenal mass (254). In cases of hyperaldosteronism or bilateral masses, a suppression scan improves the sensitivity of scintigraphy (255). As shown in Fig. 6, scintigraphy can delineate a functional mass after dexamethasone suppression of the normal adrenal cortex.

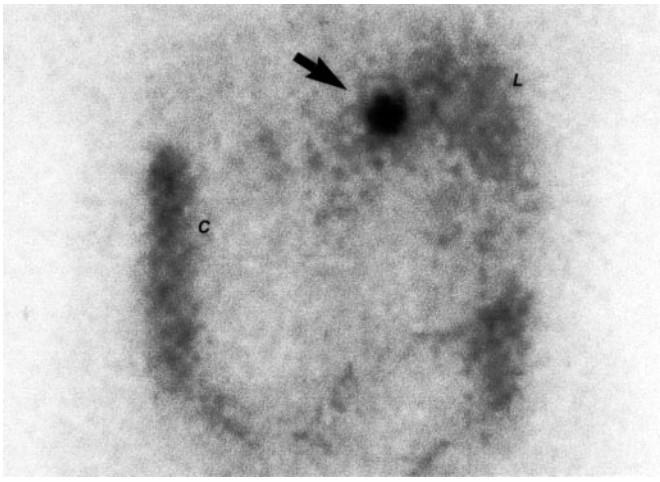

FIG. 6. Scintigraphy of an aldosterone-secreting adenoma. Posterior abdominal NP-59 scintigraphy in a 63-yr-old woman with bilateral incidentaloma, endocrine testing revealed primary hyperaldosteronism. Imaging 72 h after administration of 37 MBq NP-59 demonstrates a focal enhancement of the right adrenal (*arrow*) with minimal visualization of the contralateral gland and normal background activity of the liver (L) and colon (C) after dexamethasone suppression (0.5 mg three times daily for 3 wk). A right-sided laparoscopic adrenalectomy resulted in postoperative normalization of ALD and ALD/PRA. The histopathological diagnosis confirmed the presence of a 2.3-cm aldosterone-producing adenoma.

There is much variation in the definition of a positive test among studies evaluating NP-59 or ^{75}Se-selenomethyl-19-norcholesterol scintigraphy to distinguish malignant from benign lesions (38, 49, 58, 254, 256–259). Overall, scintigraphy achieved high sensitivity (71–100%) with varying specificity (50–100%) to differentiate malignant from benign adrenal masses. Some researchers found that scintigraphy may also be capable of differentiating or identifying autonomously secreting adenomas or hyperplasia from nonfunctioning adenomas and other adrenal diseases (256, 260–262). On the other hand, Osella *et al.* (74) concluded that NP-59 uptake simply reflects the presence of an enlarged adrenal gland and is not able to provide a functional characterization of an adrenal mass. Other authors believe scintigraphy is a more sensitive tool than biochemical testing for detection of SAGH (263).

For the localization and identification of pheochromocytomas and other sympathomedullary diseases, the radiopharmaceuticals ^{123}I-MIBG and ^{131}I-MIBG and ^{111}In-octreotide have been most commonly used (252). Any focal uptake 24–72 h after administration of ^{131}I-MIBG should be suspected of pheochromocytoma. The sensitivity of MIBG for detecting pheochromocytoma ranges between 80 and 90%, with a specificity of 90–100% (264–266). The synthetic somatostatin analog ^{111}In-octreotide seems less sensitive but is able to visualize tumors that are undetected by MIBG scan (267). In the diagnostic algorithm of clinically inapparent adrenal masses, the application of these radiotracers should be limited to cases in which malignant or bilateral pheochromocytoma is suspected (268).

5. Positron emission tomography (PET). Most malignant tumors show an enhanced glycolytic metabolism with increased uptake of deoxyglucose that can be visualized by PET using ^{18}F-2-fluoro-D-deoxyglucose (FDG). FDG-PET has been suggested for the characterization of adrenal masses in patients with either clinically inapparent adrenal masses or cancer work-up. Using a positive test definition of an increased uptake by the adrenal mass, one study found perfect test performance in differentiating malignant from benign adrenal masses (51). Other studies confirmed these results, so this technique may be of value if CT or MRI imaging is equivocal in the work-up of cancer patients with adrenal masses (269–272). In 10 patients with adrenocortical cancer, FDG-PET revealed three previously unknown lesions, but this study was too small to evaluate FDG-PET for staging and follow-up (273). A recent development in identifying adrenocortical tissue is the 11-β-hydroxylase radiotracer ^{11}C-metomidate, which discriminates lesions of adrenal cortical origin from other lesions; however, it does not distinguish between adrenal adenomas and carcinomas (274, 275). PET using ^{18}F-6-fluorodopamine has been found to be a promising tool for identifying pheochromocytomas (276). To date, there are insufficient data to justify the use of PET to diagnose clinically inapparent masses outside clinical studies.

C. Molecular markers

The histopathological distinction between malignant and benign tumors is often difficult to make early in the diagnosis

and treatment of adrenal diseases. Various criteria, immunological and cytoskeletal markers, DNA ploidy, cell phase markers, and oncogenic probes have been proposed for the differentiation of adrenocortical and medullary masses, but have so far yielded inconsistent results. An overview is given in Table 3 (137, 188, 277–311).

For adrenocortical tumors, the histological classification system by Weiss is most commonly used (312, 313). The Weiss criteria include: 1) high nuclear grade using the criteria of Fuhrman *et al.* (314); 2) mitotic rate greater than 5 per 50 high-power fields; 3) atypical mitotic figures; 4) eosinophilic tumor-cell cytoplasm (+75% of tumor cells); 5) diffuse architecture present in at least 33% of the tumor; 6) necrosis; 7) invasion of venous structures; 8) invasion of sinusoidal structures; and 9) capsular invasion. Less than three of these features are usually present in nonmetastasizing and nonrecurring tumors, whereas metastasizing and recurring tumors generally show more than three criteria. The mitotic rate was found to be an independent predictor of disease-free survival in adrenocortical carcinoma and is, in combination with the presence of venous invasion, correlated best with metastasizing behavior (312, 315).

Analysis of cellular markers might be helpful in reaching a differential diagnosis of adrenal masses, particularly if only small tumor specimens are available. An example is the transcription factor adrenal 4-binding protein, also known as steroidogenic factor-1, which is primarily expressed in steroidogenic cells and regulates the expression of the steroidogenic enzymes (292). Expression of α_1 connexin 43, a gap-junction protein, and major histocompatibility complex (MHC) class II is diminished in adrenocortical carcinomas as a sign of dedifferentiation and loss of normal zonation. It is abundantly expressed in the zona reticularis and fasciculata in normal adrenal tissue (Fig. 3A) as well as in most benign cortical tumors (296, 304). Mutations in genes such as IGF-II and p53 with subsequent overexpression and loss of heterozygosity (LOH) of chromosomal loci are thought to be involved in tumorigenesis, and have been found in sporadic adrenocortical carcinoma with varying frequency (13, 102, 277, 280, 282). Consequently, their absence does not prove the presence of an adrenal adenoma. Routine assessment of genetic alterations has been proposed as a guide for follow-up and management of adrenocortical carcinoma, because LOH at the 17p13 locus was found to be a strong predictor of disease-free survival after curative surgery (279).

Diagnosis of malignant pheochromocytoma is generally considered impossible without any documented metastasis formation. No markers so far allow a confident characterization of dignity. Microscopic evidence for local invasion of tissue or blood vessels, however, suggests malignancy (316). Although not always reliable predictors of biological behavior criteria based on tumor size, mitotic index and DNA ploidy have been reported as helpful (317–319). More recently, a scoring system based on a variety of histological features has been proposed to distinguish malignant from benign disease (320). A number of immunohistochemical markers are specific for neuroendocrine tumors and are strongly positive in tumors of adrenomedullary origin. Chromogranin A (Fig. 3, C and D) and synaptophysin (Fig. 3, F and G) have been widely used. However, recent data have demonstrated a positive staining for synaptophysin in adrenocortical tumors as well, reducing the value of this marker (136, 137, 307). Survivin, an apoptosis inhibitor, is a novel neuroendocrine marker for chromaffin cell tumors, but does not reliably distinguish benign from malignant tumors (308). Besides the well-described mutations of the RET protoon-

TABLE 3. Molecular and cellular markers in the diagnosis of adrenal masses

Markers	Tumors	Expression
LOH 17p13/p53 mutation	ACC	Present, overexpression of p53 (277–279)
LOH 11q3	ACC	Present (280)
LOH 11p15.5/IGF-II mutation	ACC	Present, overexpression of IGF-II (281–283)
RET protooncogen, VHL tumor suppressor gene, SDHD, SHDB	Pheo	Present in 24% of sporadic tumors (284)
Bcl-2	Malignant pheo	Higher expression (285)
TGF 1mRNA	ACC	Reduced (286)
Telomerase activity	ACC	High activity (287, 288)
	Malignant pheo	High activity (289)
Ploidy	Malignant pheo	Non-diploidy commonly present (290, 291)
Adrenal 4 binding protein	ACC	Adrenocortical marker (292)
ACTH	Malignant pheo	Overexpression (293)
Chromogranin A	Pheo	Increased plasma levels (188, 294, 295)
α1 Connexin 43	ACC	Decreased (296)
Cyclooxygenase 2 (Cox-2)	Malignant pheo	Elevated (297)
NSE	Malignant pheo	Increased (298, 299)
Ki-67	ACC	Increased (277, 300, 301)
	Malignant pheo	Increased (302, 303)
MHC class II	ACC	Absent (304)
Nuclear D11 immunoreactivity	ACC	Present (305–307)
Survivin	Pheo	Strongly expressed (308)
Tenascin	Malignant pheo	Strongly expressed (309)
Inhibins/activins	Malignant pheo	Reduced (310)
Synaptophysin	ACC	Present (307)
	PPNAD	Present (137)
	Pheo	Present (311)

ACC, Adrenal cortical carcinoma; NSE, neuron-specific enolase; Pheo, pheochromocytoma; PPNAD, primary pigmented nodular adrenocortical disease.

cogene and the tumor-suppressor gene VHL, which are associated with familial and syndromic disease (MEN II and VHL), mutations of the succinate dehydrogenase subunit D (SDHD) and subunit B (SDHB) have recently been demonstrated in pheochromocytoma (94, 284). Interestingly, Neumann *et al.* (284) found mutations of RET, VHL, SDHD, and SDHB in one fourth of more than 270 patients with sporadic pheochromocytoma.

D. Fine-needle aspiration (FNA)

Transcutaneous needle biopsy or FNA of adrenal mass has been advocated for the investigation of incidentally discovered adrenal masses (321). The biopsy is generally performed under either CT or US guidance. The literature on FNA is problematic in that many studies investigating the test performance for FNA to diagnose adrenal masses either did not clearly define the reference standard or, in part, used FNA as both test under investigation and reference standard. Nevertheless, excluding biopsies that were inconclusive, eight studies showed that sensitivity for all patients (or masses) to diagnose malignancy ranged from 81–100% and specificity ranged from 83–100%, whereas one reported only that accuracy was 91% (322–327). Between 6 and 50% of biopsies were reported to be inconclusive.

Test performance based on mass size and needle size was analyzed in one study (328). The authors found higher sensitivity and accuracy in masses larger than 3 cm and when 19-gauge or larger needles were used. Another study reported that accuracy depended on the size of the needle used to perform the biopsy but not on the size of the lesion (326). However, the evidence is too sparse to draw conclusions about the test performance of different methods of adrenal biopsy (such as FNA *vs.* coring biopsy).

The risk of complications due to FNA has primarily been reported in retrospective studies (36, 235, 322–326, 328–333). Only two studies found explicitly reported data on metastatic spread of cancer along the needle tract (326, 333). In a 1-yr follow-up of 277 adrenal biopsies in 270 patients, none of the patients developed metastases along the needle tract (326). With a 7-month follow-up in 78 patients, one needle-track lung tumor metastasis was detected in the liver of a patient who had had two passes using the supine transhepatic approach (333). Neither paper provided data on the number of subjects with adrenal carcinoma, so no conclusions can be offered about the risk of needle-track metastases from FNA biopsy of adrenal carcinoma. In total, 36 complications (4%) have been reported on 888 adrenal mass biopsies, including 26 complications that were potentially serious and nine patients (1%) requiring in-hospital treatment. Because of the wide variety of biopsy techniques, generally unclear or incomplete reporting, and small study sizes, no reliable estimates can be made about the relative safety of different biopsy techniques.

Because a benign cytological diagnosis from FNA does not exclude malignancy, FNA cannot be recommended as a standard procedure in the diagnostic work-up. However, FNA may be helpful in the diagnostic evaluation of patients with a history of malignancy and those with a suspicious adrenal mass on imaging (334, 335). Importantly, to prevent a potentially life-threatening hypertensive crisis, FNA should not be attempted before exclusion of pheochromocytoma by endocrine testing.

IV. Treatment

A. Surgical procedures

Initially, all adrenalectomies were performed via the transabdominal route. In the 1980s, the posterior approach was adopted by the majority of surgeons due to a perceived decrease in surgical morbidity. The posterior approach was first used for small tumors and later for large tumors, pheochromocytomas, and metastases.

In the early 1990s, Gagner *et al.* (336) applied the laparoscopic technique to the transperitoneal approach. As with the posterior approach, initial indications were limited due to concerns about bleeding, the safety of removing pheochromocytomas (especially under carbon dioxide insufflation, which might theoretically trigger a hypertensive crisis), the inability to perform en bloc resections of invasive tumors, and the fear that removing cancers laparoscopically could result in metastatic seeding along the trocar port. As surgeons gained experience, indications for laparoscopic adrenalectomy expanded to include large tumors, pheochromocytomas, and metastases. Similar to other procedures, a significant reduction of mean operative time and mean blood loss due to learning curves has been reported for laparoscopic adrenalectomies (337–340).

Other surgical techniques have been recently developed, including retroperitoneal laparoscopic adrenalectomy, needlescopic surgery using laparoscopic instruments with a diameter of no more than 3 mm, interstitial adrenal cryoablation, and robotic telepresent adrenalectomy (341–349). The techniques of open and laparoscopic adrenalectomy have been covered elsewhere (350, 351).

There are a number of surgical series reports on either individual experiences with a given adrenalectomy technique or technique comparisons. Many studies, however, have overlapping data, because authors presented their initial experience with the procedure, then included those same cases in larger (accrued) case series or regional experience reports. A summary of surgical approaches is given in Table 4 (337–339, 344, 345, 352–431).

There are 31 studies covering more than 1600 patients that compared open and laparoscopic approaches for adrenalectomy (337, 394–421, 431, 432). All studies consisted of a case series collected prospectively or retrospectively and compared with historical controls, and occasionally matched for surgical indication and tumor size. Because most studies did not use matched controls, tumor sizes and types are often not comparable between study arms, introducing a considerable bias. In general, a series of open approaches had a higher percentage of pheochromocytomas and adrenocortical carcinomas and a larger tumor size than laparoscopic approaches.

Although most studies reported all complications, only five of them applied statistical methods for comparison of the complication rates. Sprung *et al.* (414) reported a higher rate of hypotension with anterior open adrenalectomy (AA) com-

TABLE 4. Summary of surgical approaches

Studies (N)	Patients (N)	Tumor type (%)	Tumor size (cm)[a]	Surgery time (min)[a]	Blood loss (ml)[a]	Length of stay (d)[a]	Complications (%)		
							Death	Major	Minor
Open transperitoneal adrenalectomy case series (352)									
1	55	Pheo 38, ACC 0, Met nd	4.7 (0.7–8)	nd	nd	nd	0	13	9
Open retroperitoneal adrenalectomy case series (353–360)									
8	470	Pheo 0–41, ACC 0–13, Met 0–6	1.5–4.3 (0.5–14)	84–200 (45–355)	232–237 (30–4500)	4.3–8 (1–21)	0–3	2–24	0–14
Comparative studies of open adrenalectomy techniques (361–364)									
4	AA 228	Pheo 0–24; ACC 0–48, Met 0	6.8/160 g	95–160	405–1050	9–16	0–6.8	6–47	2–36
	PA 338	Pheo 0–17, ACC 0–6, Met 0	7.0/12 g	85–101	288–300	5–13	0–1.5	4–25	15–20
TLA case series (339, 365–383)									
20	1189	Pheo 0–38, ACC 0–4, Met 0–19	2.0–5.1 (0.5–14)	92–253 (70–360)	49–216 (20–1300)	2.0–11.6 (1–23)	0–1	0–25	0–72
RLA case series (384–393)									
10	537	Pheo 0–22, ACC 0–1, Met 0–10	1.7–3.4 (0.2–7)	97–248 (45–419)	44–240 (0–800)	1.0–10.6 (1–21)	0–1	0–10	0–63
Open *vs.* endoscopic adrenalectomy techniques (337, 394–421, 431, 432)									
31	1650	See text for specific information							
Comparative studies of endoscopic adrenalectomy techniques (338, 344, 345, 370, 422–430)									
13	1217	See text for specific information							

ACC, Adrenal cortical cancer; Met, metastatic cancer; N, number of subjects; nd, no data; Pheo, pheochromocytoma.
[a] Mean (range).

pared with the transperitoneal laparoscopic adrenalectomy (TLA) for pheochromocytoma. Jacobs *et al.* (404) found fewer major complications from TLA compared with a mixture of open approaches. Bonjer *et al.* (395) found fewer overall complications from retroperitoneal laparoscopic adrenalectomy (RLA) than from the posterior open approach (PA). Vargas *et al.* (418) also reported fewer complications from TLA than from open procedures, although the difference did not reach statistical significance. Finally, Thompson *et al.* (416) found a comparable rate of early complications between TLA and PA, but an increased rate of late complications with PA, specifically muscle weakness and pain at the incision site. In two studies, AA and TLA each resulted in one death, neither of which was considered by the authors to be related to the surgery; there were no deaths from PA or RLA (397, 398).

PA was significantly quicker than TLA in most studies and quicker than RLA in one of two studies (395–397, 401, 403, 409, 416, 417, 431). However, TLA resulted in less blood loss and a shorter length of stay (395, 397, 401, 404, 406, 409, 416, 417, 431). The remaining studies did not find any significant differences between specific techniques. Studies comparing mixed open approaches or mixed laparoscopic techniques showed similar findings; laparoscopy usually took longer, but resulted in less blood loss and a shorter hospital stay (404, 405, 407, 410, 411, 413, 415, 418–420).

In a cost-effectiveness analysis, costs of hospital admission for laparoscopy (TLA) were significantly reduced by 38% in comparison to open adrenalectomy (AA and PA), mostly due to a reduced postoperative stay (3.7 *vs.* 5.8 d) (421). These data are consistent with results from other retrospective cost analyses of laparoscopic and open adrenalectomy (399, 411). Because there was no difference in the overall costs per patient, the authors concluded that from the economic perspective, greater savings must come from a reduction in the presurgical diagnostic process, which constituted the lion's share of the total costs (421).

Ten studies comparing different laparoscopic approaches, which included 1014 patients (338, 344, 345, 422–427, 429), as well as two studies that compared surgery for large and small tumors using TLA (428, 430), were generally of better quality than earlier series comparing laparoscopic and open adrenalectomy. There is even one small, prospective, randomized controlled trial (370). A few studies collected data prospectively, but because the surgeon still dictated the choice of approach, it is possible that bias may have been introduced. Patients were generally well-matched by tumor size and type. Most studies found no significant difference in operating time or blood loss, although one study found RLA to be quicker than TLA (423) and another found that lateral TLA was quicker than either anterior TLA or RLA (427). None of the studies demonstrated any difference in length of stay, and none applied statistical methods to complication rates. One study comparing needlescopic surgery to traditional TLA demonstrated that the needlescopic group had shorter operating time, less blood loss, and shorter hospitalization, although tumors removed needlescopically both were larger and contained a higher percentage of pheochromocytomas (344). There were also fewer complications in the needlescopic group, but due to the small sample size, the difference did not reach statistical significance.

In a study that compared surgery for large (mean, 5.2 cm) and small (mean, 2.1 cm) tumors using TLA in 150 patients, the authors found no difference in operating time, length of stay, or complication rate (428). A subsequent study investigating TLA in 53 patients with large (median, 8.0 cm) or small (median, 2.5 cm) adrenal tumors reported successful completion of all procedures without any differences in outcome or complication rate (430). Finally, transperitoneal needlescopic adrenalectomy may offer the least morbid procedure, with the least blood loss, the shortest hospital stay, and a low complication rate. However, given that only a small number of these procedures have actually been reported, it would be premature to assign needlescopic surgery any role in adrenalectomy (344, 345).

Despite the large number of studies involving thousands of patients, the quality of the evidence comparing surgical techniques is poor. Randomized, controlled trials are lacking, and nonrandomized series risk a significant selection bias because surgeons routinely assign more difficult cases, larger tumors, and invasive cancers to the control group. Nevertheless, the evidence consistently points in the same direction for small, nonmalignant tumors, and possibly for large tumors as well. The PA appears to offer an advantage over the AA in terms of surgical morbidity, as measured by postoperative hospital stay and perhaps in terms of operating time and blood loss as well (361–364). Similarly, both laparoscopic techniques, the RLA and TLA, result in shorter hospital stays than open surgery. TLA and RLA result in less blood loss and probably fewer major complications, but PA is quicker. When performing laparoscopic adrenalectomy, lateral TLA may be quicker and cause less blood loss than either RLA or anterior TLA, but in terms of hospital stay and complication rates, no approach appears to be superior to the others. Although randomized, controlled trials would offer the best measure of the safety of laparoscopy *vs.* open surgery, it is unlikely that such trials will be conducted given the ostensible benefit seen in the nonrandomized trials and the current prevailing thought among surgeons.

For invasive carcinomas and very large tumors, the best approach has yet to be determined. Few reports have examined these specific indications, and many authors consider them contraindications to laparoscopy (433, 434). Others, however, have challenged these limitations, operating on large tumors and potential carcinomas, although the latter are usually converted to open procedures once they are definitively identified (435, 436). Especially in these areas still open to debate, randomized controlled trials are most needed and most appropriate.

B. Surgery vs. nonsurgery management

Surgery should be considered in all patients with functional, clinically apparent cortical tumors, whereas treatment strategies for patients with asymptomatic adrenal hormone excess are not always straightforward.

Prompt surgical resection is the standard curative modality for all patients with pheochromocytoma because of the risk of hypertensive crisis and its complications (86, 94). For patients with benign pheochromocytoma localized to the adrenal gland, survival after adrenalectomy is similar to that of the normal age-matched population. For patients with unresectable, recurrent, or metastatic disease, long-term survival is possible with an overall 5-yr survival of less than 60% (437, 438). Pharmacological treatment of the catecholamine excess is mandatory, and surgery, radiation therapy, or chemotherapy may provide some palliative benefit.

If primary aldosteronism can be attributed to an adrenal mass, surgical resection is the treatment of choice (439). Prolonged hypertension, however, may not resolve with excision (353, 355). If surgery is contraindicated, long-term medical therapy consists of potassium-sparing diuretics. The aldosterone antagonist, spironolactone, often corrects the hypertension; in most patients, hypokalemia can be controlled (439). A disadvantage of long-term use is the antiandrogenic side effects of spironolactone, which often result in impotence and gynecomastia.

SAGH presents a diagnostic and therapeutic problem. Both adrenalectomy and careful observation have been proposed as alternative treatment options (153). Although adrenalectomy has been shown to correct the biochemical abnormalities associated with this condition, its effect on prognosis and quality of life is unknown (67, 70, 81, 162). Some preliminary results suggest that after surgery, hypertension, obesity, and non-insulin-dependent diabetes mellitus may improve, but data are still inconsistent (67, 70, 81, 173). After adrenalectomy for SAGH, adrenocortical insufficiency is a major risk (81). Patients undergoing mass excision for SAGH should receive perioperative glucocorticoids and should be monitored for HPA axis recovery and clinical improvement (440). Guidelines for follow-up of patients who do not undergo resection have yet to be defined.

In patients with nonfunctioning incidentally discovered adrenal masses, management begins after distinguishing between malignant and benign tumors. Size has traditionally been the major predictor of malignancy. Benign adenomas account for more than 60% of masses under 4 cm in diameter, but less than 15% of those over 6 cm. The risk of primary adrenal carcinoma, on the other hand, is less than 2% in inapparent adrenal masses under 4 cm, but rises to 25% in lesions greater than 6 cm according to surgical series reports. Therefore, the general practice is to excise lesions larger than 6 cm. Lesions smaller than 4 cm, defined as low risk by imaging criteria, are unlikely to be malignant and are generally not resected. For intermediate lesions between 4 and 6 cm, either adrenalectomy or close follow-up is reasonable. If the findings from imaging studies, growth rate, decreased lipid content, and other features suggest that the lesion is not an adenoma, adrenalectomy should be strongly considered. Importantly, various size criteria are to some degree arbitrary and should not be the sole basis for treatment decisions (203, 207, 441, 442).

Early detection of adrenocortical carcinoma is crucial, because surgical resection of localized carcinoma (stage I and II) offers the only prospect for cure. At more advanced stages, surgical debulking may increase the efficacy of adjuvant therapy if total or near-total excision can be achieved (102, 114, 437), although published data on this approach have been conflicting (109, 118, 119, 443). Table 5 presents an overview of the outcomes of adrenocortical carcinoma after surgical excision (97, 98, 106–116, 118, 444–458). Most of

these studies are retrospective, with wide variations in the quality and quantity of reported information about tumor size, patient characteristics, surgical approaches, and outcomes. Eighteen studies reported 5-yr survival data that ranged from 19–62%, with a median of 35% (weighted average, 34%). In cases where total surgical extirpation was not possible, the 5-yr survival rates were 10–30%. Although overall survival rates are comparable in earlier and more recent series, the studies included patients from a wide range of years, making it difficult to discern any temporal trend. Neither age nor tumor size appears to influence prognosis after surgery.

Finally, there is no established clinical benefit to be derived from adrenalectomy in those patients who are diagnosed with a metastasis from a known or unknown primary neoplasm during their evaluation for a clinically inapparent adrenal mass (121, 459–462). Nevertheless, long-term survival has been reported in selected patients, mostly with non-small cell lung cancer, after early resection of isolated adrenal metastasis. Chemotherapy or radiation should be considered depending on the histology of the tumor.

C. Follow-up

There have so far been few studies with prespecified protocols that have prospectively investigated changes in tumor size or the development of hormone overproduction in untreated adrenal masses (45, 202, 463). Most data originate from studies with variable stringency, so the limited and incomplete evidence available precludes making any specific recommendations for follow-up (30, 54, 57, 63, 201, 464–467).

Long-term follow-up studies suggest that the large majority of adrenal lesions remain stable, whereas 3–20% enlarge and 3–4% may decrease in size (57, 63, 202, 467). For those patients whose lesions have not been excised, a CT study repeated within 6–12 months of the first imaging is reasonable. For lesions that do not increase in size, there are no data to support continued radiological evaluation. This observation is based on longitudinal studies of up to 10 yr reporting that the risk of developing adrenal cortical carcinoma remains extremely low (63, 202). However, small changes of size may apparently reflect a more aggressive growth rate. When a mass increases in diameter by one fourth, its volume approximately doubles.

Endocrine hyperactivity may develop in up to 20% of patients during follow-up, but is unlikely in lesions smaller than 3 cm. Cortisol hypersecretion is the most common disorder to develop. Progression to overt Cushing's syndrome may occur, but this is rare (202). At variance with previous reports, Barzon *et al.* (151) have recently reported that SAGH carries an estimated cumulative risk of 12.5% of developing Cushing's syndrome after 1 yr. Prevalence data, though, have found that the vast majority (99.7%) of patients with SAGH do not progress to overt Cushing's syndrome (154). The onset of catecholamine overproduction or hyperaldo-

TABLE 5. Morbidity and mortality of adrenocortical carcinoma after surgical excision

Author, year (ref.)	N	Enrollment period	Tumor size[a]	Long-term survival
Sullivan 1978 (444)	28	1950+	(3.5–20 cm)	5 yr 30%
King 1979 (445)	49	1956–77	12.4 cm	9/49 alive, mean 7.2 yr post-surgery
Didolkar 1981 (108)	42	1929–77	(1–30 cm)	5 yr 62%
Nader 1983 (97)	77	1950–81	nd	5 yr 23%
Henley 1983 (118)	62	1960–80	12.4 cm	5 yr 32%
Lefevre 1983 (446)	42	1958–80	~350 g (20–1400)	1 yr post-surgery 82%
Watson 1986 (447)	80	1970–79	10.5 cm	2 yr 33%
Nakano 1988 (113)	91	1965–82	~730 g (12–2900)	Mean, 18.5 months
Venkatesh 1989 (116)	110	1944–87	nd	5 yr DF, 42% overall
Luton 1990 (112)	88	1963–87	~530 g (14–3000)	5 yr 22%
Ribeiro 1990 (448)	40	1966–87	256 g	Overall 51%
Grondal 1990 (109)	54	1974–83	(5–40 cm)	5 yr overall 19%
Soreide 1992 (98)	99	1970–85	nd	6 yr ~60%
Icard 1992 (110)	156	1978–91	12 ± 6 cm (SD)	5 yr overall 34%
Pommier 1992 (114)	73	1980–91	nd	5 yr 47%
Sabbaga 1993 (449)	55	1969–91	nd	2 yr overall 46%
Zografos 1994 (450)	53	1950–90	(0.3–35 cm)	5 yr overall 19%
Kasperlik-Zaluska 1995 (111)	50	1965–94	(3.2–20 cm)	2 yr 29%
Lee 1995 (451)	23	1965–91	14.5 (1.7–25) cm	Overall median, 29 months
Boscaro 1995 (107)	35	1978–93	12 cm (4.5–21)	Mean, 18.5 months
Evans 1996 (452)	56	nd	15 cm (5.5–25)	5 yr ~40%
Sandrini 1997 (453)	58	1966–92	nd	DF, 60 months median
Michalkiewicz 1997 (454)	20	1988–94	68.5 g (11–195)	Mean, 29.6 months
Barzon 1997 (106)	45	1978–95	11 cm (4–21)	5 yr overall 29%
Khorram-Manesh 1998 (455)	18	1975–97	~11.9 cm	5 yr overall 58%
Teinturier 1999 (456)	54	1973–93	28/54 > 10 cm	5 yr overall 49%
Harrison 1999 (457)	46	1986–96	15 cm (2.5–27)	5 yr 36%
Tritos 2000 (115)	24	1966–96	10 cm (2–25)	5 yr 26%
Kendrick 2001 (458)	58	1980–96	12.5 cm (5–23) 604 g (32–3060)	5 yr 37%

DF, Disease-free; N, number of evaluated subjects; nd, no data.
[a] Mean (range).

steronism during long-term follow up is very rare (202). To rule out new endocrine activity, an overnight 1-mg dexamethasone suppression test and urine catecholamines/metabolites at yearly intervals may be reasonable. The risk of tumor hyperfunction appears to plateau after 3–4 yr. However, the limited and incomplete evidence available precludes any specific recommendations.

V. Conclusion

Clinically inapparent adrenal masses are neither a single pathological entity nor a disease. Overall, sparse data exist that might help guide their management. Most of the available studies are either too low in numbers to provide meaningful results, or they suffer from methodological problems. A strict definition of clinical inapparent adrenal masses would help in the interpretation of results from clinical studies; however, it will not be sufficient to address the diverse manifestations of this condition that are also clinically relevant. The prevalence of incidentally discovered adrenal masses and the likelihood of underlying pathologies vary according to the defining criteria. In studies of general population, adenoma is generally the most common cause of clinically inapparent adrenal masses, whereas metastases are most common in studies with cancer work-up patients. Many studies assumed that the major purpose of the further evaluation of adrenal incidentalomas is the detection of adrenal carcinomas. Given the rarity of this tumor and the lack of effective therapy in the later stages, the overall benefit of detection is small. In contrast, biochemically active, subclinical adenomas are common. Given the high prevalence of this condition and the significance of hypertension and diabetes as causes of cardiovascular diseases, the detection of these tumors and the expected health benefits from optimal management may become the prime reason for aggressive intervention with clinically inapparent adrenal masses. A better understanding is needed of the prevalence and long-term clinical outcomes of this condition.

Recently, the NIH State-of-the-Science Conference proposed a minimal standard evaluation based on the prevalence of hypersecretory adrenal masses, cost-effectiveness analysis, and good evidence for testing of clinically suspected adrenal diseases (Fig. 7) (19, 20). Accordingly, pheochromocytomas should be ruled out in all patients. Emerging data suggest that plasma free metanephrines can be measured with high diagnostic accuracy and may replace or complement the measurement of urine metanephrines and catecholamines. An overnight 1-mg dexamethasone suppression test should be performed in all patients to detect SAGH, even if the link between this disorder and long-term morbidity is still controversial or if treatment to reverse subtle glucocorticoid excess is beneficial. In all patients suffering from hypertension, serum potassium and ALD/PRA ratios should also be determined to evaluate potential cases of primary aldosteronism. Exceptions to these recommendations would include patients with myelolipoma imaging characteristics or adrenal cysts. Given the rarity of sex hormone-secreting incidentalomas, evaluation of these parameters should be restricted to patients in which hypersecretion is suspected, such as in cases of suspected adrenocortical carcinoma. There are insufficient data to support biochemical testing for the diagnosis of malignant tumors.

In contrast, imaging study is an essential component in the diagnostic algorithm of clinically inapparent masses. Unenhanced CT characterizes a homogeneous mass with an attenuation value of less than 10 HU as a benign adrenal adenoma with high specificity and acceptable sensitivity. Alternatively, contrast-enhanced dynamic and delayed CT with values of less than 30–37 HU (depending on the duration of delay) or a relative washout of more than 50–60% suggests a benign mass, whereas lower relative washout percentages strongly suggest a malignant lesion (196, 198, 214, 215, 217). Chemical-shift MRI does not provide additional information beyond what is already available on unenhanced CT, but MRI may also be useful in ambiguous cases. Due to the augmented accuracy of CT evaluation that includes delayed enhanced CT for characterizing lipid poor adenomas, CT seems be more accurate than MRI for distinguishing adenomas from metastasis. Radionuclide scintigraphy using NP-59 for the evaluation of adrenocortical lesions and MIBG for pheochromocytoma as well as PET are not yet widely available, and there are insufficient data regarding their clinical usefulness in clinically inapparent adrenal masses.

There is little in the way of substantial data regarding the utility of FNA in patients with an incidentally detected adrenal mass, but without a history of malignancy. There are also no reliable tumor markers yet that can differentiate between benign and malignant adrenocortical or adrenomedullary tumors. Thus, FNA cannot be recommended as a standard procedure in these patients' diagnostic work-up. FNA may be helpful in the diagnostic evaluation of patients with a history of cancer (particularly lung, breast, and kidney), but without any other outward clinical signs of metastasis and a heterogeneous adrenal mass with a high attenuation value on unenhanced CT (>20 HU). It is important to note that a benign cytological diagnosis on FNA does not totally exclude malignancy. If FNA is attempted, pheochromocytoma should always be excluded to avoid hypertensive crisis.

Surgery should be considered in all patients with functional cortical tumors associated with clinical symptoms and is strongly recommended for pheochromocytomas. Whether or not patients with subclinical hypersecretory adrenocortical masses profit from surgery is still unclear. The generally accepted recommendation regarding nonfunctional masses is to excise lesions larger than 6 cm, whereas masses less than 4 cm without suspect imaging are not generally resected. For lesions between 4 and 6 cm, either close follow-up or adrenalectomy is considered a reasonable approach. The high growth rate (or short doubling time) and extremely low incidence of adrenocortical carcinomas suggest that a judicious follow-up strategy is sufficient to reassure incidentaloma patients. A reasonable approach for unresected masses includes a CT study repeated 6–12 months after the initial imaging and periodic hormonal testing at annual intervals (or earlier if clinically indicated) for 3–4 yr. However, the clinical condition and personal concerns of an individual

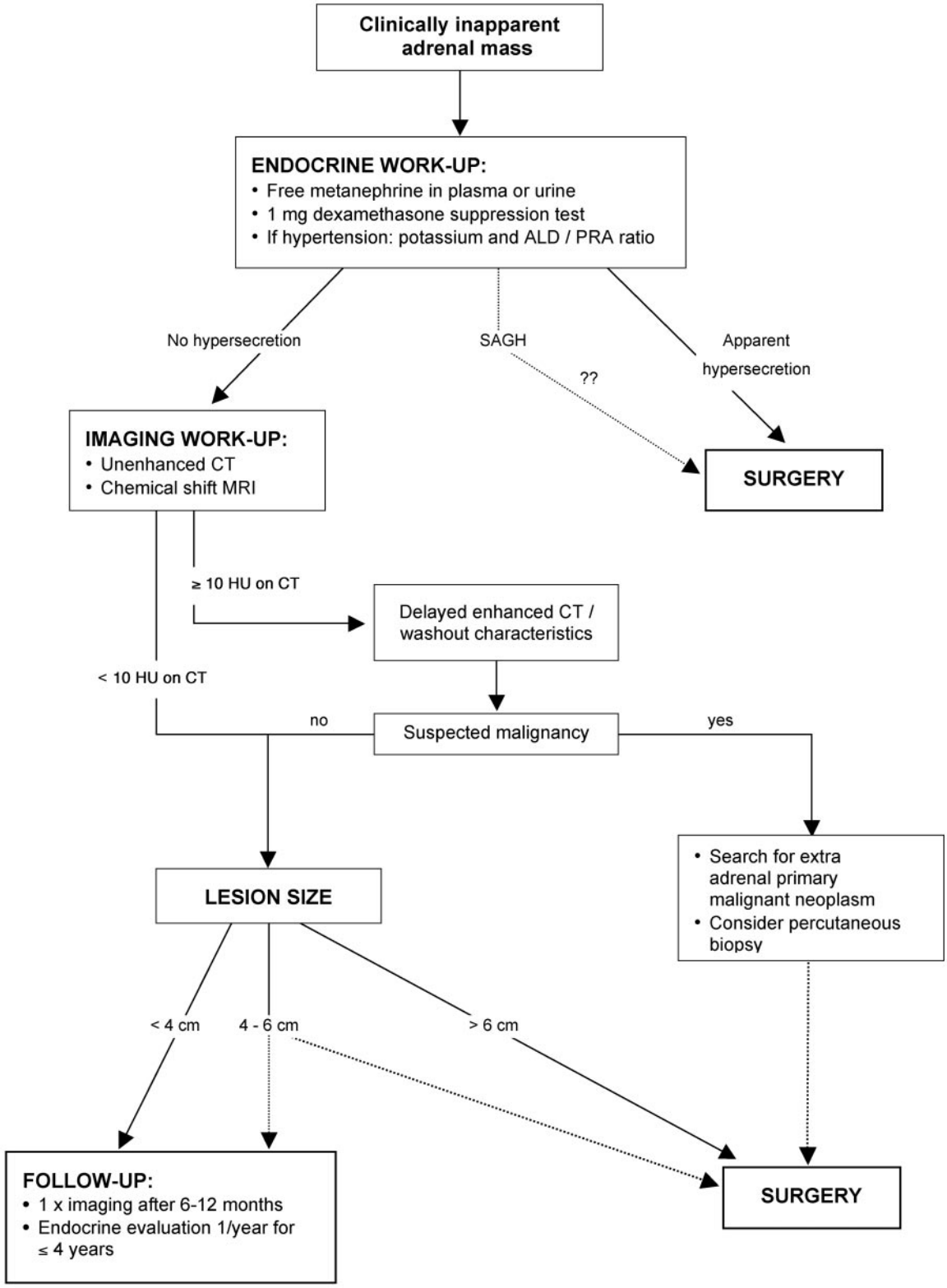

FIG. 7. Recommendations for practical management of clinically inapparent adrenal masses as proposed by the NIH State-of-the-Science Conference (19). pheo, Pheochromocytoma.

patient should be taken into account when making treatment and follow-up recommendations.

If resection of the mass is warranted, open and laparoscopic adrenalectomy are both acceptable procedures. Whereas in most specialist centers laparoscopic adrenalectomy is currently the procedure of choice, there are no pro-

spective, randomized trials comparing open and laparoscopic adrenalectomy. The laparoscopic approach may have advantages over the open approach when performed by a surgical team experienced in advanced laparoscopic techniques, including decreased postoperative pain, reduced time to return of bowel function, decreased length of hospital stay, and the potential for earlier return to work. Operative mortality associated with adrenalectomy is less than 2%, and for many indications less than 0.5%. There are no studies that demonstrate a consistent benefit of one laparoscopic approach over another. At present, relative contraindications to laparoscopic adrenalectomy are a definitive or presumed diagnosis of invasive adrenocortical carcinoma or circumstances, such as large tumors, that make a minimally invasive approach technically difficult.

VI. Perspectives

Management of adrenal masses will remain a complex decision-making process involving a range of possible diagnoses for consideration, choosing additional diagnostic tests and interpreting their results, understanding the natural history of various adrenal pathologies, estimating the benefits and risks of interventions, and customizing the therapy based on patient age and lesion size. Besides endocrine testing to reveal hormone-producing masses, imaging studies play a fundamental role in the diagnosis of an adrenal mass. The use of advanced radiological techniques can rule out malignancies with high confidence. Still, treatment outcomes for advanced adrenocortical carcinomas are poor. Gene therapy has been recently proposed for adrenal tumors, but all of these studies are still at the preclinical stage (468–470). Although treatment strategies for hormonally active tumors are widely accepted, the impact of subclinical Cushing/SAGH on morbidity and mortality is unclear. Because clinical signs of manifest Cushing's syndrome are not necessarily present and many of its symptoms are nonspecific, future studies prospectively investigating SAGH should clarify which signs and symptoms may be missing in SAGH and specify the threshold of clinical abnormality (such as obesity, diabetes, or hypertension). As a perspective, the question of treatment for mild hypercortisolism may be readdressed by the development of novel CRH antagonists (471, 472). Recent workshops, national networks, interest groups, and international consortia for both adrenocortical and adrenomedullary tumor will facilitate the formation of registries, tissue banks, and multicenter studies needed in the field.

Future efforts should be directed toward obtaining a larger database to define the true natural history of clinically inapparent adrenal masses as a function of size and biochemical behavior with prospective clinical studies as a basis. Individual studies should apply rigorous inclusion criteria for each scenario or provide careful analyses of defined subgroups. To conclude, well-designed, prospective clinical trials are needed to provide the most reliable evidence regarding the management of patients with clinically inapparent adrenal masses. In addition, the creation of an international registry of patients with well-documented adrenal incidentalomas using standardized definitions and inclusion criteria would be extremely valuable.

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