Adrenal Neoplasms

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1. Introduction

The adrenal glands are paired retroperitoneal organs that play a critical role in endocrine and neurocrine function. They weigh 5-7 grams, measure 4-6 cm by 2-3 cm, and are located within Gerota's fascia above each kidney. The adrenal gland is composed of two distinct regions; the **cortex** (outer layer) and **medulla** (inner layer). These regions have different embryologic origins resulting in distinct functions.

The adrenal **cortex** arises from the **intermediate mesoderm** of the urogenital ridge between weeks 5-8 of embryonal development and has purely endocrine function. The cortex is comprised of three zones with distinct endocrine functions: **zona glomerulosa** (which produces mineralocorticoids such as aldosterone), **zona fasciculata** (which produces glucocorticoids such as cortisol), and the **zona reticularis** (which produces sex steroids such as estrogens/androgens).

The adrenal **medulla** develops from **neural crest cells** from the adjacent sympathetic ganglia in the 9th week of embryonal development and has purely neurocrine function. The adrenal medulla, which accounts for about **10% of the gland**, is composed of **chromaffin cells** innervated by pre-ganglionic sympathetic fibers from T11-L2. The medulla secretes **catecholamines** (epinephrine/norepinephrine/dopamine), which are derived from the amino acid tyrosine.[1] Due to the diverse function of the adrenal gland, neoplastic processes of the gland often result in clinical stigmata related to excess hormone production.

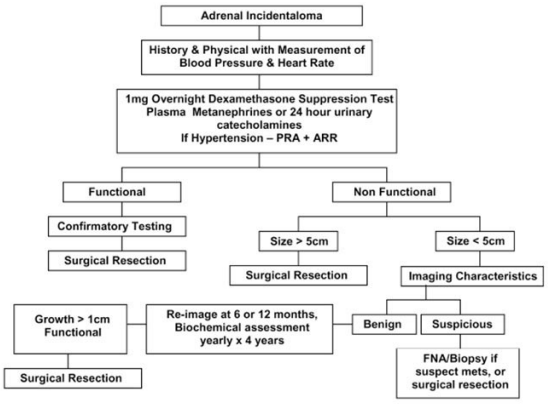
2. Incidental Adrenal Mass

2.1 Definition

Adrenal **incidentalomas** are defined as any unsuspected adrenal mass detected incidentally on radiologic imaging obtained for another indication. Based on autopsy studies, it is estimated that an adrenal incidentaloma will be detected in **~9% of individuals in autopsy series**.[2] As biochemical testing of adrenal incidentalomas has increased, there has been an increasing number of incidentalomas deemed functional, such that up to an estimated **20% of adrenal incidentalomas are metabolically active**.[1,2]

2.2 Patient Evaluation

Figure 1. Suggested Algorithm For Evaluation And Management Of Adrenal Incidentalomas.



PRA: plasma renin activity; ARP: aldosterone renin ratio; FNA: fine needle aspiration; Mets:metastases.

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Figure 1. Suggested Algorithm for Evaluation and Management of Adrenal Incidentalomas[2]

Once an adrenal incidentaloma has been detected, there are two separate evaluations that must be undertaken to completely characterize the incidentaloma and guide future management. First, a **biochemical workup** determines if the incidentaloma is hormonally active. Second, **adrenal-specific** imaging studies estimate the malignant potential of the indeterminate adrenal mass. Malignant tumors of the adrenal gland are discussed separately below. This section will focus on hormonal evaluation of the adrenal incidentaloma, according to the algorithm presented in **Figure 1**.[2]

The **evaluation** of an adrenal incidentaloma should include clinical, biochemical, and radiographic evaluation for signs and symptoms of **hypercortisolism** (Cushing syndrome), **hyperaldosteronism** (if hypertensive), **pheochromocytoma**, and **malignant tumor**.[3] The relevant clinical signs and symptoms of hormonal excess may variably include **substantial weight gain, centripetal obesity, easy bruising, severe and uncontrolled hypertension, diabetes, virilization, proximal muscle weakness, or fatigue**. It is important to obtain a careful history regarding extra-adrenal malignant disease, as an estimated 19-58% of patients with a history of metastatic cancer and an incidental adrenal mass will have a metastatic lesion within the adrenal gland.[4,5]

All adrenal incidentalomas should undergo biochemical testing unless the imaging is unequivocal for **myelolipoma** (e.g., low CT attenuation of **-10 to -20 Hounsfield units or the presence of macroscopic fat**) in which case biochemical testing may not be necessary. However, if there is a clinical suspicion for endocrine functionality based on the clinical history, then a biochemical evaluation should be completed as a small subset of myelolipomas (10-15%) can be functional. Conversely, recent data suggest that if the incidentaloma has HU <10 in the non-contrast phase, then testing for pheochromocytoma is not necessary. [6]

2.2.1 Testing for Cortisol Hypersecretion

Hormonal assessment of an adrenal incidentaloma should begin with a test for cortisol hypersecretion (or **Cushing syndrome**) with one of three first-line tests:

i. **Overnight low-dose (1-mg) dexamethasone suppression test (OST)**
ii. **Late-night salivary cortisol test (SCT)**
iii. **24-hour urinary-free cortisol evaluation (UFC)**

Of these tests, the SCT is the simplest to complete for patients. However, of all the tests, **the OST has the highest sensitivity for detecting sub-clinical Cushing syndrome**.

To perform the OST, a dose of 1 mg dexamethasone is given at 23:00 hours followed by measurement of serum cortisol and dexamethasone the following morning at 08:00.[2] **A putative diagnosis of Cushing Syndrome is made if the serum cortisol level is >5 micrograms/dL following an OST**. An ACTH level can be checked to ascertain whether it is ACTH-independent or -dependent. A low/suppressed ACTH or DHEA-sulfate supports an adrenal source.

One of these three evaluations is required to diagnose hypersecretion of cortisol and it should be stressed that **"spot" or random serum cortisol levels should not be used in this setting**. It is worth mentioning that the **UFC is considered a standard test** but can be more time-intensive for the patient due to the need to collect urine for a 24-hour period.

2.2.2 Testing for Aldosterone Hypersecretion

Excess aldosterone production may be responsible for **up to 10% of patients with refractory hypertension**. Hyperaldosteronism can be the result of either a single adrenal adenoma or bilateral adrenal hyperplasia. Bilateral hyperplasia is not a surgically curable disease. However, hyperaldosteronism due to a single adrenal nodule (**Conn syndrome**), is a surgically curable form of hypertension.[2,7] Unfortunately, recent studies have shown that the screening guidelines for hyperaldosteronism are rarely followed, and thus many patients remain undiagnosed.[8] Although the classic syndrome includes **hypertension, hypokalemia, and alkalosis**, **up to 40% of patients with this syndrome are normokalemic**.[2] For this reason, screening consists of more than just testing for serum potassium. Testing of select hypertensive patients is therefore warranted, with a screening test assessing the **morning plasma aldosterone (ng/dL) to renin (ng/mL/hr) ratio (ARR)**. **An ARR≥20** along with a concomitant **aldosterone concentration above 15 ng/mL** suggests the diagnosis of primary hyperaldosteronism. Potassium-sparing diuretics (e.g., spironolactone) and mineralocorticoid receptor blockers may affect test results and should be stopped 6 weeks prior to testing. **Current Endocrine Society guidelines recommend screening for hyperaldosteronism in the following clinical situations**:

1. Any patient with sustained blood pressure above 150/100 on three separate measurements taken on different days
2. Hypertension resistant to 3 antihypertensives
3. Hypertension controlled with four or more medications
4. Hypertension and low potassium
5. Hypertension and a newly diagnosed adrenal incidentaloma
6. Hypertension and concomitant sleep apnea
7. Hypertension and a family history of early onset hypertension or stroke before age 40
8. All first-degree relatives of patients with a diagnosis of primary aldosteronism

A positive ARR screen should prompt a confirmatory **24-hour urine study with salt loading** to assess for primary aldosteronism.[1] It is also important to note that positive testing for aldosterone hypersecretion does not guarantee a unilateral source, and therefore, **adrenal venous sampling** is recommended prior to surgical intervention.[9] Furthermore, it can be difficult to **differentiate between primary hyperaldosteronism and bilateral adrenal hyperplasia**, although **imaging and adrenal venous sampling** can be helpful in these cases.[2]

2.2.3 Testing for Pheochromocytoma

As 4-5% of patients with adrenal incidentalomas are diagnosed with pheochromocytomas, all patients with an adrenal mass should be evaluated with **plasma-free metanephrine and normetanephrine levels or 24-hour total urinary metanephrines and fractionated catecholamines**.[2,10] Metanephrines are increasingly used due to improved diagnostic sensitivity in detecting silent pheochromocytoma.[2] **Metanephrines are more sensitive than catecholamines** since metabolism is continuous, unlike catecholamine release which occurs episodically.[2] The higher sensitivity of metanephrines also means they have a higher false positive rate. However, elevation above designated thresholds (>2x the upper limit of normal) in either study suggests the presence of pheochromocytoma. Levels between 1-2x the upper limit of normal may represent a false positive result and thus further testing is warranted prior to making the diagnosis of pheochromocytoma. In conjunction with laboratory testing, review of patient medications is particularly important. Several medications can cause falsely elevated metanephrines and catecholamines such as **levodopa, monoamine oxidase inhibitors, benzodiazepines, tetracycline, and rapid withdrawal from clonidine**.[2] If possible, these medications should be discontinued prior to the screening test.

For those patients with pheochromocytoma and age <50, family history, or extra-adrenal pheochromocytoma, investigation for familial syndromes with genetic testing is warranted, with emphasis on mutation of the **RET proto-oncogene** (multiple endocrine neoplasia type 2), **VHL (von Hippel-Lindau disease)**, or **succinate dehydrogenase genes**.[3,10]

2.2.4 Testing for Excess Sex Hormones

Adrenocortical carcinoma is found in approximately 3% of patients with adrenal incidentalomas, and excess sex hormones are noted in **62-79% of these cases**.[11] Testing for excess sex hormones is not warranted unless the patient is suspected of having an adrenocortical carcinoma (**mass >4 cm**) and/or obvious clinical stigmata of feminization or virilization.[2,3] In these cases, **serum dihydroepiandosterone (DHEA) should be measured, along with 17-ketosteroids. For women with virilization, a serum testosterone should be obtained while 17β-estradiol should be measured in men exhibiting feminization.**[2]

Table 1 summarizes first and alternative biochemical testing for adrenal incidentalomas.

Table 1 First and Alternative Biochemical Testing to Identify Functional Adrenal Adenomas

	Cushing's	Pheochromocytoma	Aldosteronoma	Sex Hormones*
First Line Tests	Overnight Dexamethasone Suppression	Plasma free metanephrines and normetanephrines	Plasma aldosterone to renin ratio	DHEA and 17-ketosteroids
Alternative Test Options	Late Night Salivary Cortisol	24-hr urinary metanephrines	Salt-loaded 24-hr urinary aldosterone	Serum Testosterone for Women
	24-hr urinary free cortisol	24-hr urinary fractionated catecholamines		17β-estradiol for men

2.3 Imaging

The primary goal of imaging is to distinguish between adrenal adenoma, carcinoma, pheochromocytoma, and metastatic lesions. However, **imaging cannot reliably differentiate between functional and non-functional adenomas**. Because imaging cannot determine whether a lesion is functional, it must be performed with the appropriate biochemical evaluation as described above.[3]

By definition, adrenal incidentalomas will be found on imaging studies that were not performed for the purpose of evaluating an adrenal lesion. Therefore, the initial imaging study may not yield the information needed to accurately characterize an adrenal incidentaloma. In the majority of cases, the imaging will need to be repeated as an adrenal protocol study in order to fully characterize the adrenal lesion. However, immediate repeat adrenal protocol imaging may not be necessary in certain cases (see **Figure 2**).

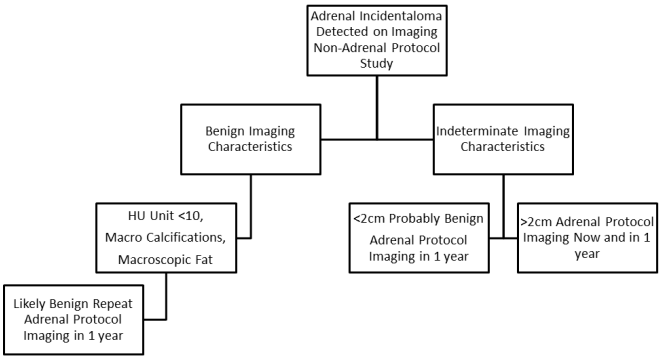

Figure 2. Recommendations for Initial Imaging after detection of an Adrenal Incidentaloma*

*Adapted from American College of Radiology White Paper on Adrenal Incidentalomas[6]

The diagnosis of an adrenal adenoma can be made using several different imaging modalities, including lipid density measurements on non-contrast CT, in-phase and out-of-phase MRI, or contrast-washout kinetics on contrast-enhanced CT.

Lesions with an attenuation below 10 HU on non-contrast CT are considered adenomas.[12] Recent American College of Radiology[6] guidelines suggest that if an incidentaloma has HU<10 on non-contrast imaging then the nodule can be considered benign and washout characteristics are not needed for further characterization. However, contrast-washout kinetics can further specify the diagnosis if necessary.

An adrenal protocol CT scan is a triphasic study. The first phase of the study is without contrast. This is followed by imaging immediately after intravenous administration of contrast. The final phase is imaging after 10 to 15 minutes. Adrenal washout can be presented as **absolute percentage contrast-washout** ((enhanced HU – 15-min delayed HU)/(enhanced HU – unenhanced HU) x 100%) or as **relative percentage contrast-washout** ((enhanced HU – 15-min delayed HU)/enhanced HU x 100%). The 2017 ACR guidelines denote thresholds of >60% absolute percentage washout or >40% relative percentage washout as characteristic of benign adenoma.[6]

Pheochromocytomas measure greater than 10 HU on unenhanced CT scans and will enhance to more than 100 HU on contrast studies, often exhibiting a well-circumscribed appearance with or without necrotic or cystic elements.[2,3] Recent data suggest that if HU are <10 then biochemical testing for pheochromocytoma is not necessary. The classic "**light bulb**" signal on T2-weighted MRI may be helpful, but recent studies suggest that this sign is less sensitive and specific than previously thought.[2] Additional imaging, such as **meta-iodobenzylguanidine (MIBG) scanning** may also be warranted in this setting, especially if assessing for an extra-adrenal, metastatic, or recurrent pheochromocytoma.

Adrenocortical carcinomas are typically >4 cm and exhibit a heterogeneous appearance on CT, with calcifications and necrosis often present.[2] **HU measurement on non-contrast CT are typically >25 HU with <50% washout demonstrated at 10 minutes post-contrast imaging**. Adrenal metastasis may also have a similar appearance, which belies the importance of clinical history in this setting. Lipid-poor adenomas may have attenuation values of 20-40 HU, but a washout of >50% is believed to distinguish these lesions from adrenal carcinomas.[13]

2.4 Management of Adrenal Incidentalomas

Management for adrenal incidentalomas depends largely on lesion size and functionality. Lesion size informs the need for adrenalectomy. **Only 2% of adrenal masses <4 cm will be primary adrenocortical carcinomas**. **However, 25% of masses >6 cm are primary adrenocortical carcinomas, and these tumors should be considered malignant until proven otherwise and surgically removed**.[3] **There is some controversy over the management of masses between 4-6 cm**. The American Association of Clinical Endocrinologists/American Association of Endocrine Surgeons (AACE/AAES) guidelines **recommend removal of all masses over 4 cm regardless of functional status or imaging characteristics, unless it is clearly a myelolipoma**[3,14] In general, those patients diagnosed with Cushing syndrome, primary adrenal hyperaldosteronism, or pheochromocytoma on biochemical evaluation should undergo adrenalectomy, regardless of tumor size, to avoid long-term sequelae of hormonal imbalance or risk of metastases (pheochromocytoma).

Patients with **excessive glucocorticoid production** are at risk for development of **metabolic syndrome, including hypertension, medical issues related to obesity, cardiovascular disease, and diabetes**. If a patient is not a candidate for adrenalectomy, medical treatment such as **aminoglutethimide, metyrapone or ketoconazole** should be initiated while simultaneously monitoring for adrenal insufficiency.[2] For patients with **sub-clinical Cushing syndrome**, surgical resection is reserved for those with worsening hypertension, dyslipidemia, abnormal glucose tolerance, or

osteoporosis.[3] Following surgical resection, patients may experience adrenal crisis or insufficiency and require glucocorticoid replacement therapy.

For those patients with **primary aldosteronism**, excess plasma aldosterone is harmful and can lead to **myocardial fibrosis, left ventricular hypertrophy, cardiac ischemic events, and clotting abnormalities**, even if blood pressure is controlled.[3] Therefore, **adrenalectomy is preferred** unless the patient is not an operative candidate. **Adrenal vein sampling** is nearly universally performed prior to surgery to identify laterality, even in the case of micronodularity or bilateral adrenal masses. However, in the setting of a **unilateral hyperdense nodule >1cm with a positive aldosteronoma screen, unilateral adrenalectomy is indicated**. Caution should be exercised if pursuing partial adrenalectomy in these cases, since the dominant nodule may be nonfunctioning, leading to surgical failure.[3] **Prior to surgery, patients are given a mineralocorticoid receptor antagonist, antihypertensive and potassium repletion**. Following surgery, antihypertensives are weaned slowly. Almost all patients will exhibit improvement in hypertension following adrenalectomy with complete normalization seen in approximately 60%. The **Aldosteronoma Resolution Score** can be used to predict the likelihood of discontinuing anti-hypertensives following surgery.[15] Patients who are not surgical candidates may be treated with **spironolactone or eplerenone**. The latter is believed to have less side effects as it is a corticosteroid-based competitive mineralocorticoid receptor antagonist with little androgen activity.[3] Adrenal insufficiency and hyperkalemia may also occur post-adrenalectomy.

All patients diagnosed with pheochromocytoma should undergo adrenalectomy following preoperative alpha- and beta-adrenergic blockade (see **section 3.4**).

In patients with **negative functional evaluation** who do not undergo surgical resection, **follow-up is required to evaluate for possible changes in lesion size, functionality, and imaging washout characteristics**.[2] The reasoning for continued follow-up is based on data that suggest that at 1-, 2-, and 5-years the risk of a previously non-functional tumor secreting excess hormones is 17%, 29%, and 47%, respectively. Furthermore, growth >1 cm is observed in 6%, 14%, and 29%, respectively. These data led the AACE/AAES to recommend **radiographic re-evaluation at 3-6 months and then annually for 1-2 years** for all adrenal incidentalomas, even in the setting of benign radiographic characteristics initially.[3] **Hormonal evaluation should be performed at time of diagnosis and annually for 5 years**.[3] **If the lesion size increases by ≥1 cm or develops functionality, surgery should be considered**. However, 75-95% of incidentalomas remain stable in size while 2-8% of previously non-functioning lesions develop functionality, with hypersecretion of cortisol being the most common finding.[2]

Recently, controversy has developed regarding follow-up imaging recommendations for benign appearing incidentalomas managed expectantly. The recommendations described above are taken from the AACE/AAES3 guidelines published in 2009. In 2017, the Korean Endocrine Society (KES) published a set of guidelines that mirror the imaging follow-up recommendations of the American recommendations.[16] However, in 2016 the European Society of Endocrinology and European Network for the Study of Adrenal Tumors (ESE/ENSAT) guidelines recommended **no further follow-up imaging for an incidentaloma that showed benign imaging (non-contrast HU <10) and was under 4 cm in size**.[17] For tumors >4 cm or with indeterminate imaging characteristics, additional imaging was recommended at 6-12 months. Similar recommendations were put forth in 2017 by the American College of Radiology (ACR), [6] which **recommended against follow-up imaging for incidentalomas with unequivocally benign characteristics, regardless of size on initial imaging including the presence of macroscopic fat, low CT density (non-contrast HU <10), cystic features, hemorrhage, absence of enhancement, and loss of MRI signal between in-phase and opposed-phase images on chemical shift MRI.** However, for masses measuring 1-4 cm with indeterminate radiographic features, additional risk-stratified imaging follow-up vs. advanced imaging (e.g. PET-CT), biopsy, or extirpation are recommended accordingly.

Table 2. Surveillance Recommendations for Adrenal Incidentalomas

	AACE/AAES[3]	ESE/ENSAT[17]	KES[16]	ACR[6]
Location	USA	Europe	Korea	USA
Year	2009	2016	2017	2017
Imaging	6 months then annually for 2 years	If Non-Contrast HU<10 and tumor <4cm, no further imaging. All others, repeat imaging in 6-12 months	If Non-Contrast HU<10 and tumor <4cm, no further imaging. All others, repeat imaging in 6-12 months	If benign characteristic, no further imaging regardless of size
Biochemical workup	Annually for 5 years	No further workup unless new clinical signs or if associated comorbidities worsen (e.g., DM, HTN)	Annually for 5 years if tumor >2 cm in size	N/A

3. Pheochromocytoma

3.1 Epidemiology

Pheochromocytomas are relatively rare tumors that arise from the **chromaffin cells** of the adrenal medulla, accounting for **4-5% of adrenal incidentalomas** and **0.1%-1% of patients with hypertension**. The incidence is estimated to be **2-8 per million persons per year** with no apparent gender predilection. Hereditary pheochromocytomas tend to present at a younger age (average 25 years) than sporadic cases (average 44 years). Extra-adrenal pheochromocytomas occur 1-25% of the time and are known as **paragangliomas.** The **organ of Zuckerkandl,** between the aortic bifurcation and root of the inferior mesenteric artery, is one of the most common locations for paragangliomas to occur.[1,18]

3.2 Risk Factors

Approximately 25% of pheochromocytomas present as a manifestation of a familial syndrome (multiple endocrine neoplasia [MEN] type 2A/2B, von Hippel-Lindau disease (type 2 variant), and familial paraganglioma syndrome (types 1 and 4). Mutations in the rearranged transfection proto-oncogene (**RET**), **von Hippel-Lindau** (VHL), **neurofibromatosis type 1 (NF1)** and **mitochondrial succinate dehydrogenase** (SDHD, SDHAF2, SDHC, SDHB, SDHA) genes have been implicated in each of these syndromes with varying degrees of risk for the development of pheochromocytoma. Up to 50% of those with MEN-2 will develop a pheochromocytoma, whereas **the highest incidence of malignant pheochromocytomas (30-50%) are seen with familial paraganglioma syndrome type 4 associated with SDHB mutations**. Genetic counseling and testing are now recommended for all patients with pheochromocytomas or paragangliomas.[19] **If a mutation is identified, screening should be offered to asymptomatic at-risk family members**.[1,18,19,20]

3.3 Clinical Presentation

The classic presenting symptom of **paroxysmal hypertension is seen in 30-50%** of patients, while **the remainder of patients generally present with sustained hypertension**. The most common clinical manifestations include **headache, palpitations, sweating, anxiety, and pallor**. Additional common symptoms include nausea, panic attacks, and flushing. **Episodic hypertensive episodes may be triggered by a variety of events such as anesthesia induction, childbirth, direct instrumentation or biopsy of the tumor, tyramine-rich foods (red wine, chocolate, cheese), and strenuous physical activity**. These paroxysmal episodes can be difficult to control medically. **Catecholamine-induced cardiomyopathy** may present as congestive heart failure and cardiac arrhythmias.[1,18]

3.4 Malignant Pheochromocytoma

The diagnosis of a malignant pheochromocytoma depends on whether the tumor demonstrates **extracapsular invasion** into adjacent structures or **distant metastatic disease**. In patients with MEN-2 and VHL, malignant pheochromocytomas are rare. Meanwhile, patients with a SDHB mutation (familial pheochromocytoma type 4) have a high risk of malignant pheochromocytoma. The most common sites of pheochromocytoma spread are **bone, liver, regional lymph nodes, lung, and peritoneum**. Most metachronous metastases will present within the first 5 years of diagnosis; however, **lifelong annual biochemical follow-up is recommended** as recurrences have been noted to occur more than 15 years following surgery.[1,21] In the past, imaging such as MIBG for metastatic pheochromocytoma were initially widely used then dropped out of favor as data accumulated demonstrating poor sensitivity[22] Even so, **MIBG is still considered useful for the detection of extra-adrenal pheochromocytoma and** should be performed if treatment with Iodine-131 MIBG is being considered. For the evaluation of metastatic disease, recent data also suggests superior detection rates of with 68-Gallium DOTATATE PET, 18F-fluorodeoxyglucose (F-18 FDG) PET and 18F-flourodihydroxyphenylalainine PET (F18 DOPA).[19,23,24] For patients with metastatic disease, 68-Gallium DOTATE PET is the imaging modality of choice.[25]

3.5 Treatment

Complete surgical resection, when technically feasible, remains the mainstay of therapy for pheochromocytoma with various open and laparoscopic approaches described, including both transperitoneal and retroperitoneal.[26,27] However, partial adrenalectomy has been employed in patients predisposed to development of bilateral, multifocal, and recurrent pheochromocytoma.[28]

The perioperative management of patients undergoing resection of pheochromocytoma is critical with most modern series reporting an operative mortality rate of I<3% in appropriately treated patients. All patients with pheochromocytoma should undergo a thorough **preoperative cardiac evaluation**. The preoperative medical management is diagrammed in **Figure 3**.[29] **Alpha-adrenergic blockade**, typically with phenoxybenzamine (an irreversible non-selective alpha blocker) or doxazosin (a selective alpha-1 adrenergic receptor blocker), is started 7-14 days prior to surgery and titrated to a blood pressure of 120-130/80mmHg. This is **followed by beta blockade** with atenolol or metoprolol if tachycardia or arrhythmias develop. Use of metyrosine to block catecholamine synthesis is not commonly needed but can be used in combination with alpha-blockade. Calcium channel blockers have been advocated by some as an adjunct to or in lieu of traditional alpha blockade. **Intra-vascular volume expansion is also necessary due to the chronically vasoconstricted state. This can be achieved through preoperative and intraoperative hydration and a high salt diet**. This should be initiated 7-14 days prior to surgery.[19]

Close intraoperative monitoring is imperative. Inhalational agents that minimize cardiac depression are preferred. **Hypertensive spikes** can be controlled with nitroprusside, nicardipine, nitroglycerine, or phentolamine, and are more commonly in older patients.[30] **Tachyarrhythmias** are treated with esmolol or lidocaine. Once the adrenal vein has been ligated, severe hypotension may necessitate large volume replacement and alpha-adrenergic agonists. Rebound hyperinsulinemia with resulting hypoglycemia may also occur.[1]

Life-long postoperative follow-up is essential due to the **risk of recurrence, which occurs in up to 16% of patients**, with 50% of these representing malignant recurrence. Guidelines vary regarding the optimal follow-up schedule, though most recommend at least annual blood pressure monitoring and biochemical screening with imaging as needed through year 10 after surgery.[1,19] For patients with a history of metastatic pheochromocytoma and for

those with a history of gene mutation with increased risk of metastatic pheochromocytoma, more frequent follow-up and imaging may be indicated.[31]

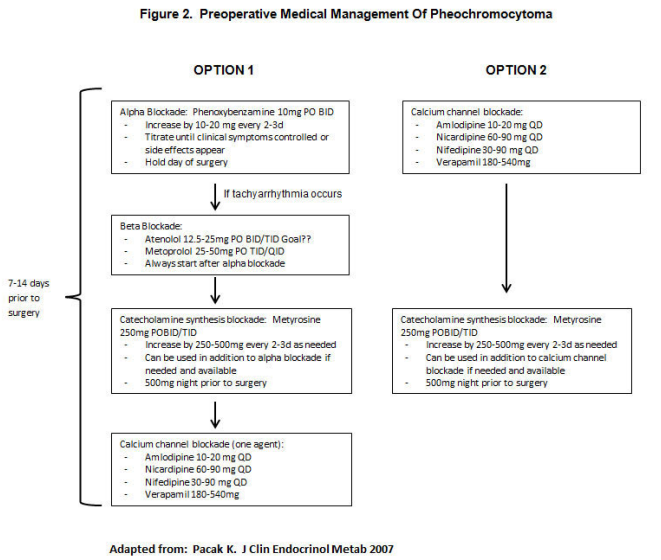

Figure 3 Preoperative Medical Management of Pheochromocytoma

4. Malignant Tumor of the Adrenal Gland (Adrenocortical Carcinoma)

4.1 Epidemiology

Adrenocortical carcinoma (ACC) is a rare and aggressive malignancy that arises from the adrenal cortex. ACC represents 0.05-0.2% of all cancers with an incidence of approximately 1-2 per million population per year. There is a bimodal age distribution with children under age 5 and adults in their 40s and 50s at highest risk; median age at diagnosis is 55 years and there is a slight female predominance (~60% of all cases).[32] While the overwhelming majority of cases are spontaneous and unilateral, **2-6% are bilateral**, and cases can be associated with **familial syndromes such as Li-Fraumeni, Beckwith-Wiedemann, MEN-1, McCune-Albright, and Carney complex**.[1,21] Accordingly, approximately 20% of patients with ACC have other concurrent primary malignancies.[32] Patients with suspected familial syndromes should be referred to genetic counseling and testing.

4.2 Histopathology, Molecular Analyses, and Genomics

Similar to pheochromocytomas, **benign and malignant adrenal cortical tumors cannot be reliably distinguished by histologic criteria alone.** The **Weiss criteria** are pathologic and clinical findings that have been associated with malignancy. These 9 criteria are **high nuclear grade, high mitotic rate, atypical mitoses, low percentage of cells with clear cytoplasm, diffuse cellular architecture, necrosis, invasion of venous structures, invasion of sinusoidal structures, and invasion of the tumor capsule. The presence of three or more of the Weiss criteria is predictive of a malignant phenotype (sensitivity 100%, specificity 96%).**[1,21]

ACC is a heterogeneous cancer with several proposed genetic and molecular drivers. The more common genetic alterations resulting in ACC are generally related to the various familial cancer syndromes associated with ACC, though some develop sporadically. **Tumor protein 53 (TP53)** and **insulin growth factor II (IGF-II)** are most closely associated with familial ACC given the close relationship with **Li-Fraumeni syndrome**. **Dysregulation of the WNT signaling pathway** is another frequently seen mechanism as is c-MET overexpression, which is thought to contribute to chemo-resistance.[33] In a small, prospective study, 21% of ACCs were programmed death-ligand 1 (PD-L1) positive, and 16% were microsatellite-high and/or mismatch repair deficient (MSI-H/MMR-D):[34] **Genetic counseling and testing is recommended by the NCCN to screen for inherited genetic syndromes.**

4.3 Clinical Presentation

Although the incidental detection of ACC has increased, **most patients present with tumor-related symptoms**, either due to locally advanced or metastatic disease or hormonal hypersecretion. Approximately 80% of cases present with **hypersecretion of glucocorticoids, mineralocorticoids, and androgens.** The most common functional presentations are **Cushing's syndrome (33-53%), Cushing's syndrome with virilization (20-24%), virilization alone (10-20%), and feminization (6-10%).** Mixed hormonal hypersecretion and elevated levels of sex steroids **(DHEA-S, 17-ketosteroids)** suggests carcinoma. Functional biochemical evaluation is recommended for all suspected ACCs (see 2.2). Local tumor growth may also present with signs and symptoms related to inferior vena cava tumor thrombus extension, or invasion into adjacent organs.[20] The AJCC 8th Edition TMN staging for ACC is detailed in **Table 3a** and **Table 3b**.[35]

Table 3a: TMN Staging of Adrenocortical Carcinoma	
Primary Tumor (T)	
pTx	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pT1	Tumor ≤5cm in greatest dimension, no extra-adrenal invasion
pT2	Tumor >5cm in greatest dimension, no extra-adrenal invasion
pT3	Tumor of any size with extra-adrenal invasion, but not invading adjacent organs
pT4	Tumor of any size with invasion of adjacent organs (kidney, diaphragm, spleen, liver, etc)
Regional Lymph Nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases in regional lymph node(s) (retroperitoneal)
Distant Metastasis (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
From AJCC Cancer Staging, 8th Ed.	

Table 3b: Adrenal Stage Grouping			
Stage Grouping			
Stage	**T**	**N**	**M**
Stage I	pT1	N0	M0
Stage II	pT2	N0	M0
Stage III	pT1-2	N1	M0
	pT3-4	N0-1	M0
Stage IV	Any T	Any N	M1
From AJCC Cancer Staging, 8th Ed.			

4.4 Imaging

ACC generally presents as a large adrenal mass with **over 90% of ACC measuring greater than 6 cm** at diagnosis. **Typical radiographic features include irregular shape, heterogeneous enhancement, calcifications, and necrosis with cystic degeneration**. Mean attenuation on non-contrast CT is significantly higher with **ACC (mean ~34 HU)** compared with **adenomas (mean ~8 HU).** Furthermore, when CT washout curves are considered, the sensitivity and specificity approaches 100% for CT in distinguishing benign adenomas from ACC, such that ACC will not demonstrate the washout of >60%.

On **MRI**, ACC tends to show **increased signal on T2 images, marked enhancement with contrast, only moderate washout of contrast, and weak chemical shift** compared to adenomas. Adrenal scintigraphy, utilizing cholesterol derivatives such as 131-Iodine-6-betaiodomethyl-norcholesterol (NP-59) can also be used to determine whether an adrenal lesion arose from the adrenal cortex or from another source.[1,21]

Functional imaging with F-18 FDG PET has been shown to be helpful for both diagnosis and staging in small series of patients and has been incorporated into the NCCN Guidelines as of 2021.[36,37] Other novel tracers and targeted molecular imaging are being developed.

4.5 Management and Prognosis

Complete surgical excision with negative margins (i.e., R0) remains the mainstay of therapy for ACC. This may involve resection of adjacent organs, including the ipsilateral kidney, depending on the extent of local involvement.[38] While minimally invasive (laparoscopic or robotic-assisted) adrenalectomy is frequently utilized by experienced surgeons, specifically for tumors <6 cm, many still advocate an open approach (see Section 5. Adrenalectomy).[38,39,40] Adrenalectomy and resection of regional lymph nodes and limited abdominal metastasis should be considered (if >90% of tumor burden can be removed),[19] but **adrenalectomy should not be performed in the setting of widespread metastatic disease**.[41]

The main prognostic factors are **tumor stage and completeness of the surgical resection. The reported 5-year survival rates are 30-45%, 13-57%, 5-18%, and 0% for stages I through IV**, respectively. The most common sites for **metastases are liver (48%), lung (45%), lymph nodes (29%), and bone (13%)**. Local invasion into the kidney (26%) and IVC (9-19%) can also occur. **Median survival for stage IV disease is typically less than a year. If complete tumor excision can be achieved, 5-year survival rates vary from 32-58%. Positive surgical margins are associated with a 1.7-2.1-fold decrease in overall survival**.

Historically, there was no well-defined role for adjuvant therapy though it was considered in patients with high-risk features (e.g., **positive margins, ruptured capsule, large size, high Ki67 index**). A recent retrospective study identified platinum-based chemotherapy as a potential way to reduce the risk of recurrence in select patients though the design of this study limits the immediate clinical impact of the findings.[42] There is also some recent data to suggest that adjuvant radiation in the setting of positive surgical margins can reduce local recurrences and potentially improve survival.[17,43,44,45] Most promisingly, a meta-analysis of five observational studies with 1249 patients found **adjuvant mitotane** to be associated with improved recurrence-free and overall survival.[46] Two international, phase 3 randomized controlled trials (ADIUVO and ADIUVO-2) looking at adjuvant mitotane in patients are also ongoing (ClinicalTrials.gov Identifiers: NCT00777244 and NCT03583710). The ADIUVO trial randomized patients at low-intermediate risk of recurrence (Stage I-III, R0, Ki-67 <10%) to either adjuvant mitotane or observation. There was no difference in recurrence-free survival or overall survival among the two treatment arms and the 5-year recurrence-free survival was 75% among all included patients. These findings, when mature, will support observation as the preferred adjuvant management strategy for low-intermediate risk patients as to avoid the toxicities of mitotane therapy.[47] ADIUVO-2 is randomizing patients at high-risk of recurrence to either mitotane or mitotane plus cisplatin and etoposide. There are no preliminary results available as of yet and trial completion is expected early 2025.

Tumor recurrences may be resected if technically feasible or treated locally (e.g., ablative therapies, radiation) if not resectable.[18] There also may be a role for cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy for recurrent ACC confined to the peritoneal cavity. A recent single center experience of 11 patients demonstrated a median intraperitoneal progression-free survival of 19 months.[48]

Systemic therapy for metastatic ACC typically involves **mitotane**, with clinical response rates in 20-40% and relief of hormonal symptoms in up to 70% of cases. Combination chemotherapy (e.g., etoposide, doxorubicin, and cisplatin) with mitotane may improve objective response rates (9-49%) but with added toxicity and limited improvements in progression-free survival (**Table 4**).[19] The FIRM-ACT trial was an international phase III RCT with a cross over design which randomized patients with metastatic ACC to either etoposide, doxorubicin, cisplatin, and mitotane versus streptozotocin and mitotane. They found no significant difference in overall survival (14.8 vs. 12.0 months, HR 0.79, 95% CI 0.61-1.02, p=0.07) but the response rate was better with the etoposide, doxorubicin, cisplatin, mitotane regiment. There was also a survival benefit among those that did not cross over (17.1 vs. 4.7 months) indicating efficacy among those who responded. Although there were no differences in the rate of series adverse events between the two arms, the toxicity of chemotherapy plus mitotane is an important consideration.[49]

Recent Phase I-II trials have investigated the role of checkpoint inhibitors in patients with advanced ACC, showing some antitumor activity.[34,50,51] In a study of 39 patients with unresectable or metastatic ACC treated with pembrolizumab, the disease control rate was 52% and objective response rate was 23% although the median progression-free survival was only 2.1 months.[34] Median overall survival in this cohort was 25 months, and there were no significant differences in response based on PD-L1 or MSI-H/MMR-D status. Similar outcomes and safety profiles have been seen in other small series of patients treated with nivolumab and avelumab.[50,51] Other adrenalytic agents (metyrapone, aminoglutethamide, and ketoconazole) can also be utilized for palliation of severe hormonal symptoms with advanced ACC.[21] For these agents and mitotane, adrenal replacement therapy may be required.

Table 4 Systemic Therapy Options for Locoregional or Metastatic ACC (adapted from NCCN Guidelines version 1.2022)

Preferred Regimens	Other recommended regimens	Useful in some circumstances
- Cisplatin + etoposide +/- doxorubicin +/- mitotane - Carboplatin + etoposide +/- doxorubicin +/- mitotane	- Pembrolizumab +/- mitotane - Mitotane monotherapy - Avelumab (platinum refractory)	- Streptozocin +/- mitotane

5. Adrenalectomy

Adrenalectomy can be performed via an open, laparoscopic, or robotic-assisted laparoscopic technique, utilizing either a transperitoneal or retroperitoneal approach.[27,52,53,54,55,56] Regardless of technique, **early identification and control of the adrenal vein** facilitates mobilization of the adrenal and avoids troublesome bleeding, especially when dealing with the relatively short right adrenal vein as it inserts into the posterior aspect of the vena cava. On the left side, the inferior phrenic vein, which joins the left adrenal vein, may also require dissection, clipping, and division. Adrenal arterial branches are usually small and can be controlled with electrocautery or one of the various electrosurgical or ultrasonic vessel-sealing devices.

Laparoscopic and robotic-assisted adrenalectomy have become the preferred treatment for the majority of benign, functional and non-functional adrenal adenomas.[57] With the widespread integration of the daVinci robotic system in the surgical armamentarium of the urologist, robotic-assisted laparoscopic adrenalectomy has been advocated, with a meta-analysis demonstrating shorter hospital stays, lower blood loss, and possibly decreased perioperative complications with no differences in conversion rates or operative times compared to the pure laparoscopic approach.[58] However, the cost-effectiveness of the technique remains controversial.[59] Laparoendoscopic single-site[60] and single-port robotic-assisted[61] approaches have been reported though their widespread applicability remains to be determined. Refinements and continued technical advances in instrumentation will likely further advance minimally invasive surgical access to the adrenal.

Partial adrenalectomy has been advocated for select patients with hereditary pheochromocytomas and some aldosterone-producing tumors due to the risk of bilateral disease.[62] Use of the robotic platform with and without the aid of intravenous indocyanine green dye with near-infrared fluorescence imaging may help with mass identification, excision, and preservation of the cortical remnant.[63,64]

Open adrenalectomy remains the standard treatment for ACC allowing for wide resection and *en bloc* excision of potentially involved organs as necessary to achieve an R0 resection.[40,65,66] In recent years, laparoscopic and robotic-assisted adrenalectomy for ACC has gained more popularity.[67,68] However, high-quality comparative effectiveness data remains lacking due to the low incidence of ACC and its typical diagnosis post adrenalectomy. Two recent reviews highlight the difficulty in comparing laparoscopic versus open adrenalectomy given the retrospective, generally small, and inherently biased nature of included studies. While some show short-term recovery benefits (e.g., hospitalization length, blood loss) and similar cancer outcomes, others show greater risk of positive margin, cancer recurrence, and peritoneal carcinomatosis with laparoscopic adrenalectomy.[69,70] Even less data is available for robotic-assisted adrenalectomy though a recent analysis comparing laparoscopic, robotic-assisted, and open adrenalectomy found laparoscopic but not robotic-assisted adrenalectomy to be associated with positive margins.[71] Regardless of approach, these data highlight the import of tumor stage, margin status, and surgeon experience to cancer outcomes.

Lastly, adrenal tumors with venous tumor thrombus extension into the IVC may require further exposure of the retrohepatic and intrapericardial IVC or even cardiopulmonary bypass, which are facilitated by the open approach. A variety of surgical incisions have been described (thoracoabdominal, anterior subcostal, Chevron, posterior, supra-11th rib flank) to gain access to the adrenal via transperitoneal, retroperitoneal, and even transthoracic routes.[72] The decision to utilize a particular incision depends on surgeon preference, size of the tumor, and potential for adjunctive procedures.

A summary of common adrenal pathology and associated clinical and radiographic characteristics is included in **Table 5**.

Table 5 Common Adrenal Pathology and Associated Characteristics*

Adrenal Pathological Subtype	Malignant Potential	Incidence	Metabolic Activity	Radiographic Characteristics	Recommended Treatment
Adrenocortical Carcinoma	Malignant	1-2 cases per million per year	Up to 50% non-functional, hypercortisolism most common; virilization in 10-20%, feminization in 6-10%; hyperaldosteronism <5%	Mean non-enhanced CT attenuation 34 HU, ~100% >10 HU; no signal dropout on in-and-out phase MRI; general lack of contrast washout on CT (exceptions exist in the literature)	Resection; mitotane +/- cytotoxic chemotherapy
Adenoma	Benign	9% Population on autopsy	Up to 20% (excess cortisol, aldosterone, sex hormones)	Mean non-enhanced CT attenuation <10 HU (70%); 70% signal dropout on in-and-out phase MRI; ≥ 60% absolute percentage washout at 15 minutes, ≥ 40% relative percentage contrast washout at 15 minutes	Resection if metabolically active or if large (>4-6 cm) since adenoma cannot be differentiated from ACC on percutaneous biopsy
Myelolipoma	Benign	~0.1% Population	Uncommon (<10-15%)	Macroscopic lipid content on CT/MRI	No treatment necessary unless symptomatic due to size.
Pheochromocytoma	5% Malignant (high rates of malignancy in extra adrenal disease); 95% benign	2-8 cases per million per year	Excess catecholamine secretion best tested with measurement of plasma metanephrines	>HU on non-contrast CT (cases of lipid rich pheochromocytoma); no signal dropout on in-and-out phase of MRI; generally lack contrast washout at 15 min on contrast enhanced CT	Resection with appropriate perioperative catecholamine blockade and intensive perioperative monitoring
Ganglioneuroma	Benign but can encase critical structures (e.g. great vessels)	Rare	None, metabolic evaluation necessary since definitive diagnosis cannot be made preoperatively	Generally <40 HU on non-contrast CT with stippled calcifications	Diagnosis made upon resection.

Cysts	Benign but up to 7% are associated with malignancy	~0.1% population on autopsy	None, metabolic evaluation is variably advised.	Well circumscribed, non-enhancing cystic lesions often with associated calcification	Controversial – but some recommend resection in young healthy patients.
Oncocytoma	30% malignant; 70% benign	Rare, case reportable	10% secrete sex hormones, cytokines, and/or cortisol	No characteristic radiographic signature	Diagnosis made upon resection
Metastases	Malignant	51% lung cancer, 28% renal cell carcinoma	none	>10 HU on non-contrast CT; no signal dropout on in-and-out phase of MRI; commonly lack contrast washout at 15 min on CT	Resection in patients with solitary adrenal metastases of lung and kidney origin. Biopsy can be considered if suspected and rule out pheochromocytoma.
See Reference *73					

6. List of Tables and Figures

Key Takeaways

- For an incidental adrenal mass, a biochemical workup should be performed to determine hormonal active.
- Adrenal-specific imaging can be used to estimate the malignant potential of the indeterminate adrenal mass.
- Functional masses or those concerning for malignancy typically warrant surgical resection.

Videos

ROBOT-ASSISTED ADRENALECTOMY: TIPS, TRICKS AND SURGICAL TECHNIQUE

Posterior Retroperitoneoscopic Adrenalectomy: When and How

Synchronous and Simultaneous Posterior Reroperitoneoscopic Bilateral Adrenalectomy

Robotic partial adrenalectomy for symptomatic aldosterone-secreting adenomas: technique and outcomes

Robotic Assisted Laparoscopic Adrenalectomy In The Setting Of An Incidental Adrenal Mass

Robotic-Assisted Thoracoscopic Transdiaphragmatic Adrenalectomy (RATTA) for Metastatic Renal Cell Carcinoma

Robotic radical adrenalectomy for pheochromocytoma associated with adrenal and renal vein tumor thrombectomy

Adrenal Neoplasms Highlights

Presentations

Adrenal Neoplasms Presentation 1

References

† Kutikov A CP, Uzzo RG.: Pathophysiology, Evaluation, and Medical Management of Adrenal Disorders. Campbell-Walsh Urology, 10th Edition:1685-736, 2011.

1 Testing algorithms are also provided for functional evaluation of the most common adrenal conditions, including Cushing syndrome, primary aldosteronism, and pheochromocytoma. Further information is provided for adrenal malignancies. The chapter concludes with a useful description of the evaluation of adrenal lesions in urologic practice.

☆ † Mandeville J, Moinzadeh A.: Adrenal Incidentalomas, Lesson 4, Volume 29: 34-39, AUA Update Series, 2010.

2 This recent AUA update provides a quick-reference guide to evaluation and management of the adrenal incidentaloma. Indications for observation, biopsy, surgical resection and medical management are also reviewed succinctly. A brief algorithm for evaluation of the adrenal incidentaloma is also provided.

† Zeiger MA Thompson GB, Duh Q-Y, et al.: American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons Medical Guidelines for the Management of Adrenal Incidentalomas. Endocrine Practice, 15:1-20, 2009.+

3 This document provides systematically developed guideline recommendations provided by the American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons for the management of adrenal incidentalomas. A listing of the executive summary of recommendations is provided, along with evidence grading to allow the reader to understand the strength of evidence for each statement.

4 Boland GW, Goldberg MA, Lee MJ, et al.: Indeterminate adrenal mass in patients with cancer: evaluation at PET with 2-[F-18]-fluoro-2-deoxy-D-glucose. Radiology, 194:131-4, 1995.

5 Burt M, Heelan RT, Coit D, et al.: Prospective evaluation of unilateral adrenal masses in patients with operable non-small-cell lung cancer. Impact of magnetic resonance imaging. J Thorac Cardiovasc Surg, 107:584-8, 1994.

6 William W. Mayo-Smith, Julie H. Song, Giles L. Boland, Isaac R. Francis, Gary M. Israel, Peter J. Mazzaglia, Lincoln L. Berland, Pari V. Pandharipande, Management of Incidental Adrenal Masses: A White Paper of the ACR Incidental Findings Committee, Journal of the American College of Radiology, Volume 14, Issue 8, 2017, p. 1038-1044, https://doi.org/10.1016/j.jacr.2017.05.001. (http://www.sciencedirect.com/science/article/pii/S1546144017305513)

7 Fardella CE, Mosso L, Gomez-Sanchez C, et al.: Primary hyperaldosteronism in essential hypertensives: prevalence, biochemical profile, and molecular biology. J Clin Endocrinol Metab, 85:1863-7, 2000

8 Ruhle BC, White MG, et al. Keeping primary aldosteronism in mind: Deficiencies in screening at-risk hypertensives. Surgery. 2019 Jan;165(1):221-227. doi: 10.1016/j.surg.2018.05.085. Epub 2018 Nov 8.

9 Rossi GP, Auchus RJ, Brown M, et al.: An expert consensus statement on the use of adrenal vein sampling for subtyping of primary aldosteronism. Hypertension, 63:151-60, 2014.

10 Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99:1915-42.

11 Cawood TJ, Hunt PJ, O'Shea D, et al.: Recommended evaluation of adrenal incidentalomas is costly, as high false-positive rates and confers a risk of fatal cancer that is similar to the risk of adrenal lesion becoming malignant; time for a rethink? Eur J Endocrinol, 161:513-27, 2009

12 Hamrahian AH, Ioachimescu AG, Remer EM, et al.: Clinical utility of noncontrast computed tomography attenuation value (Hounsfield units) to differentiate adrenal adenomas/hyperplasias from nonadenomas: Cleveland Clinic Experience. J Clin Endocrinol Metab, 90:871-7, 2005.

13 Caoili EM, Korobkin M, Francis IR, et al.: Adrenal masses: characterization with combined unenhanced and delayed enhanced CT. Radiology, 222:629-33, 2002.

14 NIH. State-of-the-science statement on management of the clinically inapparent adrenal mass ('incidentaloma'). NIH Consensus and State-of-the-Science Statements, 19:1-25, 2002.

15 Zarneger R, Young WF, Lee J, et al.: The aldosteronoma resolution score: predicting complete resolution of hypertension after adrenalectomy of aldosteronoma. Ann Surg, 247:511-8, 2008.

16 Lee JM, Kim MK, Ko SH, et al. Clinical Guidelines for the Management of Adrenal Incidentaloma. Endocrinology and Metabolism. 2017;32(2):200-218. doi:10.3803/EnM.2017.32.2.200.

17 Fassnacht, M., Arlt, W., Bancos, I., Dralle, H., Newell-Price, J., Sahdev, A., Tabarin, A., Terzolo, M., Tsagarakis, S., & Dekkers, O. (2016). Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors, European Journal of Endocrinology, 175(2), G1-G34. Retrieved Aug 30, 2018, from https://eje.bioscientifica.com/view/journals/eje/175/2/G1.xml

18 National Cancer Institute (8/3/2012): Pheochromocytoma and paraganglioma treatment (PDQ) Health Professional Version. Accessed August 17, 2013 from www.cancer.gov/cancertopics/pdq/treatment/pheochromocytoma/HealthProfessional/

19 Shah MH, Goldner WS, Benson AB, et al. Neuroendocrine and Adrenal Tumors, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(7):839-868. Published 2021 Jul 28. doi:10.6004/jnccn.2021.0032

20 ☆ Daneshvar M, Bratslavasky G. Diagnosis and Management of Pheochromocytoma. AUA Update Series Volume 38, 2019.

21 ☆ Novakovic K, Ersahin C, Picken M, et al.: Malignant adrenal tumors. Lesson 30, Volume 23:242-247, AUA Update Series, 2004.

22 Ilias I, Divgi C, Pacak K. Current role of metaiodobenzylguanidine in the diagnosis of pheochromocytoma and medullary thyroid cancer. Seminars in Nuclear Medicine. 2011 Sep;41(5):364-368. DOI: 10.1053/j.semnuclmed.2011.03.003.

23 Chang CA1, Pattison DA1,2, Tothill RW3, Kong G1, Akhurst TJ1,3, Hicks RJ1,3, Hofman MS4,5. (68)Ga-DOTATATE and (18)F-FDG PET/CT in Paraganglioma and Pheochromocytoma: utility, patterns and heterogeneity. Cancer Imaging. 2016 Aug 17;16(1):22. doi: 10.1186/s40644-016-0084-2.

24 Janssen I1, Blanchet EM2, Adams K3, Chen CC4, Millo CM5, Herscovitch P5, Taieb D6, Kebebew E7, Lehnert H8, Fojo AT9, Pacak K10. Superiority of [68Ga]-DOTATATE PET/CT to Other Functional Imaging Modalities in the Localization of SDHB-Associated Metastatic Pheochromocytoma and Paraganglioma. Clin Cancer Res. 2015 Sep 1;21(17):3888-95. doi: 10.1158/1078-0432.CCR-14-2751. Epub 2015 Apr 14.

25 Granberg D, Juhlin CC, Falhammar H. Metastatic Pheochromocytomas and Abdominal Paragangliomas. J Clin Endocrinol Metab. 2021;106(5):e1937-e1952. doi:10.1210/clinem/dgaa982

26 ☆ MP69-20RETROPERITONEAL VERSUS TRANSPERITONEALLAPAROSCOPIC ADRENALECTOMY: A COMPARISON OFPERIOPERATIVE OUTCOMES IN MORE THAN TWENTY YEARSSINGLE SURGEON'S EXPERIENCE.Francesco Porpiglia*, Roberto Mario Scarpa, Daniele Amparore,Matteo Manfredi, Enrico Checcucci, Gabriele Volpi, Diletta Garrou,Giovanni Cattaneo, Razvan Gabriel Niculescu, Giorgio Alleva,Roberta Aimar, Cristian Fiori, J Urol. E991. Vol 201. No. 4S, Supplement)

27 ☆ V09-06 POSTERIOR RETROPERITONEOSCOPIC ADRENALECTOMY:HOW AND WHEN. Patricio Garcia Marchi~nena, Diego Santillan, Agustin Romeo, CapitalFederal, Argentina; Ignacio Costabel, Buenos Aires, Argentina;Guillermo Gueglio, Alberto Jurado. J Urol. E938, Vol. 201, No. 4S, Supplement)

28 ☆ MP69-07LONG-TERM FUNCTIONAL AND ONCOLOGIC OUTCOMES OFPARTIAL ADRENALECTOMY FOR PHEOCHROMOCYTOMAPatrick T. Gomella*, Peter A. Pinto, Adam R. Metwalli,Gennady Bratslavsky, W. Marston Linehan, Mark W. Ball. J Urol. E986. Vol 201. No. 4S, Supplement.

29 Pacak K.: Preoperative management of the pheochromocytoma patient. J Clin Endocrinol Metab, 92:4069-79, 2007.

30 MP69-06 RISK FACTORS FOR HEMODYNAMIC INSTABILITY DURINGLAPAROSCOPIC ADRENALECTOMY FORPHEOCHROMOCYTOMA.Toshikazu Takeda*, Kimiharu Takamatsu, Yu Teranishi,Kyohei Hakozaki, Nobuyuki Tanaka, Kazuhiro Matsumoto,Shinya Morita, Takeo Kosaka, Ryuichi Mizuno, Toshiaki Shinojima,Eiji Kikuchi, Hiroshi Asanuma, Mototsugu Oya. J Urol e985. Vol 201, No. 4S, Supplement

31 Nölting S, Bechmann N, Taieb D, et al. Personalized Management of Pheochromocytoma and Paraganglioma. Endocr Rev. 2022;43(2):199-239. doi:10.1210/endrev/bnab019

32 Sharma E, Dahal S, Sharma P, Bhandari A, Gupta V, Amgai B, Dahal S. The Characteristics and Trends in Adrenocortical Carcinoma: A United States Population Based Study. J Clin Med Res. 2018;10(8):636-640.

33 Ahmed AA, Thomas AJ, Ganeshan DM, Blair KJ, Lall C, Lee JT, Morshid AI, Habra MA, Elsayes KM. Adrenal cortical carcinoma: pathology, genomics, prognosis, imaging features, and mimics with impact on management. Abdom Radiol (NY). 2020;45(4):945-963.

34 Raj N, Zheng Y, Kelly V, et al. PD-1 Blockade in Advanced Adrenocortical Carcinoma. J Clin Oncol. 2020;38(1):71-80. doi:10.1200/JCO.19.01586

35 Amin MB, Edge S, Greene F, et al. AJCC Cancer Staging Manual. 8th ed. Cham, Switzterland: Springer International Publishing; 2017.

36 Boland, G. W., Dwamena, B. A., Jagtiani Sangwaiya, M., Goehler, A. G., Blake, M. A., Hahn, P. F., et al. (2011). Characterization of adrenal masses by using FDG PET: a systematic review and meta-analysis of diagnostic test performance. Radiology 259, 117–126. doi: 10.1148/radiol.11100569

37 Deandreis, D., Leboulleux, S., Caramella, C., Schlumberger, M., and Baudin, E. (2014). FDG PET in the management of patients with adrenal masses and adrenocortical carcinoma. Horm. Cancer 2, 354–362. doi: 10.1007/s12672-011-0091-5

38 ☆ Ng L, Libertino JM.: Adrenocortical carcinoma: diagnosis, evaluation and treatment. J Urol, 196:5-11, 2003.

39 Autorino R, Bove P, De Sio M, Miano R, Micali S, Cindolo L, Greco F, Nicholas J, Fiori C, Bianchi G, Kim FJ, Porpiglia F. Open Versus Laparoscopic Adrenalectomy for Adrenocortical Carcinoma: A Meta-analysis of Surgical and Oncological Outcomes. Ann Surg Oncol. 2016;23(4):1195-1202.

40 Gaujoux S, Mihai R; joint working group of ESES and ENSAT. European Society of Endocrine Surgeons (ESES) and European Network for the Study of Adrenal Tumours (ENSAT) recommendations for the surgical management of adrenocortical carcinoma. Br J Surg. 2017 Mar;104(4):358-376. doi: 10.1002/bjs.10414. PMID: 28199015.

41 Fassnacht M, Dekkers O, Else T, Baudin E, Berruti A, de Krijger RR, Haak HR, Mihai R, Assie G, Terzolo M. European Society of Endocrinology Clinical Practice Guidelines on the Management of Adrenocortical Carcinoma in Adults, in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2018 Jul 24. pii: EJE-18-0608. doi: 10.1530/EJE-18-0608. [Epub ahead of print]

42 Kimpel O, Bedrose S, Megerle F, Berruti A, Terzolo M, Kroiss M, Mai K, Dekkers OM, Habra MA, Fassnacht M. Adjuvant platinum-based chemotherapy in radically resected adrenocortical carcinoma: a cohort study. Br J Cancer. 2021;125(9):1233-1238.

43 Viani GA, Viana BS. Adjuvant radiotherapy after surgical resection for adrenocortical carcinoma: A systematic review of observational studies and meta-analysis. J Cancer Res Ther. 2019;15(Supplement):S20-S26. doi:10.4103/jcrt.JCRT_996_15

44 Tella SH, Kommalapati A, Yaturu S, Kebebew E. Predictors of survival in Adrenocortical Carcinoma: An analysis from the National Cancer Database (NCDB). J Clin Endocrinol Metab. 2018 Jun 21. doi: 10.1210/jc.2018-00918. [Epub ahead of print]

45 Nelson DW, Chang SC, Bandera BC, Fischer TD, Wollman R, Goldfarb M. Adjuvant Radiation is Associated with Improved Survival for Select Patients with Non-metastatic Adrenocortical Carcinoma. Ann Surg Oncol. 2018 Jul;25(7):2060-2066. doi: 10.1245/s10434-018-6510-x. Epub 2018 May 10.

46 Tang Y, Liu Z, Zou Z, Liang J, Lu Y, Zhu Y. Benefits of Adjuvant Mitotane after Resection of Adrenocortical Carcinoma: A Systematic Review and Meta-Analysis. Biomed Res Int. 2018;2018:9362108. Published 2018 Jun 4. doi:10.1155/2018/9362108

47 Berruti A, Fassnacht M, Libè R, Lacroix A, Kastelan D, Haak H, Arlt W, Decoudier B, Lasolle H, Bancos I, Quinkler M, Barisson Villares Fragoso MC, Canu L, Puglisi S, Bourdeau I, Baudin E, Berchialla P, Beuschlein F, Bertherat J, Terzolo M. First randomized trial on adjuvant mitotane in adrenocortical carcinoma patients: The Adjuvo study. J Clin Oncology. 2022;40(6_suppl):1-1.

48 Hughes et al. Phase II Trial of Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy for Recurrent Adrenocortical Carcinoma. J Surg Res 2018 232:383-388

49 Fassnacht M, Terzolo M, Allolio B, Baudin E, Haak H, Berruti A, Welin S, Schade-Brittinger C, Lacroix A, Jarzab B, Sorbye H, Torpy DJ, Stepan V, Schteingart DE, Arlt W, Kroiss M, Leboulleux S, Sperone P, Sundin A, Hermsen I, Hahner S, Willenberg HS, Tabarin A, Quinkler M, de la Fouchardière C, Schlumberger M, Mantero F, Weismann D, Beuschlein F, Gelderblom H, Wilmink H, Sender M, Edgerly M, Kenn W, Fojo T, Müller HH, Skogseid B, FIRM-ACT Study Group. Combination chemotherapy in advanced adrenocortical carcinoma. N Engl J Med. 2012;366(23):2189-2197.

50 Le Tourneau C, Hoimes C, Zarwan C, et al. Avelumab in patients with previously treated metastatic adrenocortical carcinoma: phase 1b results from the JAVELIN solid tumor trial. J Immunother Cancer. 2018;6(1):111. Published 2018 Oct 22. doi:10.1186/s40425-018-0424-9

51 Carneiro BA, Konda B, Costa RB, et al. Nivolumab in Metastatic Adrenocortical Carcinoma: Results of a Phase 2 Trial. J Clin Endocrinol Metab. 2019;104(12):6193-6200. doi:10.1210/jc.2019-00600

52 ☆ V06-08: Robotic radical adrenalectomy for pheochromocytoma associated with adrenal and renal vein tumor thrombectomy. AUA 2018

53 ☆ V7-05: Robotic-assisted laparoscopic adrenalectomy in the setting of an incidental adrenal mass. AUA 2017

54 ☆ V6-05: Robotic partial adrenalectomy for symptomatic aldosterone-secreting adenomas: technique and outcomes. AUA 2017

55 ☆ V6-06: Robotic-assisted thoracoscopic transdiaphragmatic adrenalectomy: a novel surgical approach. AUA 2017

56 ☆ V6-03: Synchronous and simultaneous posterior retroperitoneoscopic bilateral adrenalectomy. AUA 2017

57 Chen Y, Scholten A, Chomsky-Higgins K, et al. Risk factors associated with perioperative complications and prolonged length of stay after laparoscopic adrenalectomy. JAMA Surgery. Published online August 8, 2018, doi:10.1001/jamasurg.2018.2648.

58 Brandao LF, Autorino R, Laydner H, et al. Robotic versus laparoscopic adrenalectomy: a systemic review and meta-analysis. Eur Urol 65:1154-61, 2014.

59 Probst KA, Ohlmann CH, Saar M, et al. Robot-assisted vs open adrenalectomy: evaluation of cost-effectiveness and peri-operative outcome. BJU Int 118:952-957, 2016.

60 Hu Q, Gou Y, Sun C, et al: A systematic review and meta-analysis of current evidence ocomparing laparoendoscopic single-site adrenalectomy and conventional laparoscopic adrenalectomy. J Endourol 2013; 27: 676.

61 Lee GS, Arghami A, Dy BM, et al: Robotic single-site adrenalectomy. Surg Endosc 2016; 30: 3351

62 Madala A, Daugherty M, Bratslavsky G. Partial adrenalectomy- why should it be considered? Urology Practice 2:359-365, 2015.

63 Asher KP, Gupta GN, Boris RS, et al. Robot-assisted laparoscopic partial adrenalectomy for pheochromocytoma: the National Cancer Institute technique. Eur Urol 60:118-24, 2011.

64 Manny TB, Pompeo AS, Hemal AK. Robotic partial adrenalectomy using indocyanine green dye with near-infrared imaging: the initial clinical experience. Urology 82:738-42, 2013.

65 Marincola Smith P, Kiernan CM, Tran TB, et al. Role of additional organ resection in adrenocortical carcinoma: analysis of 167 patients from the U.S. Adrenocortical Carcinoma Database. Ann Surg Oncol 25:2308-2315, 2018.

66 Ng L, Libertino JM. Adrenocortical carcinoma: diagnosis, evaluation and treatment. The Journal of urology. 2003;169(1):5-11.

67 Calcatera NA, Hsiung-Wang C, Suss NR, Winchester DJ, Moo-Young TA, Prinz RA. Minimally Invasive Adrenalectomy for Adrenocortical Carcinoma: Five-Year Trends and Predictors of Conversion. World J Surg. 2018 Feb;42(2):473-481. doi: 10.1007/s00268-017-4290-2. PMID: 29022106.

68 Hue JJ, Ahorukomeye P, Bingmer K, Drapalik L, Ammori JB, Wilhelm SM, Rothermel LD, Towe CW. A comparison of robotic and laparoscopic minimally invasive adrenalectomy for adrenal malignancies. Surg Endosc. 2022 Jul;36(7):5374-5381. doi: 10.1007/s00464-021-08827-x. Epub 2021 Nov 1. PMID: 34724582.

69 Buller DM, Hennessey AM, Ristau BT. Open versus minimally invasive surgery for suspected adrenocortical carcinoma. Transl Androl Urol. 2021 May;10(5):2246-2263. doi: 10.21037/tau.2020.01.11. PMID: 34159107; PMCID: PMC8185676.

70 Cavallaro G, Tarallo M, Chiappini A, Crocetti D, Polistena A, Petramala L, Sibio S, De Toma G, Fiori E, Letizia C. Surgical Management of Adrenocortical Carcinoma: Current Highlights. Biomedicines. 2021 Jul 28;9(8):909. doi: 10.3390/biomedicines9080909. PMID: 34440112; PMCID: PMC8389566.

71 Tseng J, Diperi T, Gonsalves N, Chen Y, Ben-Shlomo A, Shouhed D, Phillips E, Burch M, Jain M. Operative approach and case volume are associated with negative resection margins for adrenocortical carcinoma. Surg Endosc. 2022 Mar 4. doi: 10.1007/s00464-022-09167-0. Epub ahead of print. PMID: 35246741.

72 ☆ AUA Update 2014, vol 33, Lesson 19 (Kutikov et al.)

73 Sacco E, Bientinesi R, Gandi C, Di Gianfrancesco L, Pierconti F, Racioppi M, Bassi P. Patient pad count is a poor measure of urinary incontinence compared with 48-h pad test: results of a large-scale multicentre study. BJU Int. 2019 May;123(5A):E69-E78.