Tumors of the Adrenal Gland

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Adrenal Incidentaloma

Background

An adrenal mass identified on an imaging study performed for reasons other than cancer staging or adrenal disease is considered an incidentaloma. Typically, this refers to lesions that are 1 cm or greater. According to autopsy series, clinically inapparent adrenal masses have a 2.1% prevalence, increasing up to 7% among those 70 years of age or older. However, literature reviews report an incidentalomas rate of 1–5% [1–3]. These lesions can be classified as functional or nonfunctional benign masses, and malignant tumors. More than 80% of incidentalomas are nonfunctional tumors, with cortical adenomas dominating as the most commonly identified incidentaloma. Of the remainder, approximately 5% cause subclinical or clinical Cushing syndrome (SCS), 5% are pheochromocytomas, 1% are aldosteronoma, while <5% make up adrenocortical carcinoma (ACC), and 2.5% are a metastatic lesion [4] (See Box 1.1).

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Box 1.1 Differential diagnosis for adrenal incidentaloma

Functional Tumours	Pheochromocytoma	Cortisol Producing Adenoma	Aldosteronoma	Primary Adrenal Hyperplasia
Nonfunctional Tumours	Adenoma	Myelolipoma	Cyst	Ganglioneuroma
Malignant Tumours	Adrenocortical Carcinoma	Metastases		

Workup [4]

- When an adrenal mass is identified on imaging, the patient should be evaluated further to determine these key features that will help direct future management:
  - Determine if the tumor is functionally active (i.e., hypersecreting adrenal hormones)
  - Determine the risk of malignancy
- This should start with a detailed history and physical examination of the patient. The exam should focus on signs or symptoms of hormone excess, a personal history of cancer.
- To determine if the lesion is functional, a biochemical evaluation is required (see *algorithm 1*). Finally, a detailed review of the imaging which identified the lesion is required, followed with any further imaging, if necessary (Fig. 1.1).

Imaging

- Imaging is used to help distinguish between the different types of adrenal lesions in Box 1.1. Most adrenal lesions are described with CT scan or MRI [2].
- Adrenal CT protocol, which includes an unenhanced, early contrast-enhanced and delayed contrast-enhanced phase can help identify adenomas and differentiate lipid-poor adenomas from other lesions [2].
- While a formal adrenal protocol can help differentiate between adrenal adenoma, pheochromocytoma, metastatic lesions, and possibly adrenal cortical carcinoma, it does not take the place of formal biochemical testing [4].
- To differentiate the diagnosis of an adrenal lesion, radiologists rely on several imaging characteristics, including contrast enhancement, washout, and the Hounsfield units of different tumor types (see Table 1.1).
  - Size can be helpful to determine risk of malignancy as larger lesions have a much higher rate of cancer than smaller masses.
  - Specific criteria which increase the risk of a lesion include size greater than 4–6 cm on CT, tumors with ≥10 HU, a delayed washout of contrast (<40% at 15 min), calcification, irregular margins, or invasion into surrounding structures are all concerning features for malignancy [4, 5].
  - Malignant lesions typically have rapid initial enhancement with slow washout, in contrast to adenomas where contrast washout is rapid [5].

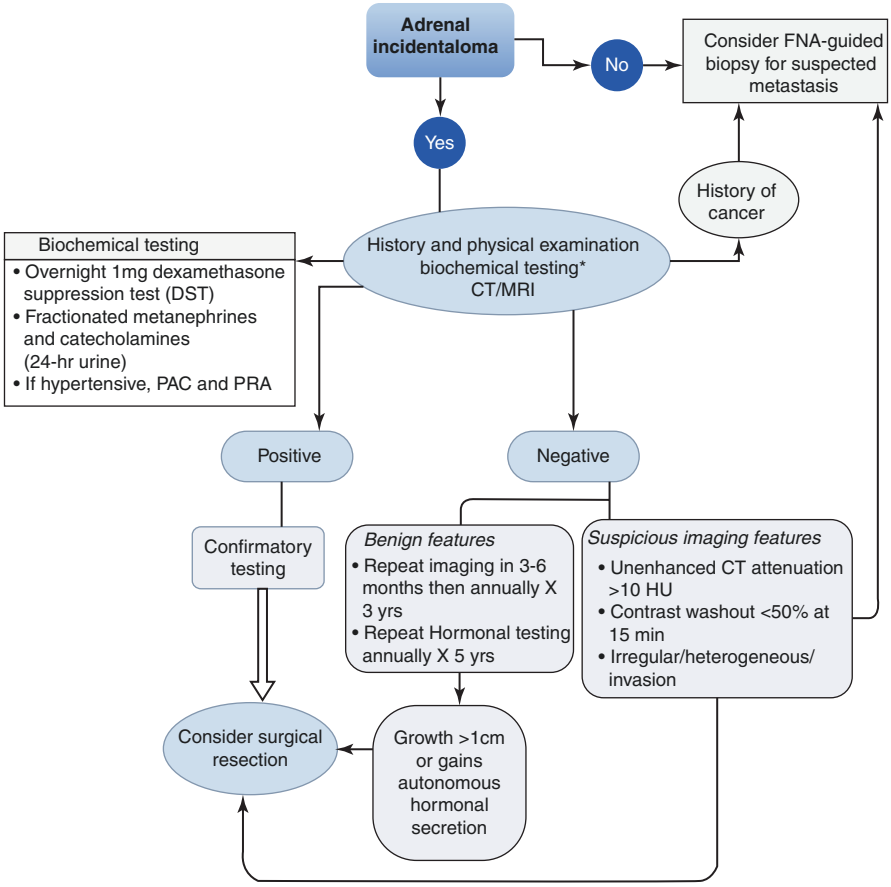

Fig. 1.1 Algorithm for workup and management of adrenal incidentaloma [23, 24]

Management and Follow-Up [4]

- There is a risk of mass enlargement or becoming functionally active.
  - One-, 2-, and 5-year risk of growth is 6%, 14%, and 29%, respectively.
  - One-, 2- and 5-year risk of hypersecreting hormones is 17%, 29%, and 47%, respectively.
- Therefore, lesions that do not meet criteria for surgical resection should be followed.
  - Repeat imaging at 6 months, then annually for 1–2 years.
  - Repeat functional testing can be considered.

Table 1.1 Imaging characteristics of benign and malignant adrenal masses [2, 4]

Lesion type	CT	MRI
Benign adenoma	Homogenous, well-defined Typically <4 cm <10HU on nonenhanced scan Enhanced CT scan with 15-min washout ≥40%	Low T2 signal intensity on MRI Loss of signal intensity on opposed-phase chemical shift sequences on MRI
Pheochromocytoma	Vascular >20HU on nonenhanced CT scan <50% washout at 15 min on contrast-enhanced CT scan	High T2 signal on MRI
Adrenocortical carcinoma	Large, heterogeneous, irregular, possible invasion into surrounding structures >18HU on nonenhanced CT scan Enhanced CT scan with 15-min washout ≤40%	Bright on T2-weighted MRI No loss of signal intensity on opposed-phase MRI images
Adrenal metastases	Irregular nonhomogeneous >20HU on nonenhanced CT scan <50% washout after 15 min on contrast-enhanced CT scan	Intermediate to high intensity on T2-weighted MRI

Indications for Adrenalectomy [4–6]

- Functional tumor
- Malignancy/potential malignancy (heterogeneous, irregular borders, invasion of surrounding structures, size ≥4 cm)
- Local symptoms
- Uncertain diagnosis
- Growth of >1 cm

Functional Adrenal Tumors

Pheochromocytoma

Overview

Workup

- All incidentalomas suspected of pheochromocytoma should be evaluated through history and physical examination.
  - Episodic headache.
  - Sweating.
  - Tachycardia.
  - Palpitations.
  - Tremor.
  - Hypertension.

Table 1.2 Workup and management of pheochromocytoma [4, 25]

Workup	Perioperative management	Surgical management	Adjunctive therapy (malignant disease)	Follow-up
History and physical *Laboratory investigations* Consider confirmatory test (i.e., clonidine suppression test) *Imaging* Thin-cut spiral CT or MRI MIBG scan (to assess for multiple tumors or malignancy) If MRI/CT negative and diagnosis still suspected >10 cm adrenal mass or paraganglionoma	*Preoperative* Alpha adrenergic blockade Fluid and electrolyte repletion Beta-blockade after alpha-blockade, as needed	*Benign disease* Laparoscopic adrenalectomy Minimal tumor handling to decrease excess catecholamine surge Early division of adrenal vein in laparoscopic anterior approach Close communication with anesthesia *Malignant disease* Resect primary and metastatic lesions if possible to reduce symptoms of hormone excess May improve efficacy of subsequent treatment	*Chemotherapy* [7] Consider in unresectable or rapidly growing tumors Combination of vincristine, cyclophosphamide, dacarbazine, doxorubicin ~50% will respond *Radiation* For bulky symptomatic primaries Bony metastases *I-131 MIBG* [8] If tumor takes up MIBG (60% of tumors) Response rate of 30% *Consider 68-Ga DOTATE or PRRT*	*Completely resected disease* Q6–12 months H&P BP check Plasma metanephrines Annually Consider imaging *Incompletely resected disease* Q3–4 months H&P BP check Plasma metanephrines Imaging

- Investigation for biochemical evidence of pheochromocytoma using measurement of plasma fractionated metanephrines and normetanephrines (more sensitive) OR 24-hour urinary metanephrines and fractionated catecholamines (more specific) [9] (see Table 1.2).
- If metastatic pheochromocytoma is suspected, further imaging may be indicated [9].
  - MIBG scan.
  - Somatostatin receptor-based imaging (i.e., ^{68}Ga-dotate PET/CT scintigraphy)[a].
  - FDG-PET/CT[b]

[a]^{68}Ga-dotatate PET/CT is more sensitive than somatostatin receptor scintigraphy for determining somatostatin receptor status [9]

[b]Both FDG-PET/CT and ^{68}Ga-dotatate PET/CT scintigraphy have >90% sensitivity, but signal intensity was significantly greater in the latter, with lower background activity [10]

Perioperative Considerations

- All patients should have α-adrenergic blockade for 1–3 weeks preoperatively [4].
  - Always start with α-blockers (e.g., phenoxybenzamine 10 mg BID or doxazosin).
  - Titrate dose until patient is normotensive or intolerable side effects develop (i.e., orthostatic hypotension).
  - May need to add β-blockade if they have persistent tachycardia or arrhythmias. Propranolol 10–40 mg q6–8 h most commonly used.
    Must not use β-blocker if alpha-blockade not optimized.
- Encourage liberal fluid and salt intake to counteract the intravascular volume depletion caused by pheochromocytoma.
- Intraoperative hypertension should be controlled with nitroprusside, nicardipine, nitroglycerine, or phentolamine. If tachyarrhythmia develops, treat with esmolol/lidocaine.
- Monitor for hypotension and hypoglycemia in immediate postoperative period
- Hold all antihypertensive agents postoperatively; add back agents as needed as some patients have underlying essential hypertension.
- Do not abruptly stop β-blockers in patients treated chronically, especially older patients with ischemic heart disease [4].

Genetic Testing

- 25% of patients with pheochromocytoma have an associated genetic syndrome [4, 11].
  - These patients tend to present at a younger age and some with bilateral disease.
- Autosomal dominant familial disorders associated with adrenal pheochromocytoma.

Von-Hippel-Lindau (VHL) [12]
Pheochromocytoma (20%); paraganglioma; hemangioblastoma; retinal angioma; renal cell carcinoma; pancreatic neuroendocrine tumors; cystadenomas of pancreas, broad ligament and epididymis.
Multiple endocrine neoplasia type 2 (MEN-2) [12]
Pheochromocytoma (50%); medullary thyroid cancer (100%); primary hyperparathyroidism (20%); primary lichen amyloidosis (5%).
Only 3–5% of pheochromocytoma in MEN-2 are malignant. Highest risk seen in RET codon mutations 918, 634, 883).
Neurofibromatosis type 1 [12]
Pheochromocytoma (2%); café au lait patches; CNS gliomas; cognitive deficits; bony abnormalities.
Familial pheochromocytoma [12]
Germ-line mutations of genes encoding succinate dehydrogenase subunits B, C, and D.
Individuals with succinate dehydrogenase B mutations are more likely to develop malignant disease [13].

- Due to a high association of pheochromocytoma with genetic disease, all patients should be considered for screening.
- Testing includes mutations for RET, VHL genes, and subunits of succinate dehydrogenase genes [4].

Cushing Syndrome

Overview

Workup [4]

- Patients should also be evaluated for cardiovascular and metabolic comorbidities (diabetes, hypertension, osteoporosis) along with signs of hypercortisolism:
  - Weight gain.
  - Proximal muscle weakness.
  - Easy bruising, striae, skin atrophy.
  - Central obesity, dorsal cervical fat pad, "moon face."
- Severe hypercortisolism suppresses immunity and predisposes to severe infections [16].
- Patients with an adenoma without physical signs of hypercortisolism may have subclinical Cushing syndrome (SCS) and require further testing (see Table 1.3).
  - A diagnosis of SCS is still controversial, and many consider it a continuum between no functional excess and Cushing Syndrome; however, many con-

Table 1.3 Workup and management of cortisol-producing adenoma

Workup	Perioperative management	Surgical management	Medical Management
History and physical *Laboratory investigations* Screen with one of the following [14, 15]: 1 mg overnight dexamethasone suppression test Midnight salivary cortisol (≥2) 24-h UFC ≥ 2 Confirmatory testing if +ve If hypercortisolemic, perform serum ACTH (8 am cortisol) *Imaging* Thin-cut adrenal CT ± MRI	*Preoperative* VTE prophylaxis (>10-fold greater risk of VTE) Manage hyperglycemia Manage HTN Postoperative Maintain glucocorticoid therapy—may need stress dosing Manage hyperglycemia	Adrenalectomy[b] Unilateral for confirmed cortisol-producing tumor Bilateral for AIMAH or PPNAD	If surgical treatment not possible or to control cortisol secretion while waiting for surgery Agents include metyrapone, ketoconazole

UFC urine free cortisol, *AIMAH* ACTH-independent macronodular adrenal hyperplasia, *PPNAD* primary pigmented nodular adrenocortical disease

sider the diagnosis established if the serum cortisol is >5.0 ng/dL after a 1-mg DST [4], while excluded if ≤50 nmol/L (≤1.8 μg/dL) [6].
  - May need a 2-day low-dose DST to confirm the diagnosis—consider referral to endocrinologist.
- The overnight 1 mg DST should be administered at 11 pm and fasting plasma cortisol and ACTH level measured between 8 and 9 AM the following day [4].
  - Cortisol suppression <1.8 ng/dL has the best negative predictive value for Cushing syndrome.

Perioperative Considerations

- Patients with SCS should have individualized treatment plan.
  - No consensus on long-term benefits of adrenalectomy (see Table 1.4)
  - Adrenalectomy typically reserved for younger patients with recent onset or worsening HTN, diabetes, dyslipidemia, or osteoporosis [4].
- Patients with long-standing hypercortisolism should be considered immunosuppressed and given antibiotic and peptic ulcer prophylaxis.
- Increased thromboembolic risk precludes preoperative VTE prophylaxis.
- Those with cortisol-producing adenomas have a suppressed HPA axis should receive glucocorticoids postoperatively until recovery (which may take 6–18 months), there has been some evidence to check ACTH stimulated cortisol in the immediate postoperative period which if not suppressed can guide steroid replacement [4].

Autonomous Cortisol Secretion (Subclinical Cushing Syndrome (SCS))

- Patients have an elevated cortisol without overt signs or symptoms of Cushing syndrome.

Table 1.4 Metabolic outcomes after adrenalectomy for SCS [18–20]

Study	Author (year)	Methods	Results
Biochemical and clinical benefits of unilateral adrenalectomy in patients with subclinical hypercortisolism and bilateral adrenal incidentalomas	Perogamvros et al. (2015) [18]	33 pts with bilateral AI 14 pts underwent unilateral adrenalectomy 19 pts f/u only Measured 0800 h plasma ACTH, 12 AM serum cortisol (MSF), 24-h urinary-free cortisol (UFC) and serum cortisol after a 2-day low-dose-dexamethasone-suppression test Assessed arterial HTN, impaired glucose tolerance or diabetes mellitus, dyslipidemia, and osteoporosis	Surgical group had a statistically significant reduction in all biochemical markers ($p < 0.05$) Comorbidities only improved in the surgical group as measured by objective tests and medication use (OGGT, BP readings, DEXA)

Table 1.4 (continued)

Study	Author (year)	Methods	Results
Adrenalectomy may improve cardiovascular and metabolic impairment and ameliorate quality of life in patients with adrenal incidentalomas and subclinical Cushing syndrome	Iacobone et al. (2012) [19]	20 pts with AI underwent laparoscopic adrenalectomy 15 managed nonoperatively Measured corticosteroid secretion, arterial blood pressure (BP), glycometabolic profile (lipid profile, hemoglobin A1C, fasting serum glucose, BMI), and quality of life (by the SF-36 questionnaire) at baseline and the end of follow-up Follow-up was median 36 months	Compared to conservatively managed group (which had no improvements): Lab corticosteroid parameters normalized in all surgical pts ($P < 0.001$) A decrease in BP occurred in 53%, glycometabolic control improved in 50%, and BMI decreased ($P < 0.01$) SF-36 evaluation improved ($P < 0.05$)
Outcome of adrenalectomy for subclinical hypercortisolism and Cushing syndrome	Raffaelli et al. (2017) [20]	Retrospective review of 29 pts with SCS and 50 pts with CS who underwent unilateral laparoscopic adrenalectomy Assessed baseline and follow-up comorbidities (BMI, HTN, diabetes) Measured ACTH, AM cortisol, 1 mg DST, UFC, blood glucose Outcomes: OR time, intraoperative/postoperative complications, need for postoperative glucocorticoid replacement, clinical and hormonal outcomes Mean F/U 51 months	Hypercortisolism resolved in all patients At long-term f/u HTN and diabetes improved significantly for all patients (no differences seen between SCS and CS groups)

Pts patients, *AI* adrenal incidentaloma, *F/U* follow-up, *HTN* hypertension, *OGGT* oral glucose tolerance test, *DEXA* dual energy X-ray absorptiometry, *SCS* subclinical Cushing syndrome, *CS* Cushing syndrome

  - However, many observational studies have reported complications typical of hypercortisolism such as obesity, diabetes, hypertension, dyslipidemia, and osteoporosis [16].
- Data is lacking for which localization studies may be effective in diagnosing SCS in patients with bilateral adrenal nodules.
- SCS is reported in 5–48% of incidentalomas making it the most frequent hormonal abnormality among these patients [17].

- The clinical relevance and optimal management of SCS are still in question [16].
- Several retrospective studies have evaluated the outcomes after adrenalectomy on patients with SCS (see Table 1.4).
- Both American and European practice guidelines recommend an individualized approach to management of these patients, accounting for age, onset, and duration of any comorbidities and how well they are controlled by medical management in addition to the extent of end-organ damage (European practice guidelines/AAES) [4, 6].
- The AACE/AAES Adrenal Incidentaloma guidelines specify those <40 years with recent onset or worsening of diabetes, hypertension, or osteoporosis should be considered for surgery, while older patients should have a more individualized approach [4].

Primary Aldosteronism

Overview

Workup [4, 6, 26]

- While only 1% of adrenal incidentalomas are aldosterone-producing adenomas, a screening workup to rule this out should still be performed specifically for those with hypertension (see Table 1.5).
- History and physical may reveal hypertension, headaches, fatigue, polydipsia, polyuria, nocturia.
- It should be emphasized that many patients with aldosteronomas *do not* have hypokalemia.

Table 1.5 Workup and management of aldosterone-producing adenoma [4]

Workup	Perioperative management	Surgical management	Medical management
History and physical *Laboratory Investigations* Electrolytes, creatinine PAC:PRA >20 Confirmatory testing if positive *Imaging* Thin-cut adrenal CT ± MRI Adrenal vein sampling (AVS) if indicated (see below)	*Preoperative* Control of HTN Manage hypokalemia (spironolactone, KCl)	Adrenalectomy Unilateral for confirmed lateralization on AVS	If no lateralization or bilateral involvement (cortical adrenal hyperplasia): K+-sparing diuretics and restriction of sodium intake (<100 mEq/day)

- A plasma aldosterone concentration (PAC) (ng/dL) to plasma renin activity (PRA) (ng/mL) (aldosterone-to-renin ratio [ARR]) should be measured when patient is off any mineralocorticoid receptor blockers.
  - A ratio >20 should prompt confirmatory testing.
  - One study reported a sensitivity and specificity of 90% and 91%, respectively, with a PAC:PRA >30 combined with a PAC >20 ng/dL.
  - This is most sensitive when measured in the morning after being seated for 5–15 min.
  - Spironolactone/eplerenone should be held for 4–6 weeks.
  - ACE inhibitors and ARBs can improve the diagnostic power of the PAC:PRA.
  - β-blockers and clonidine suppress the PRA➔ increased false positive rate.
- Confirmatory testing is positive if aldosterone or ARR suppression occurs with:
  - Oral Na + load (with >200 mEq/day of Na × 3 days) and 24-hr urine aldosterone.
  - IV Na + load (2–3 L of NaCl 0.9% over 4–6 h) with plasma aldosterone measurement.
  - Fludrocortisone suppression and ARR measurement.
  - Captopril challenge.

Adrenal Vein Sampling

- Primary hyperaldosteronism can be due to an aldosteronoma, primary (unilateral) adrenal hyperplasia (PAH).
- Adrenal vein sampling (AVS) can be performed to delineate between these lesions.
- Those with unilateral microadenomas (<1 cm) or bilateral abnormal appearing glands should be considered for AVS [27].
- It is important to have AVS done by a high volume center who is comfortable with ACTH stimulation.
- Spironolactone should be held for 6 weeks and eplerenone for 4 weeks prior to AVS [4].
- A "lateralization index" or corrected aldosterone to cortisol ratio > 4:1 is indicative of unilateral source of aldosterone excess.
  - These patients are more likely responsive to adrenalectomy [4].
- Factors associated with lateralization on AVS include an adrenal mass ≥ 3 cm on CT scan, a low renin value and high plasma ARR [28].

Perioperative Considerations

- All patients with unilateral primary hyperaldosteronism should be considered for surgical resection.

  - Untreated hyperaldosteronism can lead to myocardial fibrosis, increased clotting and ischemic events, left ventricular hypertrophy, and increased mortality from CHF [4].
  - These changes occur despite medical management of hypertension and hypokalemia.
- Preoperative medications for most patients include mineralocorticoid receptor antagonist, antihypertensive agents, potassium chloride to maintain normokalemia.
- These agents are stopped postoperatively; if blood pressure remains elevated, add back antihypertensive medications [5].
  - Normotension (without medication) may take several weeks.
  - 90% of patients will have significant reductions in blood pressure, with reduction in dosing and number of antihypertensive medication.
  - 30–60% will discontinue all medications.
  - 100% will achieve normokalemia.

Prediction of Cure (Aldosterone Resolution Score)

- There are numerous factors associated with hypertension resolution after adrenalectomy.
- Zarnegar et al. developed an aldosterone resolution score (ARS) to predict resolution of hypertension based on 4 clinical variables [21].
  - ≤2 antihypertensive medications.
  - BMI ≤25 kg/m^2.
  - Duration of HTN ≤6 years.
  - Female sex.
- Taking two or fewer antihypertensive medications has the strongest independent predictor of resolution [21].
- Other factors that have been implicated include ≤1 first-degree relative with hypertension, higher preoperative ARR, higher urinary aldosterone secretion, and strong positive response to spironolactone [22].

Adrenocortical Carcinoma

- Adrenocortical carcinomas (ACCs) are rare tumors occurring with an incidence of 0.5–2 per million patients per year. ACC has a bimodal age distribution with increased incidence in children <6 years and in adults in their 40s and 50s [29]. ACCs may be either nonfunctional or associated with symptoms of hormonal excess. An overview of the workup and management of ACC is presented in Table 1.6.
- ACC appears to be mostly sporadic; however, in ~10% of cases it is associated with a hereditary cancer syndrome including [30]:
  - Li-Fraumeni syndrome (4–8% of adult-onset ACC) or SBLA syndrome (sarcoma, breast cancer, lung cancer, and ACC) [31]

Table 1.6 The ENSAT staging system for ACC

Presentation	5-year overall survival
Tumor ≤5 cm confined to the adrenal gland without local invasion [Stage I, T1N0M0]	82%
Tumor >5 cm confined to the adrenal gland without local invasion [Stage II, T2N0M0]	61%
Any size with local invasion, ± invasion to adjacent organs/great vessels (T3–4) or regional lymph nodes (N1) [Stage III, T3-4N0-1M0]	50%
Distant metastasis [Stage IV, TxNxM1]	13%

  - Lynch syndrome (MLH1, MSH2, MSH6, PMS2 mutations) in ~3% of ACC cases (all ACCs should be screened for microsatellite instability).
  - Multiple endocrine neoplasia (MEN) type 1 [parathyroid, pituitary and pancreatic neuroendocrine tumors and adrenal tumors (ACC << adrenal adenomas)] in 1–2% of ACC cases [32].
- 60% of ACCs present with symptoms of hormone excess [29].
  - 40% Cushing syndrome alone.
  - 25% mixed virilization and Cushing.
  - <10% virilization alone.
  - <10% feminizing (all feminizing tumours in men are malignant).
  - <10% hyperaldosteronism—this is usually to cross reactivity of the aldosterone receptor from cortisol at high concentrations.

Preoperative Workup [33]

- Biochemical evaluation (as per incidentaloma)
- Imaging:
  - CT chest (evaluate for pulmonary metastases)
  - CT abdomen (adrenal protocol: precontrast, portal, and delayed venous phase) and/or MRI
  - Bone scan (if clinical suspicion)
  - FDG-PET/CT reserved for indeterminate sites of potential metastases
  - CT characteristics: Irregular, heterogeneous (due to tumor necrosis), unilateral, >20HU (Hounsfield units), heterogeneous enhancement with IV contrast, delayed washout, possible tumor calcification.
- Biopsy:
  - Generally not advisable due to low sensitivity and risk for tract seeding. Indications for biopsy include unresectable cases (where tissue is needed for initiation of systemic therapy) or high suspicion for adrenal metastasis. It is important to consider that adrenalectomy is a good diagnostic procedure as well for atypical lesions and may take the place of biopsies. Pheochromocytoma must be ruled out prior to consideration for biopsy.

Prognostic Factors

1. Stage (as per the European Network for The Study of Adrenal Tumors [ENSAT], see Table 1.6) [34]
2. GRAS parameters (Grade, R status, Age, Secretion)

- Grade: Weiss' histological scoring system includes 9 features (nuclear grade, mitotic rate, atypical mitoses, clear cell component, diffuse architecture, tumor necrosis, invasion of venous or sinus structures, or tumor capsule) [35] Weiss score <3 usually indicates benign tumor [35], while score >6 has been associated with decreased overall survival ($p = 0.03$) [36]. Markers of proliferation (KI-67 and mitotic rate) also indicate poorer prognosis [36–38].
  - R status: R0 (margin-negative) resection was the sole independent predictor of overall survival in a recent multi-institutional study (5-year OS 64.8% for R0 vs 33.8% for R1 resection, $p < 0.001$) [39]. R0 resection is also a significant predictor of recurrence (5-year RFS 30% for R0 vs 14% for R1 resection, $p = 0.03$) [39–41].
  - Age: Older age has been associated with worse survival [36, 41].
  - Secretion: Hormone secretion, especially cortisol, is associated with worse survival [36, 39, 41].

Operative Considerations

- The operation of choice is radical surgical excision with wide margins and en bloc resection of adjacent involved organs (if needed) [33].
- The role of regional lymphadenectomy is still debated, but recent retrospective studies suggest it may offer a survival benefit [42–44]. Both indications and extent need to be clarified.
- An open approach is currently recommended for ACC resection due to its friable thin capsule and potential for seeding [33]. The use of laparoscopy for ACC is being explored in Europe where retrospective series reported similar oncologic outcomes for laparoscopically resected Stage I–II tumors in highly selected patients [45, 46].
- For patients presenting with oligometastatic disease at time of initial diagnosis, surgical resection of all disease may be beneficial (in addition to systemic therapy) in selected patients specifically patients with functional disease [30, 47].

Adjuvant and Systemic Therapy

- Traditionally mitotane has been offered in the adjuvant setting, especially for high-risk tumors (Stage III, R1 resection, or Ki-67 > 10%) based on earlier retrospective studies from Europe [48, 49], but recent studies failed to demonstrate any benefit [50, 51]. The ADIUVO trial (open-label RCT comparing adjuvant

Table 1.7 Overview of the workup and management of adrenocortical carcinoma

	Management		
Workup	Localized disease	Metastatic disease	Follow-up
History and physical exam Labs: As per incidentaloma [33] Imaging: CT abdomen +/− MRI CT chest Bone scan (if clinically suspicious) PET (for indeterminate remote metastases) Biopsy: Should be avoided (risk of seeding and limited usefulness in differentiating benign vs malignant). May perform if unresectable and needed to initiate systemic therapy or if suspicious for adrenal metastasis	Surgical excision with en bloc resection of adjacent involved organs if needed Consider adjuvant mitotane and/or radiation therapy, especially in high-risk cases	Complete resection of limited oligometastatic resectable disease may be beneficial in highly selected patients Radiation for bony metastases if symptomatic RFA or embolization for hepatic metastases Mitotane monotherapy Mitotane plus chemotherapy (etoposide, doxorubicin, cisplatin)	Clinically: Cushing syndrome Virilization syndrome Labs and imaging (q 6 months): Urinary cortisol CT scan chest/abdo/pelvis for 5 years

RFA radiofrequency ablation

mitotane vs observation in Stage I–III ACC, R0 resection, and Ki-67 < 10%) completed accrual and is expect to shed further light [52].

- Adjuvant external beam radiation has been offered in the adjuvant setting for high-risk tumors and was shown to decrease local recurrence in small retrospective series [53]. Further research is needed to identify the patients in whom radiation may offer a survival advantage.
- For advanced unresectable and metastatic ACC, EDP (etoposide, doxorubicin, cisplatin)-mitotane is considered first-line therapy based on one RCT comparing it with streptozocin-mitotane [54]. Single-agent therapy with mitotane is an alternative (less toxicity). Local therapeutic measures (radiation, ablation, chemoembolization) may also be of value [55].
- Molecular targeted agents and immune checkpoint inhibitors are currently being investigated for ACC (Table 1.7).

Special Notes:

There may be role for repeat surgery for recurrent disease in patients with recurrence-free interval >12 months and completely resectable disease [56].

Metastases to the Adrenal Gland

- In patients with no history of malignancy, <1% of adrenal tumors represent metastatic disease. In patients with a history of malignancy, however, 70% of adrenal tumors represent metastases from other sites.

- The adrenal gland is the fourth most common site of metastasis after the lungs, liver, and bone.
- In Western countries, lung, breast, melanoma, kidney, thyroid, and colon cancer primaries are most common. In a large retrospective series (including autopsies) from Hong Kong, most common primaries included lung (35%), gastric (14%), esophageal (12%), hepatobiliary (11%), or pancreatic (7%) cancer [57].

Workup

- Imaging characteristics: Irregular, heterogeneous, frequently bilateral, >20 HU, enhancement with IV contrast, delayed washout.
- Workup as by the primary malignancy
- Role of FNA
  - Main utility of FNA is for diagnostic uncertainty in the setting an indeterminate adrenal lesion which may represent a metastasis and excision by adrenalectomy is not first choice by treatment team [58].
  - *Must* rule out pheochromocytoma prior to biopsy [59].
  - Laparoscopic adrenalectomy is performed for diagnostic and therapeutic purposes in adrenal incidentaloma or metastatic disease.

Indications for Resection of Adrenal Metastasis

- Potential benefit in survival for selected patients.
- Non-small-cell lung cancer: median survival 26 months [60], 5-year overall survival 34% vs 0% [61, 62].
- Colorectal cancer: median survival 29 months [60].
  - Laparoscopic approach is becoming standard for resection of metastatic disease due to lower perioperative morbidity and faster recovery and return to chemotherapy [63, 64].

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