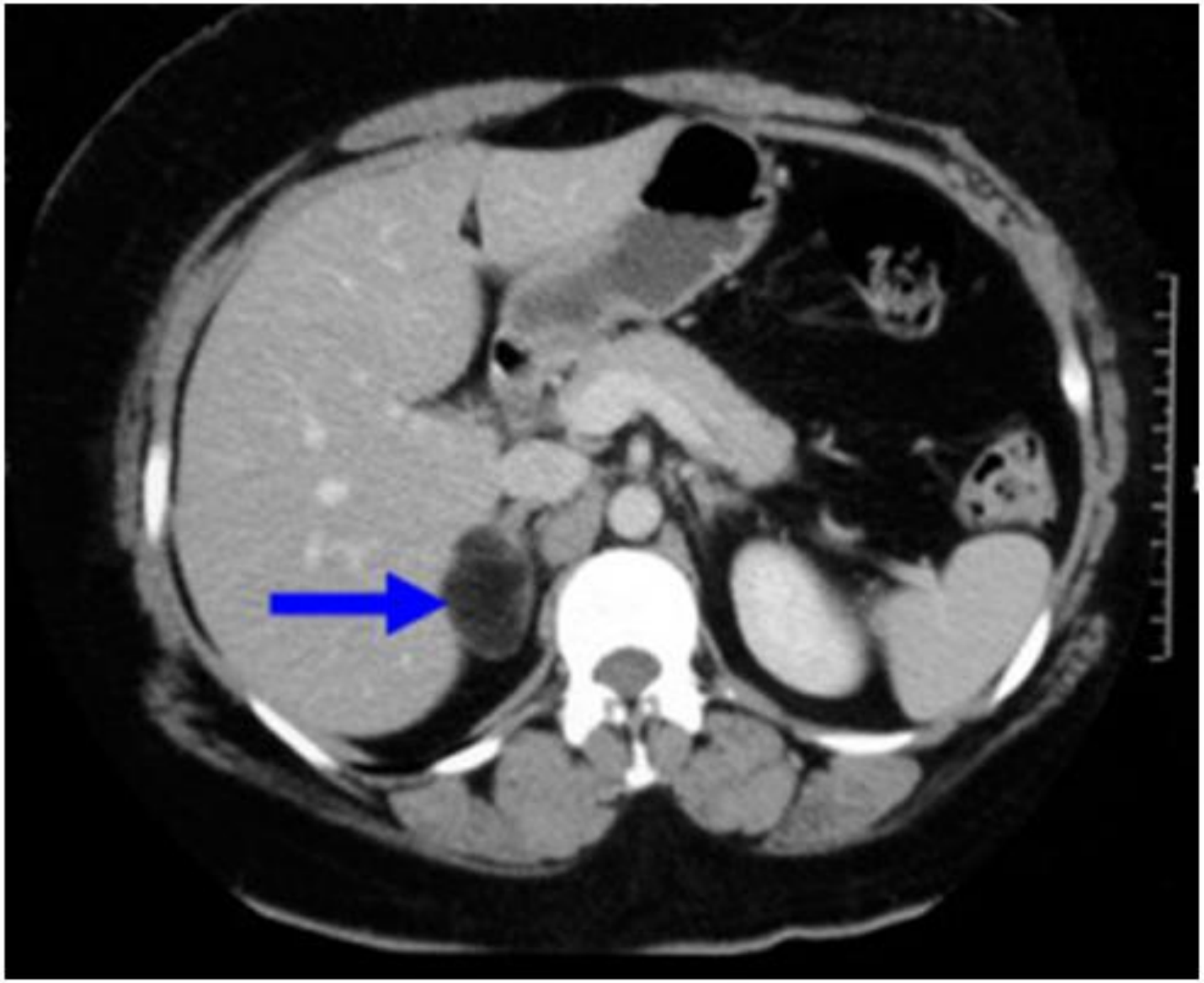
Adrenal incidentaloma

nmzmd

- **A 62-year-old woman is referred for further evaluation of an adrenal mass that was discovered after she underwent abdominal CT to investigate possible renal calculi. The mass measures 2.8 x 2.2 cm and has a density of-10 Hounsfield units without contrast. The patient has a history of hypertension treated with amlodipine. She takes no other medications.**
- **On physical examination, her height is 66 in (167.6 cm) and weight is 180 lb (81.8 kg) (BMI = 29 kg/m2). Her blood pressure is 142/89 mmHg (supine). She has evidence of non violaceous striae across her abdominal wall.**

- **Laboratory test results:**
- **Glucose = 140 mg/dL (7.8 mmol/L)**
- **Plasma renin activity = 3.5 ng/mL per h**
- **Aldosterone = 17 ng/dL (471.6 pmol/L)**
- **ACTH = 12 pg/mL (2.6 pmol/L)**
- **DHEA-S = 5 µg/dL (0.14 µmol/L)**
- **Serum cortisol (8 AM;1-mg overnight dexamethasone suppression test)=5.4 µg/dL (150.0 nmol/L)**
- **Urinary metanephrine = 281 µg/24 h (1425 nmol/d)**
- **Urinary normetanephrine = 578 µg/24 h (3418 nmol/d)**
- **Urinary cortisol = 68 µg/24 h (187.7 nmol/L)**

- **Which of the following is the most appropriate next investigation?**
- **A. Corticotropin-releasing hormone test**
- **B. DXA scan**
- **C. Repeated screening tests for cortisol excess in 6 months**
- **D. High-dose (8-mg) dexamethasone suppression test**
- **E. Adrenal-directed MRI**



- **APPROACH TO THE PATIENT: INCIDENTALLY DISCOVERED ADRENAL MASS**

Epidemiology

- Incidentally discovered adrenal masses, commonly termed adrenal "incidentalomas," are common, with a prevalence of 2–5% in the general population as documented in CT and autopsy series.
- The prevalence increases with age, with 1% of 40-year-olds and 7% of 70-year-olds harboring an adrenal mass.

Etiology

- Most solitary adrenal tumors are monoclonal neoplasms. Several genetic syndromes, including MEN 1 (*MEN1*), MEN 2 (*RET*), Carney's complex (*PRKAR1A*), and McCune-Albright (*GNAS1*), can have adrenal tumors as one of their features. Somatic mutations in *MEN1, GNAS1*, and *PRKAR1A* have been identified in a small proportion of sporadic adrenocortical adenomas. Aberrant expression of membrane receptors (GIP, α- and β-adrenergic, luteinizing hormone, vasopressin V1, and interleukin 1 receptors) has been identified in some sporadic cases of macronodular adrenocortical hyperplasia.
- The majority of adrenal nodules are endocrine-inactive adrenocortical adenomas. However, larger series suggest that up to 25% of adrenal nodules are hormonally active, due to a cortisol- or aldosterone-producing adrenocortical adenoma or a pheochromocytoma associated with catecholamine excess **(Table 379-5)**. ACC is rare but is the cause of an adrenal mass in 5% of patients. However, metastases originating from another solid tissue tumor are an additional cause of adrenal incidentaloma, and have a higher incidence in patients undergoing imaging for tumor staging or follow-up monitoring.

TABLE 379-5 Classification of Unilateral Adrenal Masses

MASS	APPROXIMATE PREVALENCE (%)
Benign	
Adrenocortical adenoma	
Endocrine-inactive	60–85
Cortisol-producing	5–10
Aldosterone-producing	2–5
Pheochromocytoma	5–10
Adrenal myelolipoma	<1
Adrenal ganglioneuroma	<0.1
Adrenal hemangioma	<0.1
Adrenal cyst	<1
Adrenal hematoma/hemorrhagic infarction	<1
Indeterminate	
Adrenocortical oncocytoma	<1
Malignant	
Adrenocortical carcinoma	2–5
Malignant pheochromocytoma	<1
Adrenal neuroblastoma	<0.1
Lymphomas (including primary adrenal lymphoma)	<1
Metastases (most frequent: breast, lung)	1–2

Note: Bilateral adrenal enlargement/masses may be caused by congenital adrenal hyperplasia, bilateral macronodular hyperplasia, bilateral hemorrhage (due to antiphospholipid syndrome or sepsis-associated Waterhouse-Friderichsen syndrome), granuloma, amyloidosis, or infiltrative disease including tuberculosis.

Differential Diagnosis and Treatment

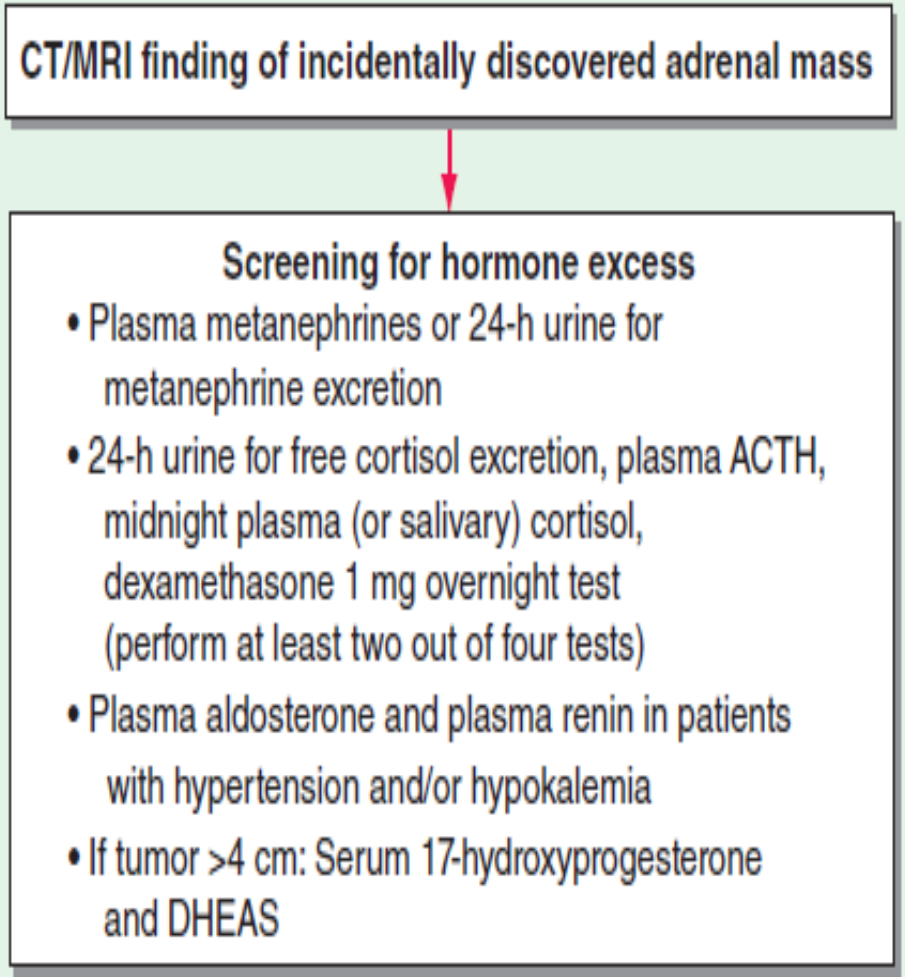
- Patients with an adrenal mass >1 cm require a diagnostic evaluation.
- Two key questions need to be addressed:
- (1) Does the tumor autonomously secrete hormones that could have a detrimental effect on health?
- (2) Is the adrenal mass benign or malignant?

- Hormone secretion by an adrenal mass occurs along a continuum, with a gradual increase in clinical manifestations in parallel with hormone levels.
- Exclusion of catecholamine excess from a pheochromocytoma arising from the adrenal medulla is a mandatory part of the diagnostic workup **(Fig. 379-13)**.

- Furthermore, autonomous cortisol resulting in Cushing's syndrome requires exclusion and, in patients with hypertension or low serum potassium, also primary aldosteronism. Adrenal incidentalomas can be associated with MACE, and patients usually lack overt clinical features of Cushing's syndrome.

- Nonetheless, they may exhibit one or more components of the metabolic syndrome (e.g., obesity, type 2 diabetes, or hypertension). There is ongoing debate about the optimal treatment for these patients.

Algorithm for the Management of the Patient with an Incidentally Discovered Adrenal Mass



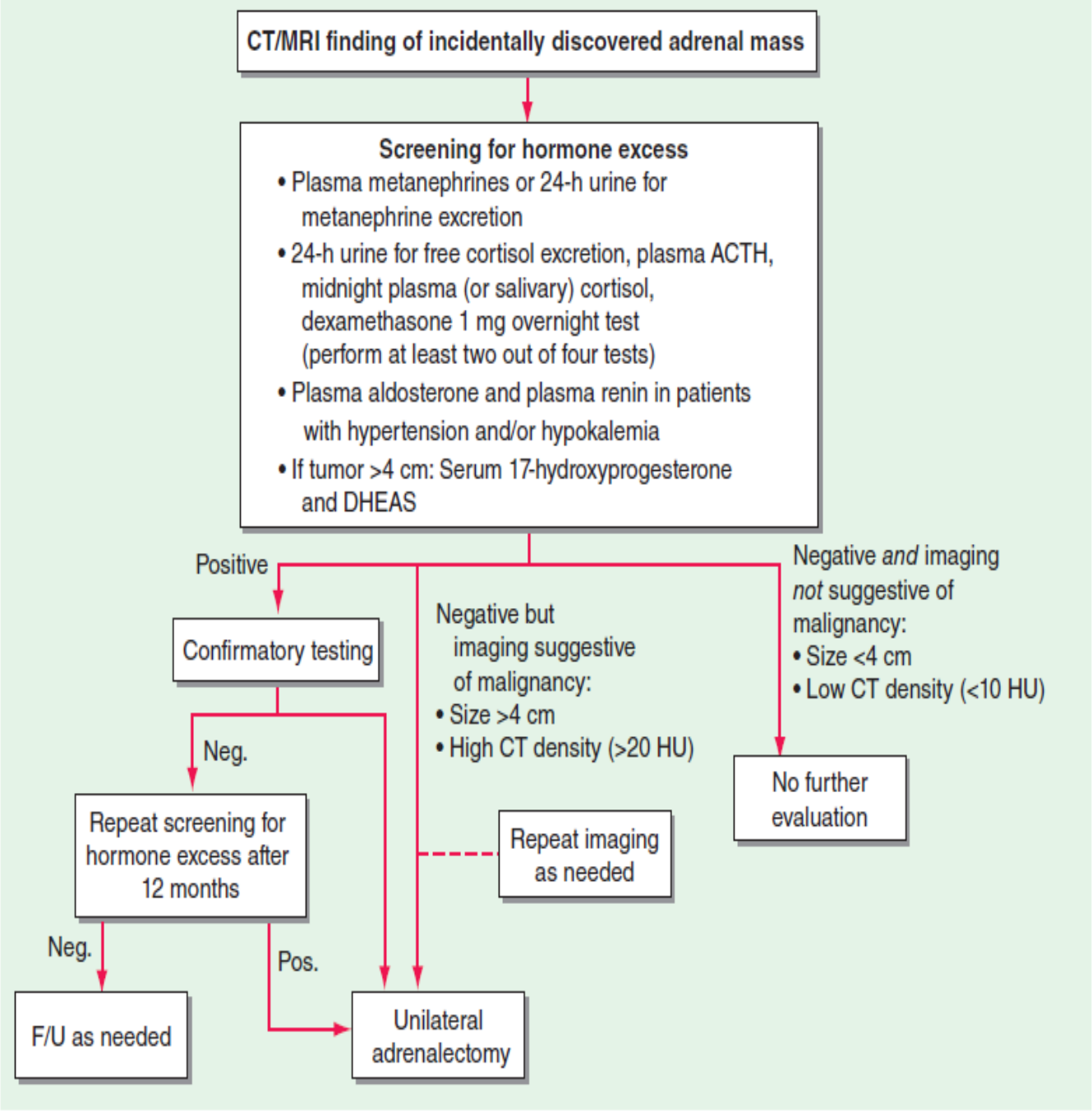


FIGURE 379-13 Management of the patient with an incidentally discovered adrenal mass. CT, computed tomography; F/U, follow-up; MRI, magnetic resonance imaging.

- Overproduction of adrenal androgen precursors, **DHEA and its sulfate**, is rare and most frequently seen in the context of ACC, as are increased levels of steroid precursors such as **17OHP.**

- For the *differentiation of benign from malignant* adrenal masses, ***imaging*** is relatively sensitive, although specificity is suboptimal.
- **Unenhanced CT is the procedure of choice** for imaging the adrenal glands (Fig. 379-11).
- A diagnosis of **ACC, pheochromocytoma**, and benign adrenal **myelolipoma** becomes more likely with increasing diameter of the adrenal mass. However, size alone is of poor predictive value, with only 80% sensitivity and 60% specificity for the differentiation of benign from malignant masses when using a **4-cm cut-off.**

- Metastases are rare but are found with similar frequency in adrenal masses of all sizes.

- **Tumor density** on unenhanced CT is of additional diagnostic value, as many adrenocortical adenomas are lipid rich and thus present with low attenuation values (i.e., densities of <10 Houns-field Units [HUs]). However, similar numbers of adrenocortical adenomas are lipid poor and present with higher HU, making it difficult to differentiate them from **ACC**s, as well as also **pheochromocytomas**, both of which invariably have high attenuation values (i.e., densities >20 HU on pre contrast scans).

- Generally, **benign** lesions are rounded and homogenous, whereas most **malignant** lesions appear lobulated and inhomogeneous.
- **Pheochromocytoma and adrenomyelolipoma** may also exhibit lobulated and inhomogeneous features.

- **MRI** also allows for the visualization of the adrenal glands with **somewhat lower resolution than CT**. However, because it does not involve exposure to ionizing radiation, it is preferred in **children, young adults, and during pregnancy**.
- MRI has a valuable role in the characterization of indeterminate adrenal lesions using **chemical shift analysis**, with malignant tumors rarely showing loss of signal on opposed-phase MRI; however this may also be observed in a proportion of benign adrenocortical adenomas.

- Fine-needle aspiration (FNA) or CT-guided biopsy of an adrenal mass is very rarely indicated.
- FNA of a **pheochromocytoma** can cause a life-threatening hypertensive crisis. FNA of an **ACC** violates the tumor capsule and can cause needle track metastasis.
- FNA should only be considered in a patient with a history of **non adrenal malignancy** and a newly detected adrenal mass, after careful exclusion of pheochromocytoma, and if the outcome will influence therapeutic management.

- It is important to recognize that in 25% of patients with a previous history of non adrenal malignancy, a newly detected mass on CT is not a metastasis.
- While FNA can diagnose extra-adrenal malignancies, it has very limited ability to differentiate between benign and malignant adrenocortical lesions, and hence should not be used for diagnosis of ACC.

- Adrenal masses associated with confirmed hormone excess or suspected malignancy are usually treated **surgically** (Fig. 379-13) or, if adrenalectomy is not feasible or desired, with **medication**.
- Preoperative exclusion of glucocorticoid excess is particularly important for the prediction of postoperative suppression of the contralateral adrenal gland, which requires glucocorticoid replacement peri- and post operatively.

- If the initial decision is for **observation**, imaging and biochemical testing should be repeated 6–12 months after the first assessment.
- However, this may be performed earlier in patients with borderline imaging or hormonal findings.

- Adrenal masses associated with normal biochemistry at diagnosis and a tumor radio density of <10 HU on unenhanced CT can be safely assumed to represent a benign adenoma and do not require further follow-up.

ADRENOCORTICAL CARCINOMA

- ACC is a rare malignancy with an annual incidence of 1–2 per million population. ACC is generally considered a highly malignant tumor; however, it presents with broad inter individual variability with regard to biologic characteristics and clinical behavior. Somatic mutations in the tumor-suppressor gene *TP53* are found in 25% of apparently sporadic ACC. Germline *TP53* mutations are the cause of the Li-Fraumeni syndrome associated with multiple solid organ cancers including ACC and are found in 25% of pediatric ACC cases; the *TP53* mutation R337H is found in almost all pediatric ACC in Brazil.

- Other genetic changes identified in ACC include alterations in the Wnt/β-catenin pathway and in the insulin-like growth factor 2 (IGF2) cluster; IGF2 over expression is found in 90% of ACC.

- Patients with large adrenal tumors suspicious of malignancy should be managed by a multidisciplinary specialist team, including an endocrinologist, an oncologist, a surgeon, a radiologist, and a histopathologist.
- FNA is not indicated in suspected ACC: **first**, cytology and also histopathology of a core biopsy cannot differentiate between benign and malignant primary adrenal masses; **second**, FNA violates the tumor capsule and may even cause needle canal metastasis.

- Even when the entire tumor specimen is available, the histopathologic differentiation between benign and malignant lesions is a diagnostic challenge.
- The most common histopathologic classification is the Weiss score, taking into account high nuclear grade; mitotic rate (>5/HPF); atypical mitosis; <25% clear cells; diffuse architecture; and presence of necrosis, venous invasion, and invasion of sinusoidal structures and tumor capsule. The presence of three or more elements suggests ACC.

- Although 60–70% of ACCs show biochemical evidence of steroid overproduction, in many patients, this is not clinically apparent due to the relatively inefficient steroid production by the adrenocortical cancer cells.
- Excess production of glucocorticoids and adrenal androgen precursors are most common.
- Mixed excess production of several corticosteroid classes by an adrenal tumor is generally indicative of malignancy.

- **Tumor staging** at diagnosis **(Table 379-6)** has important prognostic implications and requires scanning of the chest and abdomen for local organ invasion, lymphadenopathy, and metastases. Intravenous contrast medium is necessary for maximum sensitivity for hepatic metastases. An adrenal origin may be difficult to determine on standard axial CT imaging if the tumors are large and invasive, but CT reconstructions and MRI are more informative **(Fig. 379-14)** using multiple planes and different sequences.

TABLE 379-6 Classification System for Staging of Adrenocortical Carcinoma

ENSAT STAGE	TNM STAGE	TNM DEFINITIONS
I	**T1,N0,M0**	T1, tumor ≤5 cm N0, no positive lymph node M0, no distant metastases
II	**T2,N0,M0**	T2, tumor >5 cm N0, no positive lymph node M0, no distant metastases
III	**T1–T2,N1,M0** **T3–T4,N0–N1,M0**	N1, positive lymph node(s) M0, no distant metastases T3, tumor infiltration into surrounding tissue T4, tumor invasion into adjacent organs *or* venous tumor thrombus in vena cava or renal vein
IV	**T1–T4,N0–N1,M1**	M1, presence of distant metastases

Abbreviations: ENSAT, European Network for the Study of Adrenal Tumors; TNM, tumor, node, metastasis.

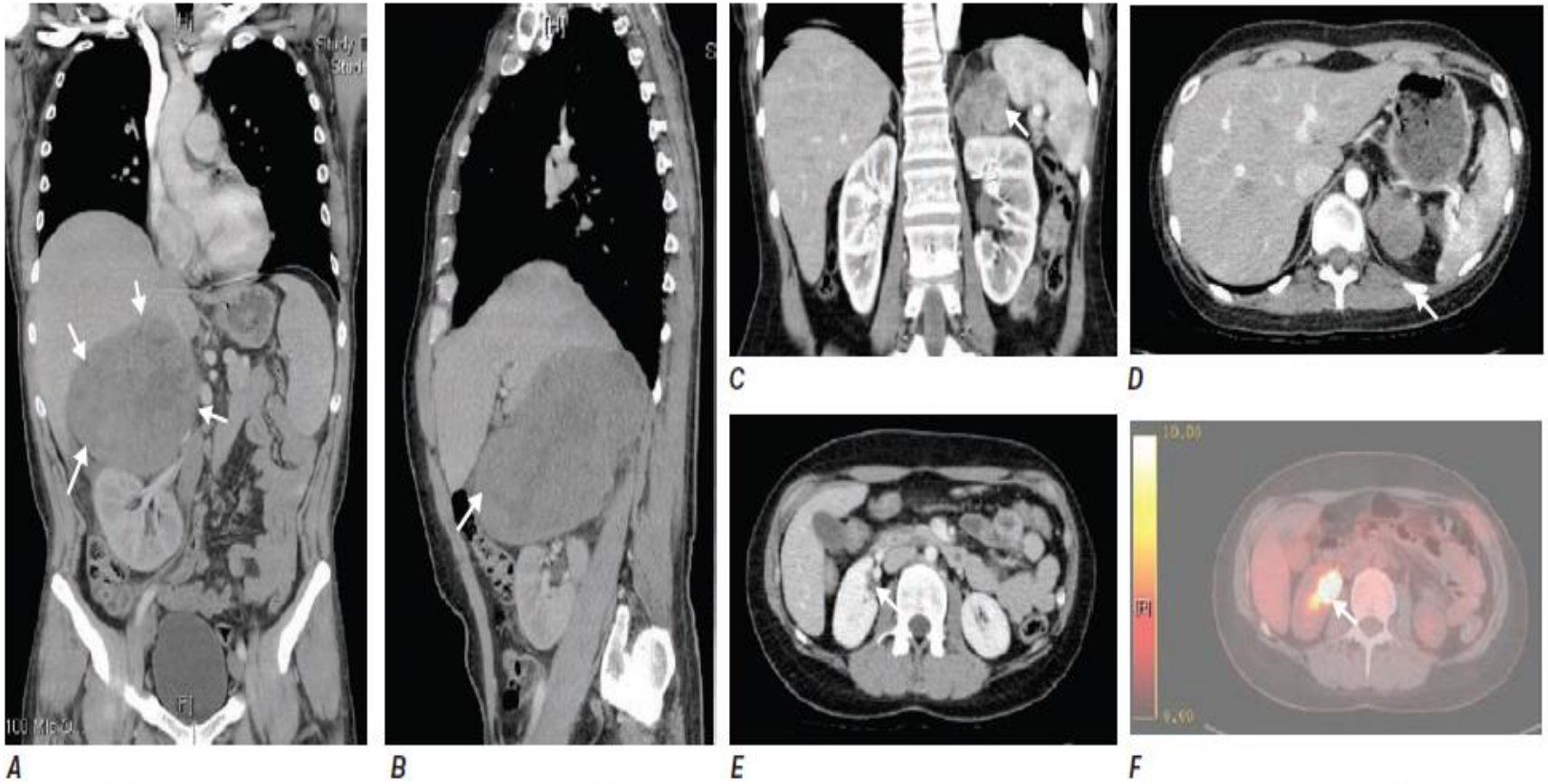


FIGURE 379-14 Imaging in adrenocortical carcinoma (ACC). Magnetic resonance imaging scan with (***A***) frontal and (***B***) lateral views of a right ACC that was detected incidentally. Computed tomography (CT) scan with (***C***) coronal and (***D***) transverse views depicting a right-sided ACC. Note the irregular border and inhomogeneous structure. CT scan (***E***) and positron emission tomography/CT (***F***) visualizing a peritoneal metastasis of an ACC in close proximity to the right kidney (*arrow*).

- Vascular and adjacent organ invasion is diagnostic of malignancy.

- 18-Fluoro-2-deoxy-d-glucose positron emission tomography (18-FDG PET) is highly sensitive for the detection of malignancy and can be used to detect small metastases or local recurrence that may not be obvious on CT (Fig. 379-14). However, FDG PET has limited specificity and therefore cannot be used for differentiating benign from malignant adrenal lesions. Metastasis in ACC most frequently occurs to liver and lung.

- There is no established grading system for ACC, and the Weiss score carries no prognostic value; the most important prognostic histopathologic parameter is the Ki67 proliferation index, with Ki67 <10% indicative of slow to moderate growth velocity, whereas a Ki67 ≥10% is associated with poor prognosis including high risk of recurrence and rapid progression.

- Cure of ACC can only be achieved by early detection and complete surgical removal. Capsule violation during primary surgery, metastasis at diagnosis, and primary treatment in a non specialist center and by a non specialist surgeon are major determinants of poor survival.
- If the primary tumor invades adjacent organs, en bloc removal of kidney and spleen should be considered to reduce the risk of recurrence and regional lymph node dissection may further reduce this risk.
- Surgery can also be considered in a patient with metastases if there is severe tumor-related hormone excess. This indication needs to be carefully weighed against surgical risk, including thrombo embolic complications, and the resulting delay in the introduction of other therapeutic options.

- Patients with confirmed ACC and successful removal of the primary tumor should receive adjuvant treatment with mitotane (o,p'DDD), particularly in patients with a high risk of recurrence as determined by tumor size >8 cm, histopathologic signs of vascular invasion, capsule invasion or violation, and a Ki67 proliferation index ≥10%.
- Adjuvant mitotane should be continued for at least 2 years, if the patient can tolerate side effects. Regular monitoring of plasma mitotane levels is mandatory (therapeutic range 14–20 mg/L; neurotoxic complications more frequent at >20 mg/L).
- Mitotane is usually started at 500 mg tid, with stepwise increases to a maximum dose of 2000 mg tid in days (high-dose saturation) or weeks (low-dose saturation) as tolerated.

- Once therapeutic range plasma mitotane levels are achieved, the dose can be tapered to maintenance doses mostly ranging from 1000 to 1500 mg tid. Mitotane treatment results in disruption of cortisol synthesis and thus requires glucocorticoid replacement; glucocorticoid replacement dose should be at least double of that usually used in adrenal insufficiency (i.e., 20 mg tid) because mitotane induces hepatic CYP3A4 activity resulting in rapid inactivation of glucocorticoids.
- Mitotane also increases circulating CBG, thereby decreasing the available free cortisol fraction.

- Single metastases can be addressed surgically or with radiofrequency ablation as appropriate.
- If the tumor recurs or progresses during mitotane treatment, cytotoxic chemotherapy should be considered; the established first-line chemotherapy regimen is the combination of cisplatin, etoposide, and doxorubicin plus continuing mitotane.
- Painful bone metastasis responds to irradiation.
- Overall survival in ACC is still poor, with 5-year survival rates of 30–40% and a median survival of 15 months in metastatic ACC.