TABLE 406-6 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	N1, positive lymph node(s)
	T3–T4,N0–N1,M0	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.

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, 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.

ADRENAL INSUFFICIENCY

Epidemiology The prevalence of well-documented, permanent adrenal insufficiency is 5 in 10,000 in the general population. Hypothalamic-pituitary origin of disease is most frequent, with a prevalence of 3 in 10,000, whereas primary adrenal insufficiency has a prevalence of 2 in 10,000. Approximately one-half of the latter cases are acquired, mostly caused by autoimmune destruction of the adrenal glands; the other one-half are genetic, most commonly caused by distinct enzymatic blocks in adrenal steroidogenesis affecting glucocorticoid synthesis (i.e., congenital adrenal hyperplasia.)

Adrenal insufficiency arising from suppression of the HPA axis as a consequence of exogenous glucocorticoid treatment is much more common, occurring in 0.5–2% of the population in developed countries.

Etiology *Primary adrenal insufficiency* is most commonly caused by autoimmune adrenalitis. Isolated autoimmune adrenalitis accounts for 30–40%, whereas 60–70% develop adrenal insufficiency as part of autoimmune polyglandular syndromes (APS) **(Chap. 408) (Table 406-7)**. APS1, also termed APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy), is the underlying cause in 10% of patients affected by APS. APS1 is transmitted in an autosomal recessive manner and is caused by mutations in the autoimmune regulator gene *AIRE*. Associated autoimmune conditions overlap with those seen in APS2, but may also include total alopecia, primary hypoparathyroidism, and, in rare cases, lymphoma. APS1 patients invariably develop chronic mucocutaneous candidiasis, usually manifest in childhood, and preceding adrenal insufficiency by years or decades. The much more prevalent APS2 is of polygenic inheritance, with confirmed associations with the *HLA-DR3* gene region in the major histocompatibility complex and distinct gene regions involved in immune regulation (*CTLA-4, PTPN22, CLEC16A*). Coincident autoimmune disease most frequently includes thyroid autoimmune disease, vitiligo, and premature ovarian failure. Less commonly, additional features may include type 1 diabetes and pernicious anemia caused by vitamin B_{12} deficiency.

X-linked adrenoleukodystrophy has an incidence of 1:20,000 males and is caused by mutations in the *X-ALD* gene encoding the peroxisomal membrane transporter protein ABCD1; its disruption results in accumulation of very long chain (>24 carbon atoms) fatty acids. Approximately 50% of cases manifest in early childhood with rapidly progressive white matter disease (cerebral ALD); 35% present during adolescence or in early adulthood with neurologic features indicative of myelin and peripheral nervous system involvement (adrenomyeloneuropathy [AMN]). In the remaining 15%, adrenal insufficiency is the sole manifestation of disease. Of note, distinct mutations manifest with variable penetrance and phenotypes within affected families.

Rarer causes of adrenal insufficiency involve destruction of the adrenal glands as a consequence of infection, hemorrhage, or infiltration

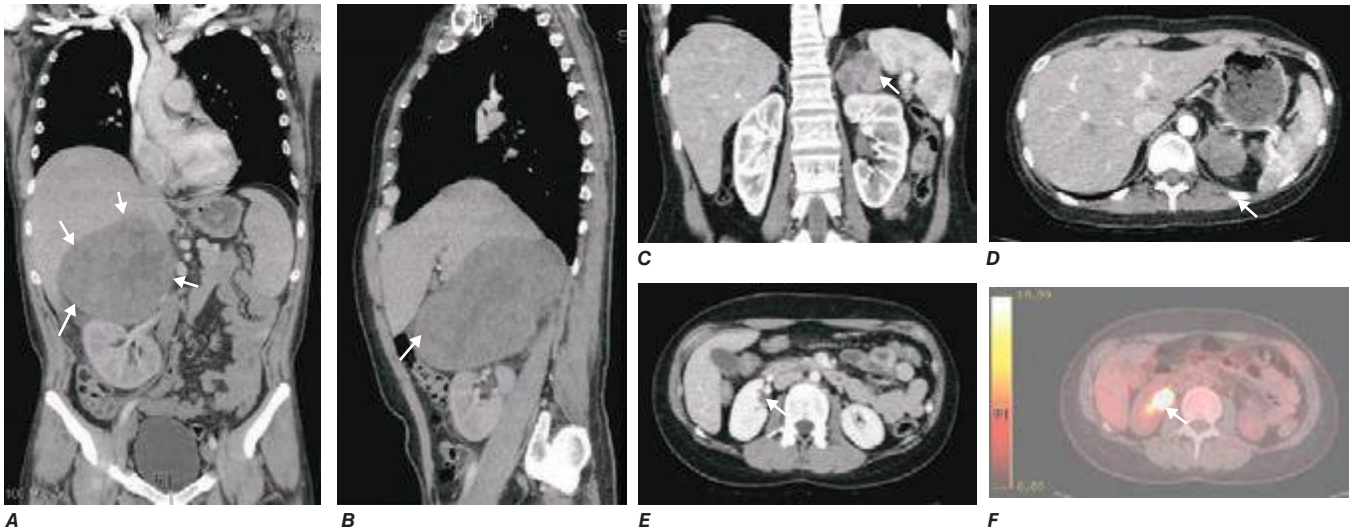

FIGURE 406-14 Imaging in adrenocortical carcinoma. Magnetic resonance imaging scan with (***A***) frontal and (***B***) lateral views of a right adrenocortical carcinoma that was detected incidentally. Computed tomography (CT) scan with (***C***) coronal and (***D***) transverse views depicting a right-sided adrenocortical carcinoma. Note the irregular border and inhomogeneous structure. CT scan (***E***) and positron emission tomography/CT (***F***) visualizing a peritoneal metastasis of an adrenocortical carcinoma in close proximity to the right kidney (*arrow*).