McCune-Albright syndrome (Chap. 412) or in a subset of somatotrope adenomas (Chap. 403), impair guanosine triphosphate (GTP) hydrolysis, causing constitutive activation of the cyclic AMP signaling pathway. In most series, activating mutations in either the TSH-R or the $G_{s\alpha}$ subunit genes are identified in >90% of patients with solitary hyperfunctioning nodules.

Thyrotoxicosis is usually mild. The disorder is suggested by a subnormal TSH level; the presence of the thyroid nodule, which is generally large enough to be palpable; and the absence of clinical features suggestive of Graves' disease or other causes of thyrotoxicosis. A thyroid scan provides a definitive diagnostic test, demonstrating focal uptake in the hyperfunctioning nodule and diminished uptake in the remainder of the gland, as activity of the normal thyroid is suppressed.

TREATMENT HYPERFUNCTIONING SOLITARY NODULE

Radioiodine ablation is usually the treatment of choice. Because normal thyroid function is suppressed, ^{131}I is concentrated in the hyperfunctioning nodule with minimal uptake and damage to normal thyroid tissue. Relatively large radioiodine doses (e.g., 370–1110 MBq [10–29.9 mCi] ^{131}I) have been shown to correct thyrotoxicosis in about 75% of patients within 3 months. Hypothyroidism occurs in <10% of those patients over the next 5 years. Surgical resection is also effective and is usually limited to enucleation of the adenoma or lobectomy, thereby preserving thyroid function and minimizing risk of hypoparathyroidism or damage to the recurrent laryngeal nerves. Medical therapy using antithyroid drugs and beta blockers can normalize thyroid function but is not an optimal long-term treatment. Using ultrasound guidance, repeated ethanol injections and percutaneous radiofrequency thermal ablation have been used successfully in some centers to ablate hyperfunctioning nodules, and these techniques have also been used to reduce the size of nonfunctioning thyroid nodules.

BENIGN NEOPLASMS

The various types of benign thyroid nodules are listed in Table 405-10. These lesions are common (5–10% adults), particularly when assessed by sensitive techniques such as ultrasound. The risk of malignancy is very low for *macrofollicular adenomas* and *normofollicular adenomas*. *Microfollicular, trabecular, and Hürthle cell variants* raise greater concern, and the histology is more difficult to interpret. Many are mixed cystic/solid lesions on ultrasound and may appear spongiform reflecting the pathology of macrofollicular structure. However, the majority of solid nodules (whether hypo-, iso-, or hyperechoic) are also benign. FNA, usually performed with ultrasound guidance, is the diagnostic procedure of choice to evaluate thyroid nodules (see the "Approach to the Patient" section on thyroid nodules). Pure thyroid cysts, <2% of all thyroid growths, consist of colloid and are benign as well. Cysts frequently recur, even after repeated aspiration, and may require surgical excision if they are large. Ethanol ablation to sclerose the cyst has been used successfully for patients who are symptomatic.

TSH suppression with levothyroxine therapy does not decrease thyroid nodule size in iodine-sufficient populations. However, if there is relative iodine deficiency, both iodine and levothyroxine therapy may decrease nodule volume. If levothyroxine is administered in this situation and the nodule has not decreased in size after 6–12 months of suppressive therapy, treatment should be discontinued because little benefit is likely to accrue from long-term treatment; the risk of iatrogenic subclinical thyrotoxicosis should also be considered.

THYROID CANCER

Thyroid carcinoma is the most common malignancy of the endocrine system. Malignant tumors derived from the follicular epithelium are classified according to histologic features. Differentiated tumors, such as papillary thyroid cancer (PTC) or follicular thyroid cancer (FTC), are often curable, and the prognosis is good for patients identified with early-stage disease. In contrast, anaplastic thyroid cancer (ATC) is aggressive, responds poorly to treatment, and is associated with a bleak prognosis.

TABLE 405-10 CLASSIFICATION OF THYROID NEOPLASMS

Benign	
Follicular epithelial cell adenomas	
Macrofollicular (colloid)	
Normofollicular (simple)	
Microfollicular (fetal)	
Trabecular (embryonal)	
Hürthle cell variant (oncocytic)	
Malignant	**Approximate Prevalence, %**
Follicular epithelial cell	
Well-differentiated carcinomas	
Papillary carcinomas	80–90
Pure papillary	
Follicular variant	
Diffuse sclerosing variant	
Tall cell, columnar cell variants	
Follicular carcinomas	5–10
Minimally invasive	
Widely invasive	
Hürthle cell carcinoma (oncocytic)	
Insular carcinoma	
Undifferentiated (anaplastic) carcinomas	
C cell (calcitonin-producing)	
Medullary thyroid cancer	<10
Sporadic	
Familial	
MEN 2	
Other malignancies	
Lymphomas	1–2
Sarcomas	
Metastases	
Others	

Abbreviation: MEN, multiple endocrine neoplasia.

The incidence of thyroid cancer is ~12/100,000 per year in the United States and increases with age. Prognosis is worse in older persons (>65 years). Thyroid cancer is twice as common in women as men, but male gender is associated with a worse prognosis. Additional important risk factors include a history of childhood head or neck irradiation, large nodule size (≥4 cm), evidence for local tumor fixation or invasion into lymph nodes, and the presence of metastases (Table 405-11). Several unique features of thyroid cancer facilitate its management: (1) thyroid nodules are amenable to biopsy by FNA; (2) iodine radioisotopes can be used to diagnose (^{123}I) and treat (^{131}I) differentiated thyroid cancer, reflecting the unique uptake of this anion by the thyroid gland; and (3) serum markers allow the detection of

TABLE 405-11 RISK FACTORS FOR THYROID CARCINOMA IN PATIENTS WITH THYROID NODULE

History of head and neck irradiation, including total-body irradiation for bone marrow transplant and brain radiation for childhood leukemia	Family history of thyroid cancer, MEN 2, or other genetic syndromes associated with thyroid malignancy (e.g., Cowden's syndrome, familial polyposis, Carney complex)
Exposure to ionizing radiation from fallout in childhood or adolescence	Vocal cord paralysis, hoarse voice
Age <20 or >65 years	Nodule fixed to adjacent structures
Increased nodule size (>4 cm)	Extrathyroidal extension
New or enlarging neck mass	Lateral cervical lymphadenopathy
Male gender	

Abbreviation: MEN, multiple endocrine neoplasia.