and, ideally, undetectable, the risk of recurrence is <5% at 5 years. Newer data indicate that rhTSH stimulation may not be required for patients with undetectable basal Tg levels in sensitive assays, if there is documented absence of Tg antibodies. These patients can be followed with unstimulated Tg every 6–12 months and neck ultrasound as indicated. Levothyroxine dosing may then be titrated to a higher TSH level of 0.5–1.5 mIU/L.

The use of WBS is reserved for patients with known iodine-avid metastases or those with elevated serum thyroglobulin levels and negative imaging with ultrasound, chest CT, and neck cross-sectional imaging who may require additional ^{131}I therapy.

In addition, most authorities advocate radioiodine treatment for scan-negative, Tg-positive (Tg >5–10 ng/mL) patients, as many derive therapeutic benefit from a large dose of ^{131}I. For such patients, rhTSH preparation is not FDA approved for the treatment of metastatic disease, and the traditional approach of thyroid hormone withdrawal should be followed. This involves switching patients from levothyroxine (T_4) to the more rapidly cleared hormone liothyronine (T_3), thereby allowing TSH to increase more quickly. Whenever ^{131}I is administered, posttherapy WBS is the gold standard to assess iodine-avid metastases.

In addition to radioiodine, external beam radiotherapy is also used to treat specific metastatic lesions, particularly when they cause bone pain or threaten neurologic injury (e.g., vertebral metastases).

New Potential Therapies Kinase inhibitors are being explored as a means to target pathways known to be active in thyroid cancer, including the RAS, BRAF, EGFR, VEGFR, and angiogenesis pathways. A multicenter randomized controlled trial of the multikinase inhibitor sorafenib in 417 patients with progressive metastatic thyroid cancer reported a doubling of progression-free survival to 10.8 months in the treatment group compared with the placebo group. Ongoing trials are exploring whether differentiation protocols with kinase inhibitors or other approaches might enhance radioiodine uptake and efficacy.

ANAPLASTIC AND OTHER FORMS OF THYROID CANCER

Anaplastic Thyroid Cancer As noted above, ATC is a poorly differentiated and aggressive cancer. The prognosis is poor, and most patients die within 6 months of diagnosis. Because of the undifferentiated state of these tumors, the uptake of radioiodine is usually negligible, but it can be used therapeutically if there is residual uptake. Chemotherapy has been attempted with multiple agents, including anthracyclines and paclitaxel, but it is usually ineffective. External beam radiation therapy can be attempted and continued if tumors are responsive.

Thyroid Lymphoma Lymphoma in the thyroid gland often arises in the background of Hashimoto's thyroiditis. A rapidly expanding thyroid mass suggests the possibility of this diagnosis. Diffuse large-cell lymphoma is the most common type in the thyroid. Biopsies reveal sheets of lymphoid cells that can be difficult to distinguish from small-cell lung cancer or ATC. These tumors are often highly sensitive to external radiation. Surgical resection should be avoided as initial therapy because it may spread disease that is otherwise localized to the thyroid. If staging indicates disease outside of the thyroid, treatment should follow guidelines used for other forms of lymphoma (Chap. 134).

MEDULLARY THYROID CARCINOMA

MTC can be sporadic or familial and accounts for about 5% of thyroid cancers. There are three familial forms of MTC: MEN 2A, MEN 2B, and familial MTC without other features of MEN (Chap. 408). In general, MTC is more aggressive in MEN 2B than in MEN 2A, and familial MTC is more aggressive than sporadic MTC. Elevated serum calcitonin provides a marker of residual or recurrent disease. All patients with MTC should be tested for *RET* mutations, because genetic counseling and testing of family members can be offered to those individuals who test positive for mutations.

The management of MTC is primarily surgical. Unlike tumors derived from thyroid follicular cells, these tumors do not take up radioiodine. External radiation treatment and chemotherapy may provide palliation in patients with advanced disease (Chap. 408).

APPROACH TO THE PATIENT: Thyroid Nodules

Palpable thyroid nodules are found in about 5% of adults, but the prevalence varies considerably worldwide. Given this high prevalence rate, practitioners commonly identify thyroid nodules either on physical examination or as incidental findings on imaging performed for another indication (e.g., carotid ultrasound, cervical spine MRI). The main goal of this evaluation is to identify, in a cost-effective manner, the small subgroup of individuals with malignant lesions.

Nodules are more common in iodine-deficient areas, in women, and with aging. Most palpable nodules are >1 cm in diameter, but the ability to feel a nodule is influenced by its location within the gland (superficial versus deeply embedded), the anatomy of the patient's neck, and the experience of the examiner. More sensitive methods of detection, such as CT, thyroid ultrasound, and pathologic studies, reveal thyroid nodules in up to 50% of glands in individuals over the age of 50. The presence of these thyroid incidentalomas has led to much debate about how to detect nodules and which nodules to investigate further.

An approach to the evaluation of a solitary nodule is outlined in Fig. 405-13. Most patients with thyroid nodules have normal thyroid function tests. Nonetheless, thyroid function should be assessed by measuring a TSH level, which may be suppressed by one or more autonomously functioning nodules. If the TSH is suppressed, a radionuclide scan is indicated to determine if the identified nodule is "hot," as lesions with increased uptake are almost never malignant and FNA is unnecessary. Otherwise, the next step in evaluation is performance of a thyroid ultrasound for three reasons: (1) Ultrasound will confirm if the palpable nodule is indeed a nodule. About 15% of "palpable" nodules are not confirmed on imaging, and therefore, no further evaluation is required. (2) Ultrasound will assess if there are additional nonpalpable nodules for which FNA may be recommended based on imaging features and size. (3) Ultrasound will characterize the imaging features of the nodule, which, combined with the nodule's size, facilitate decision making about FNA.

Evidence-based guidelines from both the American Thyroid Association and the American Association of Clinical Endocrinologists provide recommendations for nodule FNA based on sonographic imaging features and size cut offs, with lower size cut offs for nodules with more suspicious ultrasound characteristics. FNA biopsy, ideally performed with ultrasound guidance, has good sensitivity and specificity when performed by physicians familiar with the procedure and when the results are interpreted by experienced cytopathologists. The technique is particularly useful for detecting PTC. However, the distinction between benign and malignant follicular lesions is often not possible using cytology alone.

In several large studies, FNA biopsies yielded the following findings: 65% benign, 5% malignant or suspicious for malignancy, 10% nondiagnostic or yielding insufficient material for diagnosis, and 20% indeterminate. The Bethesda System is now widely used to provide more uniform terminology for reporting thyroid nodule FNA cytology results. This six-tiered classification system with the respective estimated malignancy rates is shown in Table 405-14. Specifically, the Bethesda System subcategorized cytology specimens previously labeled as indeterminate into three categories: atypia or follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm, and suspicious for malignancy.