

Chapter 34

Surgical Disorders of the Thyroid in the Elderly



Leslie S. Wu, Julie Ann Sosa, and Robert Udelsman

CASE STUDY

JK is a 75-year-old woman with a right anterior neck mass identified on physical examination by her cardiologist. She described a globus sensation and dysphagia with solid foods, and had subjective hoarseness over the last year. She did not have a history of head or neck radiation, and there was no family history of glandular abnormalities. Her past medical history was significant for hypertension, hyperlipidemia, atrial fibrillation on chronic warfarin therapy, diabetes mellitus, osteopenia, and arthritis. Her past surgical history was notable for a cholecystectomy, hysterectomy for uterine fibroids, and left breast lumpectomy and radiation therapy for ductal carcinoma in situ. Family history is significant for “bad hearts.” She was a former smoker. Her medications included warfarin, metoprolol, amlodipine, simvastatin, glucophage, glipizide, niacin, fish oil, calcium supplements with vitamin D, multivitamin, and acetaminophen as needed.

Physical examination revealed a well-developed woman in no acute distress. Her vital signs were within

normal limits, and she appeared euthyroid. Focused exam was notable for a nontender 4-cm firm but mobile mass in the right anterior neck. The trachea was distracted slightly into the contralateral neck. The left thyroid lobe contained no palpable nodules. There was no cervical lymphadenopathy. Pemberton sign was absent, and there was no carotid bruit. The remainder of her physical exam was unremarkable.

On blood work, the patient was biochemically euthyroid with a thyroid-stimulating hormone (TSH) 2.5 mIU/L (normal 0.4–4.0 mIU/L). JK’s geriatrician referred her to an endocrinologist, who, in turn, consulted a thyroid surgeon. JK underwent a dedicated neck ultrasound, which revealed a 60-g thyroid and a 4-cm nodule in the right lobe. It was hypoechoic with a small cystic component, microcalcifications, an irregular border, and possible extension into the overlying strap muscle. The left lobe contained two 4-mm nodules that were too small to characterize. Ultrasound-guided fine-needle aspiration (FNA) of the dominant right nodule was performed. Cytopathology was consistent with papillary thyroid cancer.

Introduction

The proportion of elderly people is growing steadily in Western societies as a consequence of increased life expectancy and reduced birth rates. Americans aged 80 years and older constituted 3.3% of the population in 2000; this is projected to increase to 7.7% in 2050 and 8.2% by 2070. In comparison, Americans 65–79 years of age constituted

9.3% of the population in 2000 and are projected to increase to 12.5% by 2050 and 12.9% by 2070 [1]. This phenomenon has generated numerous studies aimed at clarifying the physiologic and pathologic aspects of aging. Thyroid dysfunction can have profound clinical implications for elderly patients. Thyroid nodules are common, and the incidence of thyroid cancer increases with age.

Thyroid disease is common; 6.6% of the US population has thyroid disease, requires thyroid hormone supplementation, or both [2]. Based on results of autopsies performed on the general population, thyroid nodules have been found in up to 50% of asymptomatic patients [3]. The incidence of thyroid cancer has increased from 3.6 per 100,000 in 1973 to

J.A. Sosa (✉)
Department of Surgery, Maine Medical Center,
22 Bramhall St., Portland, ME, USA

8.7 per 100,000 in 2002 – a 2.4-fold increase – with 87% of the increase due to the diagnosis of small differentiated thyroid cancers [4]. The association between increasing age and incidence of thyroid nodules makes diagnosis and treatment an important public health issue.

All thyroid diseases are encountered in the elderly; however, their prevalence and clinical expression differ from those observed in younger patients. Symptoms of aging can be confused easily with hypothyroidism. The clinical manifestations of thyroid dysfunction can be more vague, subtle, and hidden by a background of coexistent disease. Interpretation of thyroid function studies can be problematic in elderly patients, owing to difficulty in differentiating physiologic age-associated changes from alterations secondary to acute or chronic nonthyroidal illnesses [5]. And finally, the medical and surgical treatment of thyroid disease in the elderly is associated with an increased risk of complications attributed to the treatment itself [6].

Thyroid Function

The thyroid gland synthesizes the hormones thyroxine (T_4) and triiodothyronine (T_3), iodine-containing amino acids that regulate the body's metabolic rate. Adequate levels of thyroid hormone are necessary in infants for normal development of the central nervous system, in children for normal skeletal growth and maturation, and in adults for normal function of multiple organ systems [7]. Thyroid dysfunction is one of the most common endocrine disorders encountered in clinical practice. While abnormally high or low levels of thyroid hormones can be tolerated for long periods of time, usually there are symptoms and signs of thyroid dysfunction.

The effects of thyroid hormones are diffuse and important (Table 34.1). Thyroid hormones increase the activity of membrane-bound Na^+K^+ adenosine triphosphate (ATP)-ase, increase heat production, and stimulate oxygen consumption (“calorigenesis”). Thyroid hormones also affect tissue growth

and maturation, help regulate lipid metabolism, increase cardiac contractility by stimulating the expression of myosin protein, and increase intestinal absorption of carbohydrates (Fig. 34.1) [8].

The usual biochemical measures of thyroid function, such as T_3 , T_4 , and thyroid-binding protein levels, change little with advancing age in the absence of systemic illness. Similarly, thyrotropin (TSH) levels and the production of

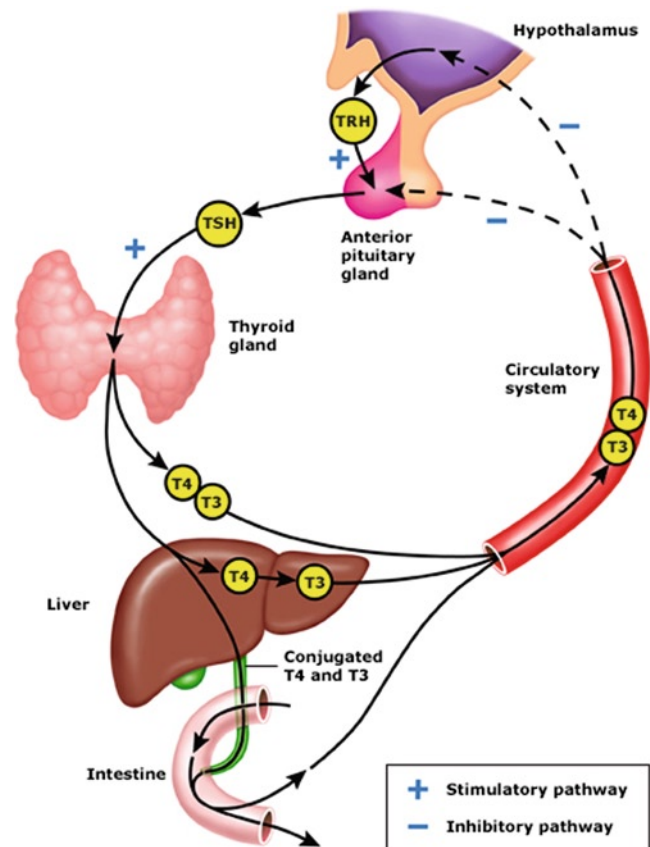


FIGURE 34.1 Hypothalamus–pituitary–thyroid axis with hormonal feedback mechanisms (reproduced with permission from Thyroid. In: Basow, DS, (Ed), Uptodate, Waltham, MA, 2010. Copyright © 2010 UpToDate, Inc. For more information, visit <http://www.uptodate.com>).

TABLE 34.1 Physiologic effects of thyroid hormones

Target tissue	Effect	Mechanism
Heart	Chronotropic	Increase number and affinity of beta-adrenergic receptors
	Inotropic	Enhance responses to circulating catecholamines
		Increase proportion of alpha myosin heavy chain (with higher ATPase activity)
Adipose tissue	Catabolic	Stimulate lipolysis
Muscle	Catabolic	Increase protein breakdown
Bone	Developmental and metabolic	Promote normal growth and skeletal development; accelerate bone turnover
Nervous system	Developmental	Promote normal brain development
Gut	Metabolic	Increase rate of carbohydrate absorption
Lipoprotein	Metabolic	Stimulate formation of LDL receptors
Other	Calorigenic	Stimulate oxygen consumption by metabolically active tissues (exceptions: adult brain, testes, uterus, lymph nodes, spleen, anterior pituitary)
		Increase metabolic rate

ATP adenosine triphosphate; LDL low-density lipoprotein

TSH in response to thyrotropin-releasing hormone (TRH) administration are relatively constant with increasing age [9]. In the past, hypothyroidism was considered an integral part of aging; however, more recent studies suggest that physiologic aging is associated with normal thyroid function [10]. The half-life of T_4 increases from 6.7 days in young adults to 9.3 days in those aged 80–90 years due to decreases in both fractional turnover rate and the distribution space of T_4 . Peripheral conversion of T_4 – T_3 is decreased, but the intrathyroidal conversion is increased, resulting in relatively stable T_3 levels in the elderly [11].

The Wickham survey documented the prevalence of thyroid disorders in a sample of 2,779 British adults, and the 20-year follow-up study was published in 1995 [12, 13]. The annual incidence of hypothyroidism was found to increase with age and correlate with the presence of thyroid autoantibodies or elevated TSH levels. Aging often is associated with an increased prevalence of antithyroid antibodies, but this age-dependent increase is observed commonly in unselected elderly subjects and not in healthy elderly populations selected for the absence of clinical or subclinical illnesses [14]. This suggests that thyroid autoimmune phenomena may not be the consequence of the aging process itself but, rather, an expression of age-associated disease.

Thyroid Dysfunction

Thyroid function can be evaluated by several biochemical measures, including total or free T_3 and T_4 , and TSH [15]. The high incidence of comorbid illness in elderly people can confound assessment of thyroid function. Malnutrition, infection, sepsis, major surgery, poorly controlled diabetes mellitus, hepatic disease, renal failure, cerebrovascular disease, heart failure, malignancy, trauma, burns, and coma are all associated with alterations in thyroid function tests [16]. Depending on severity, stage, and drug effects, these nonthyroidal illnesses are associated with changes in the parameters of thyroid function that include low serum T_3 , normal to low T_4 , and normal to low or elevated TSH – the “euthyroid sick syndrome.” Among acutely ill patients, 70% show a low T_3 state, and 30–50% of patients in intensive care units have low serum T_4 levels [17].

Findings in patients’ personal and family histories indicate increased risk of developing thyroid dysfunction. Risk factors in personal history include goiter, surgery or radiotherapy affecting the thyroid gland, previous thyroid dysfunction, vitiligo, diabetes mellitus, pernicious anemia, leukotrichia, and medications, such as lithium carbonate and amiodarone, and iodine-containing compounds. Pertinent factors in family history are thyroid disease, pernicious anemia, diabetes mellitus, and primary adrenal insufficiency [18].

Measurement of serum TSH, a sensitive indicator of free thyroid hormone concentration in the presence of normal pituitary function, is often all that is required as a screening test for thyroid function. A decision analysis by Danese et al. reported that screening for thyroid disease by TSH measurement was particularly cost-effective in elderly female patients, as the clinical symptoms of thyroid dysfunction may be atypical in this age group [19]. Analyses of free hormone levels determine what is available for cellular metabolic regulation. In addition to thyroid function tests, diagnostic determination of thyroid autoantibodies can be useful. Antibodies to the TSH receptor are present in Graves’ disease and also can be seen with other forms of autoimmune thyroid disease, such as Hashimoto’s thyroiditis. Antithyroid peroxidase antibodies and antithyroglobulin antibodies are seen with all forms of autoimmune thyroid disease and may be present in patients with multinodular goiter. Assessment of the thyroid also should include imaging studies, such as ultrasound, nuclear medicine uptake scans, computed tomography (CT) scans, and magnetic resonance imaging (MRI).

Hypothyroidism

Epidemiology

The balance between central production and peripheral action of T_3 and T_4 is required for a euthyroid state. Clinical hypothyroidism usually is associated with decreased hormone production in the thyroid gland, although states of limited thyroid hormone activity in the periphery also can occur. In many underdeveloped countries or iodine-poor regions, lack of sufficient iodine intake explains a large percentage of hypothyroid conditions [20, 21]. In more developed countries, most cases of adult primary hypothyroidism (due to direct thyroid failure) are secondary to chronic autoimmune (Hashimoto’s) thyroiditis, radioactive iodine (RAI) therapy, or surgery. Disorders of the pituitary or hypothalamus can cause diminished TSH secretion, producing hypothyroidism as a secondary or tertiary result. Finally, a host of medications, including the thioamide antithyroid drugs propylthiouracil (PTU) and methimazole (MMI), can produce hypothyroidism (Table 34.2).

There are two types of primary hypothyroidism. Clinical or overt primary hypothyroidism is characterized by elevated serum TSH and decreased serum T_3 and T_4 levels. Patients with subclinical primary hypothyroidism show mildly elevated serum TSH concentrations and normal serum thyroid hormone levels. Subclinical hypothyroidism is the most common thyroid dysfunction nationwide, with a markedly increased prevalence in the elderly, ranging from 4 to 15%

TABLE 34.2 Causes and pathogenetic mechanisms of hypothyroidism

Etiologic classification	Pathogenetic mechanism
Congenital	
	Aplasia or hypoplasia of thyroid gland
	Defects in hormone biosynthesis or action
Acquired	
Hashimoto's thyroiditis	Autoimmune destruction
Severe iodine deficiency	Diminished hormone synthesis, release
Thyroid ablation	Diminished hormone synthesis, release
Thyroid surgery	
¹³¹ I radiation treatment of hyperthyroidism	
External beam radiation therapy for head and neck cancer	Diminished hormone synthesis, release
Drugs	
Iodine, inorganic	
Iodine, organic (amiodarone)	
Thioamides (propylthiouracil, methimazole)	
Potassium perchlorate	
Thiocyanate	
Lithium	
Hypopituitarism	Deficient TSH secretion
Hypothalamic disease	Deficient TRH secretion

TSH thyroid-stimulating hormone, *TRH* thyroid-release hormone

Source: Modified and reproduced from [94], with permission of The McGraw Hill Companies

for subclinical hypothyroidism and from 0.5 to 6% for overt hypothyroidism [22]. In the Whickham study, the risk of developing hypothyroidism was significantly increased in women between 75 and 80 years [12, 13].

Clinical and Diagnostic Evaluation

A comprehensive medical history should uncover symptoms that help establish the diagnosis, such as cold intolerance, weight gain, diminished appetite, constipation, and lethargy. On physical examination, a patient may exhibit hoarseness, bradycardia, periorbital or ankle edema, generalized muscle weakness, or delayed relaxation of deep tendon reflexes. The suspicion of hypothyroidism is raised by unexplained increases in serum cholesterol and creatine phosphokinase levels, severe constipation, congestive heart failure with restrictive cardiomyopathy, or macrocytic anemia [9].

Hypothyroidism is characterized by abnormally low serum T_4 and T_3 levels. Free thyroxine levels also are depressed. The serum TSH level is elevated in hypothyroidism, except in cases of pituitary or hypothalamic disease. TSH is the most sensitive test for early hypothyroidism, and

TABLE 34.3 Clinical findings in adult hypothyroidism

Symptoms
Slow thinking
Lethargy, decreased vigor
Dry skin, thickened hair, hair loss, broken nails
Diminished food intake, weight gain
Constipation
Menorrhagia, diminished libido
Cold intolerance
Signs
Round puffy face, slow speech, hoarseness
Hypokinesia, generalized muscle weakness, delayed deep tendon reflexes
Cold, dry, thick, scaling skin; dry, coarse, brittle hair; dry, ridged nails
Periorbital edema, ascites, pericardial effusion, ankle edema
Normal or faint cardiac impulse, indistinct heart sounds, bradycardia
Mental clouding, depression
Laboratory findings
Increased serum TSH
Decreased serum free thyroxine, total T_4 and T_3 , resin T_4 or T_3 uptake, free thyroxine index
Decreased radioiodine uptake by thyroid gland
Diminished basal metabolic rate
Macrocytic anemia
Elevated serum cholesterol, creatine kinase
Decreased circulation time, low-voltage QRS complex on EKG

Source: Modified and reproduced from [95], with permission of The McGraw Hill Companies

marked elevations of serum TSH (>20 mU/L) are consistent with frank hypothyroidism. Modest TSH elevations (5–20 mU/L) may be found in euthyroid individuals with normal serum T_3 and T_4 levels and indicate impaired thyroid reserve and incipient hypothyroidism (Table 34.3) [23].

Many features of hypothyroidism are insidious and can be incorrectly attributed to aging. Hypothyroidism in elderly patients can be characterized by a paucity of specific signs and symptoms. Because of the high prevalence of hypothyroidism in women over 60 years, it is recommended that such individuals undergo annual screening with serum TSH measurement [24]. In addition, patients with other autoimmune diseases and those with unexplained depression or cognitive dysfunction should be screened with TSH measurements [25].

Treatment

The goal of therapy is to restore patients to a euthyroid state and normalize serum T_4 and TSH concentrations. Levothyroxine sodium, with its longer half-life and more stable serum concentration, is the treatment of choice for the routine management of hypothyroidism. Adults with hypothyroidism require approximately 1.7 mcg/kg of body weight per day for full replacement. For patients who are older than

50 years, a lower initial dosage is indicated, starting with 0.025–0.05 mg of levothyroxine daily, with clinical and biochemical reevaluations at 6- to 8-week intervals until serum TSH concentration is normalized [16]. In elderly patients with coexistent or suspected cardiac disease, levothyroxine therapy may precipitate angina or myocardial infarction. This is due to sensitivity to the hormone as a result of chronic depletion of catecholamines in the myocardium [10]. Monitoring serum TSH levels to ensure that they remain in the normal range will prevent the potential risk of overtreatment with levothyroxine.

Patients with subclinical hypothyroidism also can benefit from levothyroxine therapy. As many as 15% of elderly patients with subclinical hypothyroidism progress to overt hypothyroidism, particularly if the TSH concentration is greater than 10 mU/mL and thyroid autoantibodies are elevated [26]. Although early treatment prevents progression to frank hypothyroidism, hormone replacement therapy may exacerbate underlying cardiac disease. The decision whether to treat subclinical hypothyroidism should be made on an individual basis.

Hyperthyroidism

Epidemiology

The disease processes associated with increased thyroid secretion result in a hypermetabolic state. Increased thyroid secretion can be caused by primary alterations within the gland, most commonly due to Graves' disease in which TSH receptor autoantibodies stimulate thyroid follicular cells to produce excessive amounts of T_3 and T_4 . Toxic adenoma (TA) and toxic multinodular goiter (TMNG, also known as Plummer's disease) are other common causes of hyperthyroidism, second in prevalence only to Graves' disease. They can appear at any age, although they most frequently occur in patients older than 40 years. Unlike Graves' disease, TA and TMNG are not believed to have an autoimmune etiology, since TSH receptor autoantibodies are absent. Less commonly, patients with multinodular goiter may become thyrotoxic without circulating antibodies if administered inorganic iodine compounds such as potassium iodide, or organic iodine compounds, such as the antiarrhythmic drug amiodarone. Patients from regions where goiter is endemic, so-called goiter belts, can develop thyrotoxicosis when given iodine supplementation (Jod-Basedow phenomenon) [20, 21]. Rarely, TSH-secreting pituitary adenomas (secondary hyperthyroidism) or TRH-secreting hypothalamic disorders (tertiary hyperthyroidism) may occur. Most hyperthyroid states result from thyroid gland dysfunction (Table 34.4). It is important to remember that thyrotoxicosis in the elderly can be caused easily by the administration of exogenous thyroid hormone.

TABLE 34.4 Causes and pathogenetic mechanisms of hyperthyroidism

Etiologic classification	Pathogenetic mechanism
Thyroid hormone overproduction	
Graves' disease	TSH-R-stimulating antibody
Toxic multinodular goiter	Autonomous hyperfunction
Follicular adenoma	Autonomous hyperfunction
Pituitary adenoma	TSH hypersecretion
Pituitary insensitivity	Resistance to thyroid hormone
Hypothalamic disease	Excess TRH production
Germ cell tumors	hCG stimulation
Struma ovarii	Functioning thyroid elements
Metastatic follicular thyroid cancer	Functioning metastases
Thyroid gland destruction	
Granulomatous thyroiditis	Release of stored hormone
Hashimoto's thyroiditis	Transient release of stored hormone
Other	
Thyrotoxicosis medicamentosa, thyrotoxicosis factitia	Ingestion of excessive exogenous thyroid hormone

TSH-R thyroid-stimulating hormone-receptor, *TRH* thyrotropin-releasing hormone, *hCG* human chorionic gonadotropin

Source: Modified and reproduced from [96], with permission of The McGraw Hill Companies

There are two types of primary hyperthyroidism based on thyroid function tests. Clinical primary hyperthyroidism is characterized by suppressed serum TSH and elevated serum total T_4 levels. Subclinical primary hyperthyroidism is defined by suppressed TSH and normal T_4 and T_3 levels. The prevalence of hyperthyroidism in the elderly ranges from 0.5 to 2.3% [27]. The Whickham survey demonstrated that hyperthyroidism did not increase in frequency with age or positive autoantibody status [12, 13]. Approximately 5% of elderly patients have subclinical hyperthyroidism [10].

Clinical and Diagnostic Evaluation

A detailed medical history will usually reveal sufficient clues to suggest the diagnosis of hyperthyroidism. Classic symptoms include heat intolerance, weight loss, increased appetite, palpitations, and emotional lability. Physical examination findings may include hyperkinesia, lid lag, periorbital edema, proptosis, proximal muscle weakness, and tachycardia (Table 34.5). Elderly hyperthyroid patients can display few signs and symptoms; this has been referred to as "apathetic hyperthyroidism." Orbital signs are often lacking with the exception of Graves' ophthalmopathy, which, if present, is usually worse than eye disease in the young (Fig. 34.2). Tachycardia in older patients is less common than that in younger patients, although it can be found in up to 50% of older patients. Congestive heart failure and angina are more frequent. Atrial fibrillation in thyrotoxic patients ranges from 9 to 22%, with a higher prevalence in elderly male patients [9]. Several studies also have demonstrated subtle abnormalities

TABLE 34.5 Clinical findings in adult hyperthyroidism

Symptoms
Alertness, emotional lability, nervousness, irritability
Poor concentration
Muscular weakness, fatigability
Palpitations
Voracious appetite, weight loss
Hyperdefecation
Heat intolerance
Signs
Hyperkinesia, rapid speech
Proximal muscle weakness, fine tremor
Fine, moist skin; fine, abundant hair; onycholysis
Lid lag, stare, chemosis, periorbital edema, proptosis
Accentuated first heart sound, tachycardia, atrial fibrillation, dyspnea
Laboratory findings
Suppressed serum TSH
Elevated serum free thyroxine, total T ₄ , resin T ₃ or T ₄ uptake, free thyroxine index
Increased radioiodine uptake by thyroid gland
Increased basal metabolic rate
Decreased serum cholesterol

**FIGURE 34.2** Exophthalmos in Graves' disease.

of cardiac contractility in individuals with subclinical hyperthyroidism, and one prospective study found that patients over age 65 years with TSH <0.1 mU/L had a threefold greater risk of developing atrial fibrillation than those with normal TSH levels [27]. Depression, lethargy, agitation, anxiety, dementia, and confusion have been reported as primary manifestations [26]. Because overt hyperthyroidism results in bone loss – through reduced absorption of dietary calcium, increased calcium excretion, increased bone turnover, and ultimately, decreased bone mineral density – the increased risk of osteoporosis and pathologic fracture is a pertinent feature of thyrotoxicosis in the elderly.

Treatment

Treatment of hyperthyroidism is directed toward lowering serum concentrations of thyroid hormones to reestablish

TABLE 34.6 Adverse effects of major treatment modalities for hyperthyroidism

Treatment	Adverse effects
Antithyroid drugs (methimazole, propylthiouracil)	1–15% rash, arthralgias, fever, urticaria Rare: fulminant hepatitis, acute hepatic necrosis, glomerulonephritis, lupus-like syndrome, cholestatic hepatitis 15–30%: elevated transaminases within first 2 months of therapy 0.2–0.5%: agranulocytosis within first 3 months of therapy
Radioactive iodine	Transient or permanent hypothyroidism Recurrent or persistent hyperthyroidism Radiation thyroiditis Transient worsening of ophthalmopathy Hyperparathyroidism Thyrotoxic crisis Secondary gastrointestinal malignancy Radiation safety precautions
Surgery	Hypothyroidism Hypoparathyroidism Recurrent laryngeal nerve injury Hemorrhage Risk of anesthesia

a euthyroid state. There are three available modalities of treatment: antithyroid medications, radioactive iodine (¹³¹I) therapy, and thyroid surgery. Each modality carries risks and benefits (Table 34.6).

Antithyroid Medication

Antithyroid medications interfere with one or more steps in the biosynthesis and secretion of thyroid hormone and include MMI and PTU. MMI is the preferred drug. Initial doses are MMI 10–40 mg three times daily and PTU 100–300 mg three times daily; these then can be reduced to once-daily dosing after the patient is rendered euthyroid. Rapidity of response is influenced by severity of the underlying disease, size of the gland, and dose and frequency of the agent used. In general, patients become euthyroid within 6–12 weeks of starting treatment [24].

Adverse reactions to both medications occur, including pruritus, arthralgias, and hepatic abnormalities. Hepatic necrosis caused by PTU and cholestatic jaundice associated with MMI are rare but recently have been the focus of attention. Agranulocytosis in response to either drug occurs in approximately 0.3% of patients, supporting routine monitoring of white blood cell counts [24]. In addition, Imseis and colleagues demonstrated that treatment with PTU reduced the efficacy of RAI therapy, an effect that was not found with MMI use [28]. This is of critical importance for patients who do not respond appropriately to antithyroid medications.

Long-term therapy can lead to remission, but as many as 40% of patients fail to remit after 2 years of treatment. The recurrence rate of disease is 60% after 6 months of therapy, with a latent period of 2–6 weeks. Because of this high failure rate, medical therapy with curative intent is primarily indicated in patients with small goiters, mildly elevated thyroid hormone levels, and who exhibit rapid remission with reduction of gland size [29].

In addition to preventing further synthesis of thyroid hormone, blockade of the catecholamine effects of thyroid hormone is especially important in elderly patients with underlying cardiac disease. The most useful adjuncts are beta-adrenergic blockers, which can provide symptomatic relief. Unfortunately, beta-blockers are contraindicated in patients with asthma or chronic obstructive pulmonary disease and those with heart block and congestive heart failure. In these patients, a calcium channel blocker such as diltiazem may be substituted [10, 24].

Radioactive Iodine Therapy

Radioactive iodine therapy (RAI) therapy is the standard treatment for thyrotoxicosis of Graves' disease in the USA. TMNG and toxic adenoma respond to ^{131}I , but surgery is more commonly employed. Advantages of RAI are avoidance of daily medications with the associated risk of noncompliance, symptoms of hyperthyroidism, and the risk of surgery. Thyrotoxic atrial fibrillation is likely to revert to sinus rhythm after a euthyroid state is established [10]. The overall risk of hypothyroidism with RAI necessitating lifelong replacement therapy is approximately 6% at 1 year and 82% at 25 years [30]. The insidious development of hypothyroidism is likely to occur following ^{131}I administration, and most patients eventually will require lifelong thyroid hormone replacement. Euthyroidism can take 4–6 months to achieve, and multiple doses may be required [29]. Because the effects of RAI may not be immediately evident, surgical resection in patients with antithyroid drug allergies, large goiters, more urgent cardiac issues, or coincident thyroid cancer may be more favorable.

In the USA, treatment of Graves' disease with RAI is the preferred therapy for most patients over the age of 21 years. Follow-up studies have not implicated RAI as a risk factor for development of secondary malignancies [31]. The main side effect of RAI is the development of hypothyroidism; most often, this occurs in patients with severe hyperthyroidism or very large goiters. Pretreatment with antithyroid medications before RAI reduces its effectiveness, primarily due to a radioactive-iodine-uptake (RAIU) independent effect [32]. This is particularly a problem with PTU, which can have a radioprotective effect [28]. However, in patients with severe hyperthyroidism, particularly in the presence of cardiac comorbidity, antithyroid medication pretreatment should

be performed for 4–8 weeks before RAI. Pretreatment reduces thyroid hormone secretion rapidly and thereby reduces the risk of thyrotoxic crisis soon after RAI [33].

The effect of RAI for Graves' hyperthyroidism associated with significant ophthalmopathy is controversial. In a prospective randomized study, Bartalena et al. evaluated the effects of RAI versus antithyroid medications and the effects of glucocorticoids in patients with or without Graves' ophthalmopathy. Among those treated with RAI, ophthalmopathy developed or worsened in 15% of patients 2–6 months after therapy. None of the patients with baseline ophthalmopathy in this group had improvement of eye disease. Among patients treated with a combination of RAI and glucocorticoids, 67% of patients with ophthalmopathy had improvement, and no patients had progression of eye disease [34].

RAI also provides effective treatment for TMNG and TA. Patients' characteristics that favor treatment with RAI include advanced age of patients, significant comorbidities, small goiters, adequate RAIU (>25%) as measured by thyroid uptake scans, prior surgery in the anterior neck, contraindications to surgery, and lack of access to a high-volume surgeon. Nygaard and colleagues reported a 52% rate of euthyroidism after a single ^{131}I treatment for TMNG, with an associated reduction in goiter volume by 40% at 24 months [35]. For TA, Nygaard et al. noted that 75% of patients were no longer hyperthyroid after their first RAI treatment, and that nodule volume showed a median reduction of 35% by 3 months and 45% by 24 months [36]. As demonstrated by Holm et al., hypothyroidism is the main side effect of RAI, with a higher incidence in patients who require more than one treatment to eliminate the hyperthyroid state [30].

Thyroid Surgery

Thyroid surgery should be considered if a patient has hyperthyroidism refractory to medical management, symptoms or signs of compression from goiter, coexisting hyperparathyroidism requiring surgery, large goiter, substernal or retrosternal goiter, insufficient RAIU (<25%), contraindications to RAI, thyroid nodule biopsy that is indeterminate or suspicious for thyroid cancer, or need for rapid correction of the thyrotoxic state [37]. Surgery for hyperthyroidism is advantageous because treatment is rapid, avoids the possible long-term risks of RAI and antithyroid medications, and it provides tissue for histologic examination. Risk of thyroid cancer in TMNG has been estimated to be 3%, although more recent data found an elevated risk of 21% [38, 39].

The operative complication rate is low when surgery is performed by high-volume thyroid surgeons [40]. In a recent cost-effectiveness analysis, surgery was more cost-effective than RAI unless patients had significant comorbidities that increased surgical mortality [41]. Near-total or total

thyroidectomy should be performed for Graves' disease and TMNG, since subtotal thyroidectomy is associated with an attendant risk of persistent or recurrent disease. Ipsilateral thyroid lobectomy, not subtotal thyroid lobectomy or nodulectomy, is indicated for toxic adenomas [42, 43]. Hypothyroidism should be anticipated following near-total or total thyroidectomy [24, 41]. Following surgery, antithyroid medications should be stopped and beta-blockers weaned appropriately. Thyroid hormone replacement should be started at a dose appropriate for the patient's weight, with thyroid function levels monitored every 1–2 months until stable, and then at least annually. In the immediate postoperative period, serum calcium levels should be measured at 6 and 12 h after surgery, and oral calcium and vitamin D supplementation (rocaltrol) can be administered to reduce the likelihood of developing symptomatic hypocalcemia requiring readmission [44].

In the elderly, thyroidectomy has been shown to be associated with worse clinical and economic outcomes than in younger cohorts, as measured by length of hospital stay, mean total costs, immediate perioperative mortality, discharge status, and clinical complications (Table 34.7) [45]. Using the Charlson Comorbidity Index, the elderly (aged 65–79 years) and superelderly (aged >80 years) were stratified into healthy (none to two comorbidities) and sick (three or more comorbidities) subgroups. Their outcomes have been examined based on whether the procedure was performed by low-volume (1–29 thyroidectomies/year) versus high-volume (>30 thyroidectomies/year) surgeons. More experienced surgeons had better outcomes than their less experienced colleagues

(Fig. 34.3). A separate population-level study provided compelling evidence for a significant association between increased surgeon volume and improved patients' outcomes following surgical procedures for both benign and malignant thyroid disease [46]. The lowest-volume surgeons (1–9 thyroidectomies/year) operated on a substantially greater share of elderly patients, who, in turn, had less access to urban hospitals and teaching institutions [45]. For this older population, the surgical risks and benefits must be carefully weighed.

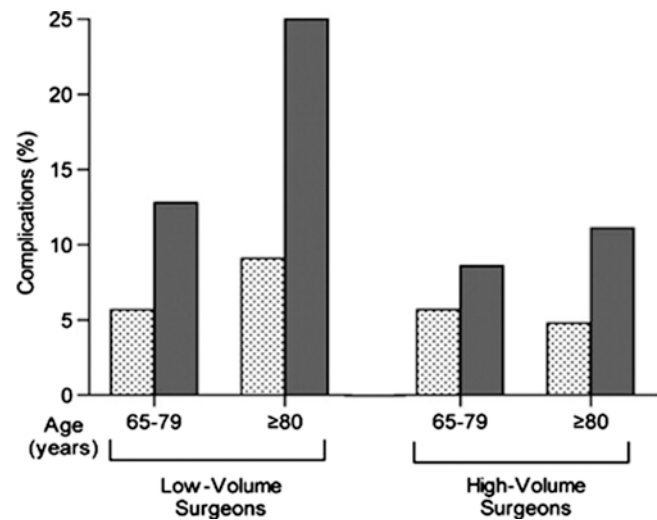


FIGURE 34.3 Complications of thyroidectomy for patients 65 years of age and older, by comorbidity and surgeon volume (reprinted with permission from [45] Copyright 2008, with permission of Elsevier).

TABLE 34.7 Unadjusted and adjusted clinical and economic outcomes from thyroidectomy, by patient age groups

Patient outcomes	Patient age groups (%)				p-Value
	18–44 years	45–64 years	65–79 years	80 years and older	
Unadjusted					
n (%)	8,053 (35.2)	9,959 (43.6)	4,092 (17.9)	744 (3.3)	
Mean total costs (\$) (95% CI)	5,316 (5,174–5,459)	5,445 (5,343–5,547)	6,067 (5,850–6,285)	8,429 (7,339–9,519)	<0.001
Mean length of stay (days) (95% CI)	1.68 (1.63–1.73)	1.73 (1.68–1.77)	2.20 (2.11–2.30)	3.67 (3.19–4.15)	<0.001
In-hospital mortality (%)	2 (0)	7 (0.1)	8 (0.2)	6 (0.8)	<0.001
Patient discharge (%)					<0.001
Routine	7,998 (99.3)	9,827 (98.7)	3,907 (95.6)	621 (83.5)	
Home health care	26 (0.3)	75 (0.8)	104 (2.5)	50 (6.7)	
Transfer to intermediate care	2 (0)	11 (0.1)	2 (0)	3 (0.4)	
Other transfers	21 (0.3)	37 (0.4)	65 (1.6)	64 (8.6)	
Complications (%)	208 (2.6)	240 (3.4)	274 (6.7)	76 (10.2)	<0.001
Endocrine-specific complications ^b (%)	87 (1.1)	123 (1.2)	99 (2.4)	27 (3.6)	<0.001
Adjusted					
Mean total costs ^c (\$) (95% CI)	4,905 (4,821–4,990)	5,263 (5,182–5,344)	5,917 (5,769–6,066)	7,084 (6,653–7,514)	<0.001
Mean length of stay ^d (days) (95% CI)	1.62 (1.58–1.66)	1.77 (1.73–1.81)	2.22 (2.15–2.30)	2.88 (2.67–3.10)	<0.001
Complications ^e (%)	6 (0.2)	15 (0.3)	41 (2.1)	19 (5.6)	<0.001

Source: Reproduced with permission from [45] Copyright 2008, with permission of Elsevier

^aSignificance was set at $\alpha=0.05$

^bEndocrine-specific complications include recurrent laryngeal nerve injury and hypoparathyroidism

^cAdjusted for race, gender, hospital region, procedure, diagnosis, comorbidity, surgeon volume, household income, primary payor, and admission type

^dAdjusted for race, gender, hospital region, procedure, diagnosis, comorbidity, surgeon volume, household income, primary payor, and admission type

^eAdjusted for gender, region, procedure, diagnosis, comorbidity, surgeon volume, household income, primary expected payor, and admission type

Nodules

Epidemiology

Elderly patients frequently harbor thyroid nodules, and the incidence of thyroid nodules increases with age. Solitary palpable nodules occur in 4–7% of individuals and are approximately four times more prevalent in women than in men [47]. High-resolution ultrasound can detect thyroid nodules in 19–67% of randomly selected individuals, with higher frequencies in women and the elderly [48]. Exposure to radiation, particularly during childhood, is associated with an increased prevalence of thyroid nodules and papillary thyroid cancer. Iodine deficiency is associated with elevated risk of follicular thyroid cancer. Rapid growth, pain, and hoarseness are concerning for malignancy. Other risk factors for thyroid cancer include male gender, familial polyposis, Gardner's syndrome, Cowden's syndrome, familial papillary or medullary

thyroid cancer, and multiple endocrine neoplasia (MEN) IIA or IIB syndrome. The clinical importance of thyroid nodules rests with the need to exclude thyroid cancer, which occurs in 5–10% of patients with thyroid nodules [47, 48].

Clinical and Diagnostic Evaluation

Following the discovery of a solitary thyroid nodule, subsequent management depends on the knowledge of a cost-effective workup. Most patients with a solitary thyroid nodule have a benign lesion; however, thyroid cancer is a consideration in all patients. Deciding between surveillance and nonoperative management or surgical therapy relies on careful analysis of the presentation and assessment with imaging modalities such as dedicated neck ultrasound and thyroid uptake scan, along with cytologic diagnosis provided by FNA biopsy (Fig. 34.4) [49].

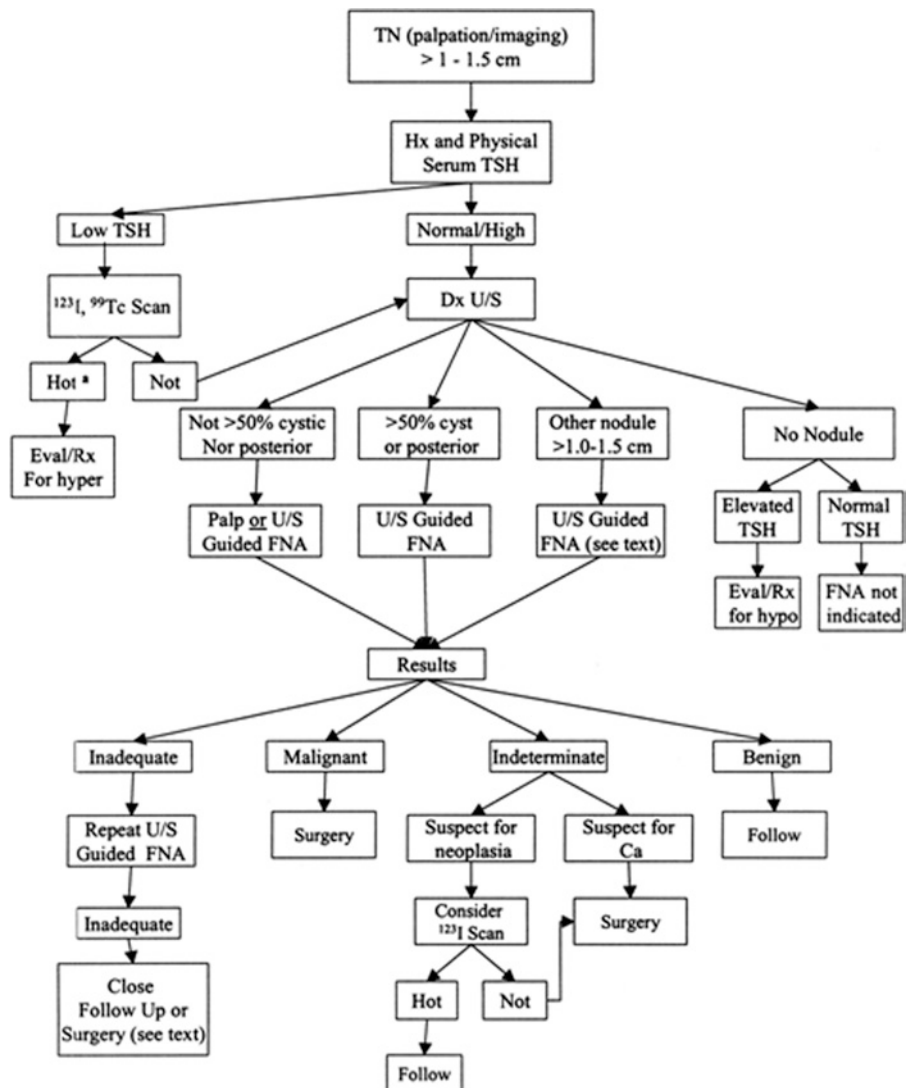


FIGURE 34.4 Algorithm for the evaluation of patients with one or more nodules (reprinted with permission from [5]).

The circumstances surrounding the onset and detection of the nodule and subsequent growth roughly correlate with malignant potential. Incidental subcentimeter nodules, identified during imaging procedures, have a very low probability of malignancy [50]. Slow growth over months to years can be seen with differentiated thyroid carcinomas or benign lesions. Rapid growth over days to weeks most commonly occurs with cyst formation in a goiter or hemorrhage into a preexisting cyst or nodule, but may rarely represent anaplastic thyroid carcinoma or primary thyroid lymphoma. Rapid onset of pain in a nodule often indicates hemorrhage into a goiter or benign adenoma. Slow onset of pain or hoarseness associated with a thyroid nodule is concerning for malignancy. Symptoms of hyperthyroidism are associated with an autonomous nodule (TA or “hot nodule”) or TMNG.

With the discovery of a thyroid nodule, a complete history and physical examination focusing on the thyroid gland and adjacent cervical lymph nodes should be performed. Risk factors for thyroid cancer are a history of head and neck irradiation in childhood or adolescence (papillary thyroid cancer), family history of thyroid cancer in a first-degree relative (familial papillary or medullary thyroid cancer, MEN IIA or IIB), and total body irradiation for bone marrow transplantation. Physical examination findings suggestive of malignancy include vocal cord paresis or paralysis, fixation of the nodule to surrounding tissues, or cervical lymphadenopathy [50].

In general, use of a complete blood count or standard electrolyte evaluation is unhelpful in the evaluation of a patient with a thyroid nodule. Thyroid function tests, including measurement of T_3 , T_4 , and TSH levels, should be employed to identify patients with hyper- or hypothyroidism. In 2006, the American Thyroid Association (ATA) Guidelines Taskforce recommended that if serum TSH is subnormal for nodules greater than 1–1.5 cm in diameter, then a radionuclide thyroid scan should be performed to determine whether the nodule is functioning with tracer uptake greater than the surrounding normal thyroid tissue (“hot”), isofunctioning (“warm”), or nonfunctioning with tracer uptake less than the surrounding thyroid (“cold”) (Fig. 34.5). In general, functional nodules rarely harbor malignancy [50]. However, a large series has shown that 16% of patients with cold nodules and 4% of patient with hot nodules had thyroid cancer documented by surgical resection [51]. It may be that the most useful current application for radionuclide scanning is in the setting of the workup for Graves’ disease.

Based on the ATA Guidelines, the finding of a nodule that is 1–1.5 cm in size warrants consideration of ultrasound and biopsy. An exception can be made for an elderly patient with a growing hot nodule. The likelihood of a hot nodule causing clinical hyperthyroidism over time is a function of its size. If there is evidence of autonomous function, an elderly patient with a large nodule should be considered for either RAI or surgery to prevent the development of atrial fibrillation or other cardiac complications prevalent in this population [10, 41].

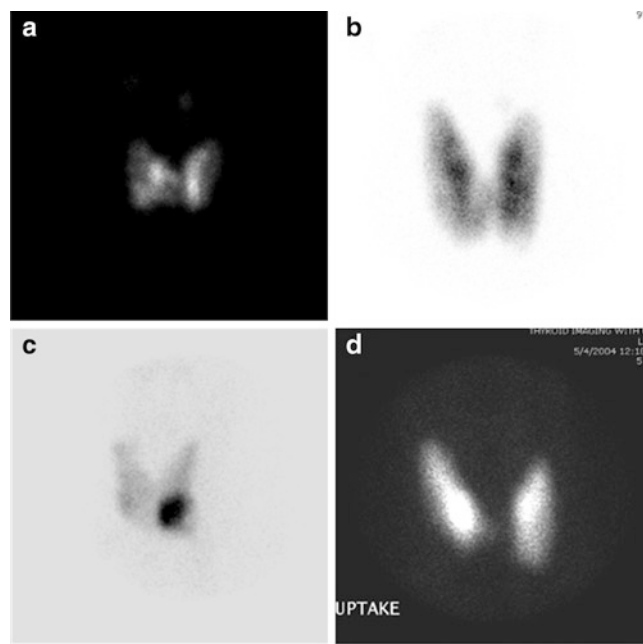


FIGURE 34.5 ^{123}I thyroid scintigraphy (thyroid “uptake” scans).

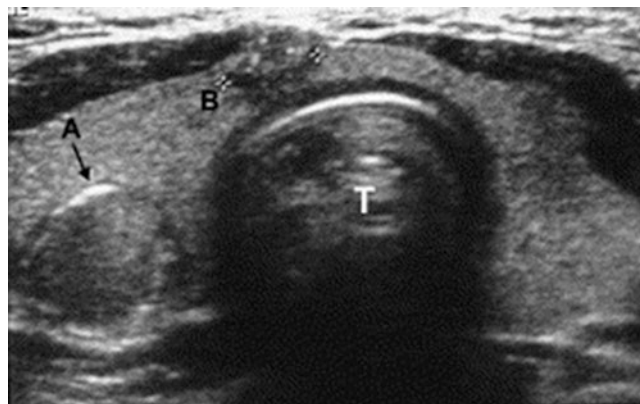


FIGURE 34.6 Transverse ultrasound image showing multifocal papillary thyroid carcinoma.

Ultrasonography of the thyroid is used as the initial imaging modality of a palpable nodule. It is helpful in determining volume and size, number of nodules, whether nodules are solid or cystic, and (with serial ultrasonography) whether there is interval growth. Use of ultrasound has expanded into the office setting and also is available for intraoperative evaluation. It is highly operator-dependent. Ultrasound cannot distinguish between benign and malignant pathologies [52]. Thyroid cancers are hypoechoic in almost 80% of cases; in 20% of cases, they appear as inhomogeneous lesions with solid hypoechoic and cystic changes. However, up to 1% of all carcinomas show a homogeneously hyperechoic echotexture. Papillary thyroid carcinomas often contain microcalcifications (Fig. 34.6), but these also can be seen within benign hyperplastic or regressive nodules [53, 54].

Subclinical, subcentimeter nodules in patients without personal or familial risk factors should undergo size assessment by ultrasound examination and follow-up studies at 6 and 12 months. FNA should be performed for nodules that are 1–1.5 cm in size, smaller nodules with irregular edges or rapid size progression, and in patients with risk factors for thyroid malignancy [55]. Ultrasound-guided FNA is the most accurate and cost-effective method for evaluating thyroid nodules and suspicious cervical lymph nodes. It can be readily performed by experienced clinicians in the outpatient setting. With the patient in a supine position and the neck extended, the skin overlying the nodule is cleansed. Infiltration of a local anesthetic agent is optional. A 23- to 25-gauge needle is inserted into the nodule. Ultrasound-guided FNA biopsy of a thyroid nodule has certain advantages, including the ability to biopsy small, nonpalpable nodules and to biopsy the solid component of a thyroid cyst. While maintaining gentle suction on the syringe, the needle is moved forward and backward through the nodule to draw tissue into the needle. Suction is released, and the needle is withdrawn. The aspirated fluid is spread on a microscope slide and air-dried or fixed according to the preferences of the examining cytopathologist [56, 57].

Assessment of FNA-acquired tissue by an experienced thyroid cytologist can identify reliably the characteristics of particular processes. The features of papillary thyroid carcinoma, such as nuclear grooves, intranuclear cytoplasmic inclusions, psammoma bodies, fine powdery chromatin, and papillary formations, may be seen. Bland follicular cells, mature lymphocytes, and hemosiderin-laden macrophages are typical of nodular goiter, Hashimoto's thyroiditis, or cystic degeneration of a benign nodule.

Traditionally, FNA biopsy results are divided into four categories: nondiagnostic, benign, indeterminate or suspicious for neoplasm, and malignant. Nondiagnostic aspirates are due to insufficient sampling and typically contain few follicular cells and scant colloid. Such results should prompt a repeat FNA biopsy [56]. If a nodule is benign on cytology, additional diagnostic studies or treatment are not routinely required. Indeterminate or suspicious cytology can be found in 15–30% of FNA specimens [37]. Follicular and Hürthle cell neoplasms fall into this category because malignancy is determined by histologic evidence of vascular or capsular invasion that only can be determined on histologic analysis. Specific molecular markers have been evaluated to improve diagnostic accuracy of cytology in the setting of these lesions. Recent ATA Guidelines do not advocate routine use of these markers; instead, ipsilateral thyroid lobectomy, or near-total or total thyroidectomy (if there are multiple or bilateral nodules) is recommended [50]. Finally, aspirates of malignant nodules have unequivocal cytopathologic features of malignancy. These specimens tend to be highly cellular and exhibit typical architectural and cytologic features of primary thyroid carcinomas (papillary, medullary, or anaplastic),

lymphomas (primary or secondary), or metastatic tumors. Approximately 5% of aspirates fall into this category [58].

In the elderly population, primary thyroid lymphoma and anaplastic thyroid carcinoma are more common and present typically with a history of rapid nodule growth, often associated with subjective respiratory compromise and stridor. Prompt differential diagnosis is critical, as treatment options vary. Surgery, radiotherapy, and/or chemotherapy can be beneficial in the setting of primary thyroid lymphoma, while the treatment of anaplastic thyroid cancer is poorly effective and includes radiotherapy, palliative debulking, tracheostomy, and/or feeding tube placement.

Treatment

Patients with benign FNA results in the proper clinical setting should be followed-up periodically with focused physical examinations, as there is a false-negative rate of up to 5% with FNA [59]. Consideration should be given to ultrasound follow-up evaluation of nodule size and contour, and repeat FNA should be performed if the nodule increases in size or develops suspicious characteristics by ultrasound appearance or physical examination.

In the past, patients with benign nodules often were treated with thyrotropin-suppressive therapy with levothyroxine, which was thought to shrink some lesions and prevent enlargement of others. However, several studies indicate that only 20% of cytologically benign thyroid nodules undergo significant shrinkage with this therapy, and that 40–50% of these nodules shrink or disappear spontaneously. This may explain the apparent effectiveness of suppressive therapy reported in many uncontrolled clinical trials. Approximately 20% of cytologically benign thyroid nodules not treated with thyroid suppression enlarge over time, but only 5% of these nodules harbor malignancy [60, 61]. Given the potential long-term skeletal and cardiac effects of thyroid hormone, permanent suppressive therapy of presumed benign nodules is probably unwise in elderly women [10]. Furthermore, current ATA Guidelines do not recommend routine suppressive therapy of benign thyroid nodules [50].

Indications for surgical intervention include FNA findings of thyroid malignancy, suspicious for malignancy, or inconclusive neoplastic lesion; nodules with progressive growth in size; and, multiple thyroid nodules in the setting of prior ionizing radiation exposure [62]. In addition to resolving questions regarding malignancy, surgery can alleviate symptoms related to local mass effect on the upper aerodigestive tract. Patients can have dysphagia, chronic cough, or in the case of a substernal goiter, difficulty breathing. Substernal goiters are more common in the elderly [63, 64]. Often, elderly patients with long-standing goiter and respiratory complaints are diagnosed with asthma or chronic obstructive

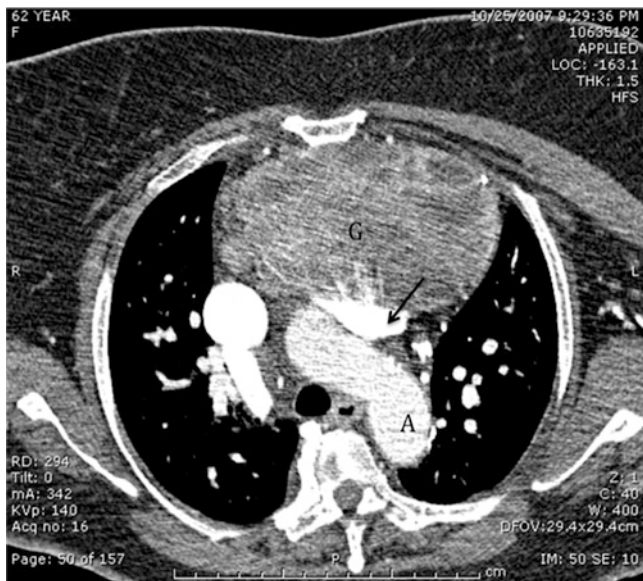


FIGURE 34.7 Computed tomography image of goiter with extensive substernal component.

pulmonary disease when the extent of airway compromise caused by the goiter is unrecognized. Routine chest radiograph, CT scan, or MRI can determine the extent of the goiter and status of the patient's airway (Fig. 34.7). In most cases, substernal goiters can be removed through a cervical Kocher incision, even in reoperative circumstances [63–65].

Neoplasia

Epidemiology

Thyroid cancer represents less than 1% of all malignancies in the USA, occurring in approximately 40 per one million people per year [1]. Six deaths per one million people occur annually. While the incidence of thyroid cancer in the USA more than doubled over the past 30 years, almost 90% of this increase was due to the diagnosis of differentiated thyroid cancers [4]. Ninety percent of thyroid malignancies are categorized as well-differentiated tumors arising from a follicular cell origin. These include papillary thyroid cancer, follicular thyroid cancer, and Hürthle cell cancer. Medullary thyroid cancer, which arises from thyroid parafollicular or C cells, accounts for about 6% of thyroid cancers, of which 20–30% are inherited in the form of familial medullary thyroid cancer or MEN types IIA and IIB. Anaplastic thyroid cancer, also derived from thyroid follicular cells, is an aggressive malignancy and is responsible for less than 1% of thyroid cancers, and 600 new cases per year. Approximately 1% of thyroid malignancies are primary thyroid lymphoma,

usually of the non-Hodgkin's B-cell type [66]. Metastatic disease to the thyroid is rare and most commonly originates from renal cell carcinomas, breast cancers, and lung cancers. Other tumors that have been shown to metastasize to the thyroid include melanoma and those from esophagus, stomach, pancreas, colon, rectum, uterus, and larynx [67, 68].

Clinical and Diagnostic Evaluation

Evaluation of a patient for thyroid cancer should begin with a thorough history and physical examination. This should be followed by ultrasonography with FNA, and occasionally, CT (usually without intravenous contrast in case it is a differentiated thyroid cancer that will necessitate adjuvant RAI therapy) or MRI. In addition to thyroid function tests, patients with medullary thyroid cancer require preoperative evaluation of calcitonin, carcinoembryonic antigen (CEA), and catecholamine levels (24-h urine measurement of epinephrine, norepinephrine, metanephrine, normetanephrine, vanillylmandelic acid, and dopamine levels), particularly if there is suspicion of MEN IIA or IIB syndrome. In addition, consideration should be given to genetic screening with a serum *RET* (rearranged during transfection) proto-oncogene screen for all patients with medullary thyroid cancer.

Papillary thyroid cancer is the most common form, representing 80% of thyroid cancers. Prognostically, it is the most favorable. This tumor tends to exhibit intra- and extraglandular lymphatic spread; unlike other malignancies, presence of lymphatic metastases generally does not adversely influence prognosis, especially in young patients under age 45 years. Recognized variants of papillary carcinoma include encapsulated, follicular, tall cell, columnar cell, clear cell, and diffuse sclerosing carcinomas. Follicular thyroid cancer is more aggressive. Malignant lesions exhibit vascular or capsular invasion, and they spread hematogeneously to lung and bone. Like follicular thyroid cancer, Hürthle cell cancer, an oncocytic tumor, is considered malignant if there is evidence of vascular or capsular invasion. Although considered well-differentiated, Hürthle cell carcinoma holds a significantly worse prognosis than its papillary or follicular counterparts, in part because only a minority of tumors demonstrate iodine avidity. While the mean age at presentation is 30–40 years for papillary carcinoma, mean age at presentation for follicular thyroid cancer is 50 years, and for Hürthle cell carcinoma, 60 years [69, 70].

Medullary thyroid cancer arises from the calcitonin-secreting parafollicular or C-cells, which are derived from neural crest cells during embryologic development. Sporadic medullary thyroid cancer represents 70% of all cases; it tends to be unilateral and occurs after 30 years of age. Inherited medullary thyroid cancer accounts for 20–30% of all cases; it is almost always bilateral, associated with C-cell hyperplasia, and usually occurs before 30 years of age. Familial medullary thyroid

cancer can occur in the absence of associated endocrinopathy or as part of the MEN II syndromes. The pathologic features of medullary thyroid cancer include the presence of amyloid, a classic “salt-and-pepper” appearance of the cells, C-cell hyperplasia, and positive immunohistochemical staining for calcitonin and CEA. Patients present with a thyroid mass associated with cervical lymphadenopathy in up to 20% of cases. Symptoms are secondary to mass effect or to hypercalcitonism, as manifested by diarrhea and flushing. Hematogenous metastases to the liver, lung, and bones occur with disease progression. Prognosis varies with extent of disease. Sporadic and MEN-II-B-associated medullary thyroid tumors are more aggressive, and they carry a worse prognosis than MEN IIA or familial forms of the disease [71].

With the reduction of iodine-deficiency-associated goiters in the USA, the incidence of anaplastic or undifferentiated carcinoma has decreased to less than 1% of thyroid cancers. It usually arises in a well-differentiated cancer and in patients older than 60 years. Patients may detail a history of rapid enlargement of a neck mass in conjunction with pain, hoarseness, dyspnea, and dysphagia. Physical examination often reveals a firm, fixed thyroid mass with palpable cervical lymph node metastases. On FNA, spindle cells, small cells, or giant cells suggest the diagnosis. In many cases, additional pathologic material will be required to obtain a histologic diagnosis. While anaplastic thyroid cancer is rare, it accounts for more than half of the 1,200 deaths attributed to thyroid cancer annually in the USA [72]. Given the overall aggressiveness of the disease as well as its late clinical presentation, prognosis is extremely poor, with a 90% mortality within a mean interval of 9 weeks [73, 74].

Primary thyroid lymphoma is usually of the non-Hodgkin's B-cell type. It tends to occur in elderly women who present with a rapidly growing, often painful, thyroid mass with compressive symptoms. The overall 5-year survival for lymphoma of the thyroid is 70%. Older age, single marital status, advanced stage (stages II–IV), and histologic subtype (large B-cell, follicular, or other non-Hodgkin's) are associated with worse survival [75]. Primary squamous cell carcinoma and metastatic disease is rare. The diagnosis is most often confirmed by FNA and rarely requires surgical intervention [73].

A number of clinical scoring systems have been developed to assess prognosis of differentiated thyroid cancer. These include AGES (age, grade, extent, size), AMES (age, metastasis, extent, size), and MACIS (metastasis, age, completeness of resection, invasion, size) [76, 77]. For well-differentiated tumors, patients younger than 20 years, males older than 40 years, and females older than 50 years with cancers greater than 4 cm that have extended through the thyroid capsule and who have distant metastases are at higher risk of dying from the disease. In contrast, patients between ages 20 and 40 years with a tumor less than 4 cm confined to the thyroid are at low risk and have an excellent prognosis. The TMN staging system adopted by the American Joint Committee on Cancer

(AJCC), as well as the International Union Against Cancer (UICC), is universally accepted and is required by tumor boards for standardized reporting (Table 34.8) [50].

Treatment

The goals of initial therapy of differentiated thyroid cancer are to (1) remove the primary tumor, disease beyond the thyroid capsule, and involved cervical lymph nodes; (2) permit accurate staging of the disease; (3) minimize treatment-related morbidity; (4) facilitate postoperative treatment with RAI if appropriate; (5) allow for accurate long-term surveillance for recurrence; and (6) minimize risk of locoregional disease recurrence and metastatic spread [50].

Successful thyroid surgery requires an appreciation of the normal anatomic relations of the thyroid and parathyroids, the recurrent and superior laryngeal nerves, and the inferior thyroid arteries, as well as their common anatomic variations. Lo Gerfo and colleagues have shown that bilateral neck exploration under regional anesthesia can be performed safely in patients with thyroid disease [78, 79]. However, most surgeons prefer general endotracheal anesthesia. The relatively short duration of the procedure and lack of significant fluid shifts and hemodynamic changes allows it to be well-tolerated, even in older patients.

According to the ATA Guidelines, near-total or total thyroidectomy are acceptable operations for papillary thyroid cancer. They are followed by a 10-year survival rate in excess of 90%. Subtotal or partial lobectomy (“nodulectomy”) is contraindicated. Total thyroidectomy is preferred over other operations because of the high incidence of multifocal disease, a clinical recurrence rate of 7% in the contralateral lobe if it is spared, and the ease of assessment for recurrence by serum thyroglobulin assay or radioiodine scan during follow-up exams. In addition, total thyroidectomy increases the efficacy of RAI therapy. Routine central compartment (level VI) neck dissection continues to be an area of great controversy. Although there are ample data that micrometastases to this level are not infrequent, central lymphadenectomy comes with increased attendant risk of recurrent laryngeal nerve injury and hypoparathyroidism. If there is palpable, biopsy-proven, or grossly apparent metastasis at the time of surgery, lymphadenectomy should be performed. However, if these conditions are not present and if postoperative RAI ablation is planned, dissection of nonpalpable central lymph nodes is debatable [80, 81]. A modified radical neck dissection (levels II–V), preserving the sternocleidomastoid muscle, spinal accessory nerve, and internal jugular vein, usually is indicated for patients with clinically palpable or biopsy-proven cervical adenopathy [82].

Patients with an FNA-diagnosis of follicular or Hürthle cell neoplasm should undergo ipsilateral thyroid lobectomy and isthmusectomy because approximately 20% of these

TABLE 34.8 American Joint Committee on Cancer (AJCC) pathologic-tumor-node metastasis (pTNM) system**Definition**

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor diameter 2 cm or less limited to the thyroid
T1a	Tumor diameter 1 cm or less limited to the thyroid
T1b	Tumor diameter 1–2 cm limited to the thyroid
T2	Primary tumor diameter >2–4 cm
T3	Primary tumor diameter >4 cm limited to thyroid or with minimal extrathyroidal extension
T4a	Tumor of any size extending beyond thyroid capsule to invade soft tissues, larynx, trachea, esophagus, recurrent laryngeal nerve (moderately advanced)
T4b	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels (very advanced)
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastases to level VI (pretracheal, paratracheal, prelaryngeal/Delphian lymph nodes)
N1b	Metastases to unilateral, bilateral, contralateral cervical or superior mediastinal lymph nodes
Mx	Distant metastases not assessed
M0	No distant metastases
M1	Distant metastases

Stage	Papillary or follicular		Medullary	Anaplastic
	Age <45 years	Age >45 years	Any age	Any age
I	Any T, any N, M0	T1, N0, M0	T1, N0, M0	
II	Any T, any N, M1	T2, N0, M0	T2, N0, M0 T3, N0, M0	
III		T3, N0, M0 T1, N1a, M0 T2, N1a, M0 T3, N1a, M0	T1, N1a, M0 T2, N1a, M0 T3, N1a, M0	
IV				
A		T4a, N0, M0 T4a, N1a, M0 T1, N1b, M0 T2, N1b, M0 T3, N1b, M0 T4a, N1b, M0	T4a, N0, M0 T4a, N1a, M0 T1, N1b, M0 T2, N1b, M0 T3, N1b, M0 T4a, N1b, M0	T4a, any N, M0
B		T4b, any N, M0	T4b, any N, M0	T4b, any N, M0
C		Any T, any N, M1	Any T, any N, M1	Any T, any N, M1

Source: Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media, LLC, <http://www.springerlink.com>

lesions will prove to be carcinomas. The diagnosis of carcinoma is confirmed by the finding of capsular and vascular invasion on permanent histology. Detection of macroinvasion necessitates completion of thyroidectomy. Indications for total thyroidectomy include obvious extension of the lesion through the thyroid capsule, lesions greater than 4 cm (50–80% prove to be malignant), and contralateral nodularity or pathology. Follicular carcinoma is associated with a 10-year survival of 85% and 20-year survival of 70% [70]. Like papillary and follicular malignancies, Hürthle cell carcinomas produce thyroglobulin, a useful marker for postoperative surveillance. However, Hürthle cells are not iodine-avid; therefore, surgical resection is the mainstay of treatment.

In patients with papillary or follicular thyroid cancer, postoperative ablation with ^{131}I is used more frequently to

eliminate residual thyroid tissue in order to decrease the risk of locoregional recurrence as well as to facilitate long-term surveillance with radioiodine scans. Several retrospective studies have demonstrated a significant reduction in the rates of disease recurrence and disease-associated mortality [70, 83]. In order to effectively administer postoperative RAI, the patient must be sufficiently hypothyroid as shown by elevated serum TSH levels. Levothyroxine is withheld or withdrawn for 4–6 weeks to maximize thyrotropin stimulation of the remaining thyroid tissue. The resulting hypothyroidism is tolerated poorly by some patients, and it may be attenuated by administration of liothyronine sodium to ensure a shorter duration of hypothyroidism. Recently, administration of recombinant human thyrotropin (rhTSH) has been used in lieu of traditional thyroid hormone withdrawal.

CASE STUDY RESOLUTION

JK's medical and surgical teams discussed the risks and benefits of total thyroidectomy with the patient, and the decision was made to proceed with surgery given the apparent aggressive nature of her cancer. Given her subjective hoarseness, indirect laryngoscopy was performed, and her vocal cord function was deemed to be intact; she had mild reflux. Appropriate medical and cardiologic clearance was obtained. The patient met with anesthesiology preoperatively. Her warfarin was stopped 5 days prior to surgery, as was her vitamin supplement. Total thyroidectomy with en bloc resection of the right strap muscle was performed, along with a right central lymph node

dissection. The patient did well postoperatively; she had no evidence for change in voice or hypoparathyroidism. Her warfarin was restarted on postoperative day 1, and she was discharged home that day with follow-up with her cardiologist later in the week. Her final pathology revealed multifocal papillary thyroid cancer. The largest focus measured 4.1 cm in the right lobe, and an additional 5 mm focus was identified in the contralateral lobe. Lymphovascular invasion was seen, and there was extension of tumor into soft tissue, but surgical margins were negative. Three of ten lymph nodes were positive for metastatic disease, giving her an AJCC pT4aN1aMx, or stage IVA, papillary thyroid cancer. She met with endocrinology regarding adjuvant RAI therapy.

Successful remnant ablation with ^{131}I was equivalent after thyroxine withdrawal compared to rhTSH stimulation when the thyroxine therapy was stopped 1 day prior to the rhTSH injections and restarted the day following RAI [84–86].

Treatment for medullary thyroid cancer generally includes total thyroidectomy and central lymph node dissection. An ipsilateral or bilateral modified radical neck dissection is performed for lateral cervical lymph node disease. Tumor debulking may be helpful in alleviating diarrhea and flushing. Nutmeg oil, a combination of atropine sulfate and diphenoxylate hydrochloride, or subcutaneous somatostatin analogue has offered some relief from symptoms of metastatic disease [71]. Postoperatively, calcitonin remains a highly sensitive tumor marker and may remain elevated in patients who present with bulky disease. Preoperative basal calcitonin levels can individualize the extent of surgery and postoperative follow-up intervals. On multivariate analysis, preoperative basal serum calcitonin levels >500 pg/ml best predicted failure to achieve biochemical remission, followed by nodal metastasis and need for reoperation. Patients with nodal or distant metastases did not achieve biochemical remission when their preoperative basal calcitonin levels exceeded 3,000 pg/ml. Nodal metastasis emerged at basal calcitonin levels of 10–40 pg/ml, while distant metastases and extrathyroidal growth appeared with basal calcitonin levels of 150–400 pg/ml [87]. Despite this, some patients with medullary thyroid cancer survive for many years with minimal symptoms despite significant tumor burden. Chemotherapy is poorly effective in the management of locally advanced and metastatic medullary thyroid cancer, and the role of radiation therapy is questionable. The best results are achieved in familial medullary or MEN II kindreds where patients can be identified presymptomatically and appropriately treated [55, 71]. More recently, tyrosine kinase inhibitors have been shown to inhibit *RET* tyrosine

kinase activity. Clinical studies are underway, but only preliminary results have been published [88, 89].

Anaplastic thyroid cancer most often is advanced at presentation, and it usually presents in the 6–7th decades of life. It is almost always unencapsulated and invades surrounding structures. Cervical lymphadenopathy and pulmonary metastases are common. It does not concentrate iodine or express thyroglobulin [90]. Although there is no satisfactory treatment for anaplastic cancer, local control can be attempted with palliative surgery, chemotherapy, or radiotherapy. Tumor debulking, tracheostomy, and feeding gastrostomy may be required for palliation [91]. In the rare instance of early anaplastic carcinoma localized to the thyroid, total thyroidectomy has resulted in long-term survival [92].

Primary non-Hodgkin's lymphoma of the thyroid is most common in elderly women, occurring most often in the background of autoimmune thyroid disease. Primary thyroid lymphoma usually is not a surgical disease, although surgeons often assist by obtaining adequate tissue to establish a diagnosis and determine tumor markers. Use of multimodality chemotherapy, particularly with anthracycline agents, and external radiotherapy results in dramatic tumor shrinkage and rapid resolution of airway compromise. The overall 5-year survival is approximately 70%, depending on stage and histologic type [71, 75, 93].

Conclusion

Thyroid disease is common in the elderly. In this population, the clinical manifestation of thyroid dysfunction can be subtle, often hidden by a background of coexistent disease. Hypo- and hyperthyroidism often are subclinical, and therapeutic decisions may be dictated by patients' preference and overall health

status. The incidence of thyroid nodules increases with age, as does the risk of thyroid malignancy and the aggressiveness of the thyroid tumor. Surgery is the mainstay of treatment for thyroid cancer. Quality-of-life issues related to voice, swallowing, and calcium metabolism are especially salient in elderly patients. Thyroid surgery in this population is associated with increased attendant risk, but it can be performed safely, especially in the hands of high-volume thyroid surgeons. It is imperative that internists, geriatricians, endocrinologists, and thyroid surgeons work together as an interdisciplinary team to formulate and tailor treatment strategies.

References

- United States Census Bureau (2008) Available at: <http://www.census.gov/population/www/projections/natdet-d1a.html>
- Wu P (2000) Thyroid disease and diabetes. *Clin Diabetes* 18:1
- Whitman ED, Norton JA (1994) Endocrine surgical diseases of elderly patients. *Surg Clin North Am* 74:127
- Davies L, Welch HG (2006) Increasing incidence of thyroid cancer in the United States, 1973–2002. *J Am Med Assoc* 295:2164
- Mariotti S et al (1995) The aging thyroid. *Endocr Rev* 16:686
- Coburn MC, Wanebo HJ (1995) Age correlates with increased frequency of high risk factors in elderly patients with thyroid cancer. *Am J Surg* 170:471
- Ganong WF (1991) The thyroid gland. In: Ganong WF (ed) *Review of medical physiology*. Appleton & Lange, Stamford, p 303
- Goodman HM (2003) Thyroid gland. In: Johnson LR (ed) *Essential medical physiology*. Elsevier, San Diego, p 587
- Mokshagundam S, Barzel US (1993) Thyroid disease in the elderly. *J Am Geriatr Soc* 41:1361
- Chiovato L et al (1997) Thyroid diseases in the elderly. *Baillieres Clin Endocrinol Metab* 11(2):251
- Gambert SR (1991) Environmental and physiologic variables. In: Braverman LE, Utiger RD (eds) *The thyroid*. Lippincott, Philadelphia, p 347
- Tunbridge WMG et al (1977) The spectrum of thyroid disease in the community: the Whickham survey. *Clin Endocrinol* 7:481
- Vanderpump MPJ et al (1995) The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham survey. *Clin Endocrinol* 43:55
- Pinchera A et al (1995) Thyroid autoimmunity and aging. *Horm Res* 43:64
- Dayan CM (2001) Interpretation of thyroid function tests. *Lancet* 357:619
- Surks MI et al (1990) American thyroid association guidelines for use of laboratory tests in thyroid disorders. *JAMA* 263:1529
- Wong KT, Hershman JM (1992) Changes in thyroid function in nonthyroid illness. *Trends Endocrinol Metab* 3:8
- Ladenson PW et al (2000) American thyroid association guidelines for detection of thyroid dysfunction. *Arch Intern Med* 160:1573
- Danese MD et al (1996) Screening for mild thyroid failure at the periodic health examination: a decision and cost-effective analysis. *J Am Med Assoc* 276:2591
- Laurberg P et al (1998) Iodine intake and the pattern of thyroid disorders: a comparative epidemiological study of thyroid abnormalities in the elderly in Iceland in Jutland, Denmark. *J Clin Endocrinol Metab* 83:765
- Szabolcs I et al (1997) Comparative screening for thyroid disorders in old age in areas of iodine deficiency, long-term iodine prophylaxis, and abundant iodine intake. *Clin Endocrinol* 47:87
- Cooper DS (2001) Subclinical hypothyroidism. *N Engl J Med* 345:260
- Greenspan FS (2007) The thyroid gland. In: Garner D, Shoback D (eds) *Basic and clinical endocrinology*. McGraw, New York, p 209
- Singer PA et al (1995) Treatment guidelines for patients with hyperthyroidism and hypothyroidism. *JAMA* 273:808
- Surks MI et al (2004) Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 291:228
- Roberts LM et al (2006) Is subclinical thyroid dysfunction in the elderly associated with depression or cognitive dysfunction? *Ann Intern Med* 145:573
- Sawin CT et al (1994) Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med* 331:1249
- Imseis RE et al (1998) Pretreatment with propylthiouracil but not methimazole reduces the therapeutic efficacy of I-131 in hyperthyroidism. *J Clin Endocrinol Metab* 83:685
- Boger MS, Perrier ND (2005) Graves' and Plummer's disease: medical and surgical management. In: Clark OH, Duh QY, Kebebew E (eds) *Textbook of endocrine surgery*. Elsevier, Philadelphia, p 54
- Metso S et al (2004) Long-term follow-up study of radioiodine treatment of hyperthyroidism. *Clin Endocrinol* 61:641
- Iagaru A, McDougall IR (2007) Treatment of thyrotoxicosis. *J Nucl Med* 48:379
- Walter MA et al (2004) Radioiodine therapy in hyperthyroidism: inverse correlation of pretherapeutic iodine uptake level and post-therapeutic outcome. *Eur J Clin Invest* 34:365
- Andrade V et al (2001) The effect of methimazole pretreatment on the efficacy of radioactive iodine treatment in Graves' hyperthyroidism: one-year follow-up of a prospective, randomized study. *J Clin Endocrinol Metab* 86:3488
- Bartalena L et al (1998) Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. *N Engl J Med* 338:73
- Nygaard B et al (1999) Radioiodine therapy for toxic multinodular goiter. *Arch Intern Med* 159:1364
- Nygaard B et al (1999) Long term effect of radioactive iodine on thyroid function and size in patients with solitary autonomously functioning toxic thyroid nodules. *Clin Endocrinol* 50:191
- Tuttle RM et al (1998) Clinical features associated with an increased risk of thyroid malignancy in patients with follicular neoplasia by fine-needle aspiration. *Thyroid* 8:377
- Kang AS et al (2002) Current treatment of nodular goiter with hyperthyroidism (Plummer's disease): surgery versus radioiodine. *Surgery* 132:916
- Pang H, Chen C (2007) Incidence of cancer in nodular goitres. *Ann Acad Med Singapore* 36:241
- Andaker L et al (1992) Surgery for hyperthyroidism: hemithyroidectomy plus contralateral resection or bilateral resection: a prospective randomized study of postoperative complications and long-term results. *World J Surg* 16:765
- Vidal-Trecan GM et al (2004) Radioiodine or surgery for toxic thyroid adenoma: dissecting an important decision. *Thyroid* 14:933
- Reeve TS et al (1987) Total thyroidectomy: the preferred option for multinodular goiter. *Ann Surg* 203:782
- Chao TC et al (1997) Reoperative thyroid surgery. *World J Surg* 21:644
- Bellantone R et al (2002) Is routine supplementation therapy (calcium and vitamin D) useful after total thyroidectomy? *Surgery* 132:1109
- Sosa JA et al (2008) A population-based study of outcomes from thyroidectomy in aging Americans: at what cost? *J Am Coll Surg* 206:1097
- Sosa JA et al (1998) The importance of surgeon experience for clinical and economic outcomes from thyroidectomy. *Ann Surg* 228:320
- Mazzaferri EL (1993) Management of a solitary thyroid nodule. *N Engl J Med* 328:553
- Tan GH, Gharib H (1997) Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. *Ann Intern Med* 126:226

49. Wong CKM, Wheeler MH (2000) Thyroid nodules: rational management. *World J Surg* 24:934
50. Cooper DS et al (2006) Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 16(2):1
51. Shaha AR (2000) Controversies in the management of thyroid nodule. *Laryngoscope* 110:183
52. Boyd LA et al (1998) Preoperative evaluation and predictive value of fine-needle aspiration and frozen section of thyroid nodules. *J Am Coll Surg* 187:494
53. Hegedus L (2001) Thyroid ultrasound. *Endocrinol Metab Clin North Am* 30:339
54. Gritzmann N et al (2000) Sonography of the thyroid and parathyroid glands. *Radiol Clin North Am* 38:1131
55. Singer PA et al (1996) Treatment guidelines for patients with thyroid nodules and well-differentiated thyroid cancer. *Arch Intern Med* 156:2165
56. Gharib H (1994) Fine-needle aspiration biopsy of thyroid nodules: advantages, limitations, and effect. *Mayo Clin Proc* 69:44
57. Gharib H, Goeliner JR (1993) Fine-needle aspiration biopsy of the thyroid: an appraisal. *Ann Intern Med* 118:282
58. Gharib H et al (1993) Fine-needle aspiration cytology of the thyroid: a 12-year experience with 11,000 biopsies. *Clin Lab Med* 13:699
59. Ylages LR et al (2004) Fine-needle aspiration of the thyroid: a cytohistologic correlation and study of discrepant cases. *Thyroid* 14:35
60. Cooper DS (1995) Thyroxine suppression therapy for benign thyroid nodular disease. *J Clin Endocrinol Metab* 80:331
61. Castro MR et al (2002) Effectiveness of thyroid hormone suppressive therapy in benign solitary thyroid nodules: a meta-analysis. *J Clin Endocrinol Metab* 87:4154
62. Kukora JS et al (2001) Thyroid nodule. In: Cameron JL (ed) *Current surgical therapy*. Mosby, St. Louis, p 636
63. Newman E, Shah A (1995) Substernal goiter. *J Surg Oncol* 60:207
64. Hsu B et al (1996) Recurrent substernal nodular goiter: incidence and management. *Surgery* 120:1072
65. Zeiger MA (2001) Nontoxic goiter. In: Cameron JL (ed) *Current surgical therapy*. Mosby, St. Louis, p 642
66. Samaan NA, Ordenez NG (1990) Uncommon types of thyroid cancer. *Endocrinol Metab Clin North Am* 19:637
67. Chen H et al (1999) Clinically significant, isolated metastatic disease to the thyroid gland. *World J Surg* 23:177
68. Wood K et al (2004) Metastases to the thyroid gland: the Royal Marsden experience. *Eur J Surg Oncol* 30:583
69. Schlumberger KJ (1998) Papillary and follicular thyroid carcinoma. *N Engl J Med* 338:297
70. Mazzaferri EL, Jhiang SM (1994) Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med* 97:418
71. Moley JF (1995) Medullary thyroid cancer. *Surg Clin North Am* 75:405
72. Demeter JG et al (1991) Anaplastic thyroid carcinoma: risk factors and outcome. *Surgery* 110:956
73. Burman KD et al (1996) Unusual types of thyroid neoplasm's. *Endocrinol Metab Clin North Am* 25:49
74. Sugino K et al (2002) The important role of operations in the management of anaplastic thyroid carcinoma. *Surgery* 131:245
75. Graff-Baker A et al (2009) Prognosis of primary thyroid lymphoma: demographic, clinical and pathologic predictors of survival in 1408 cases. *Surgery* 146(6):1105–1115
76. Cady B, Rossi R (1988) An expanded view of risk-group definition in differentiated thyroid carcinoma. *Surgery* 104:948
77. Hay ID et al (1987) Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. *Surgery* 102:1088
78. Lo Gerfo P (1998) Local-regional anesthesia for thyroidectomy: evaluation as an outpatient procedure. *Surgery* 124:975
79. Lo Gerfo P (1999) Bilateral neck exploration for parathyroidectomy under local anesthesia: a viable technique for patients with coexisting thyroid disease with or without sestamibi scanning. *Surgery* 126:1011
80. Sosa JA, Udelsman R (2006) Papillary thyroid cancer. *Surg Oncol Clin N Am* 15:585
81. Dralle H, Machens A (2008) Surgical approaches in thyroid cancer and lymph-node metastases. *Best Pract Res Clin Endocrinol Metab* 22:971
82. Hay ID (1990) Papillary thyroid carcinoma. *Endocrinol Metab Clin North Am* 19:545
83. Samaan NA et al (1992) The results of various modalities of treatment of well-differentiated thyroid carcinomas: a retrospective review of 1599 patients. *J Clin Endocrinol Metab* 75:714
84. Pacini F et al (2002) Ablation of thyroid residues with 30 mCi (¹³¹I): a comparison in thyroid cancer patients prepared with recombinant human TSH or thyroid hormone withdrawal. *J Clin Endocrinol Metab* 87:4063
85. Barbaro D et al (2003) Radioiodine treatment with 30 mCi after recombinant human thyrotropin stimulation in thyroid cancer: effectiveness for postsurgical remnants ablation and possible role of iodine content in L-thyroxine in the outcome of ablation. *J Clin Endocrinol Metab* 88:4110
86. Ladenson PW et al (1997) Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning patients with thyroid carcinoma. *N Engl J Med* 337:888
87. Machens A et al (2005) Prospects of remission in medullary thyroid carcinoma according to basal calcitonin level. *J Clin Endocrinol Metab* 90:2029
88. Cohen MS et al (2002) Inhibition of medullary thyroid carcinoma cell proliferation and RET phosphorylation by tyrosine kinase inhibitors. *Surgery* 132:960
89. Carlomagno F et al (2002) ZD6474, an orally available inhibitor of KDR tyrosine kinase activity, efficiently blocks oncogenic RET kinases. *Cancer Res* 62:7284
90. Chandrakanth A, Shaha AR (2006) Anaplastic thyroid cancer: biology, pathogenesis, prognostic factors, and treatment approaches. *Ann Surg Oncol* 13:453
91. Lang BH, Lo CY (2007) Surgical options in undifferentiated thyroid carcinoma. *World J Surg* 31:969
92. Brignardello E et al (2007) Anaplastic thyroid cancer: clinical outcome of 30 consecutive patients referred to a single institution in the past 5 years. *Eur J Endocrinol* 156:425
93. Matsuzuka F et al (1993) Clinical aspects of primary thyroid lymphoma: diagnosis and treatment based on our experience of 119 cases. *Thyroid* 3:93
94. McPhee SJ, Bauer DC (2000) Thyroid disease. In: McPhee SJ, Lingappa VR, Ganong WF, Lange JD (eds) *Pathophysiology of disease*. Lange, New York, p 491
95. McPhee SJ, Bauer DC (2000) Thyroid disease. In: McPhee SJ, Lingappa VR, Ganong WF, Lange JD (eds) *Pathophysiology of disease*. Lange, New York, p 493
96. McPhee SJ, Bauer DC (2000) Thyroid disease. In: McPhee SJ, Lingappa VR, Ganong WF, Lange JD (eds) *Pathophysiology of disease*. Lange, New York, p 487