Thyroid Gland: Anatomy, Physiology, Pathophysiology, and Ultrasonography

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Contents

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1

Case Presentation:

A 57-year-old woman presents to her provider with complaints of fatigue, low mood, weight gain, and constipation. She reports that her weight has gradually increased over the past 18 months despite no change in her activity level or eating habits. She works full time as a lab tech, and finds herself more distracted at work than normal and intermittent dozes off in front of the computer during downtimes. She has found this unsettling.

She feels her mood is down, and she lacks motivation to do anything during the weekend. Upon questioning, the patitent reports the following changes: thinning of her scalp hair and cold intolerance. Physical examination confirms dry skin, and coarse and dry hair. The only medication she takes is a multivitamin daily. She has a positive family history for autoimmune disorders and thyroid cancer.

Questions

1. What are criteria to establish the diagnosis of overt hypothyroidism?
   1. A TSH level above the reference range
   2. A free T4 concentration below the reference range
   3. Elevated antithyroglobulin autoantibodies
   4. Thyroglobulin levels that are undetectable
   5. A total serum T4 below the reference range
      - (a) Only (1) and (2) and (5) are correct.
      - (b) Only (3) and (5) are correct.
      - (c) Only (1) and (2) are correct.
      - (d) Only (2) and (4) and (5) are correct.
      - (e) All are correct.
2. What are criteria to establish the diagnosis of subclinical hypothyroidism?
   1. A TSH level above the reference range
   2. A total T4 concentration below the reference range
   3. Elevated antithyroglobulin autoantibodies
   4. Thyroglobulin levels that are undetectable
   5. A free T4 concentration within the reference range
      - (a) Only (1) and (2) and (5) are correct.
      - (b) Only (1) and (5) are correct.
      - (c) Only (1) and (2) are correct.
      - (d) Only (2) and (4) and (5) are correct.
      - (e) All are correct.
3. What are the critical components of thyroid hormone synthesis?
   1. Dietary iodine
   2. The Na/I symporter located on the basolateral membrane
   3. Activation of adenylyl cyclase by TSH
   4. Enzymatic reactions mediated by thyroperoxidase
   5. The presence of thyroid globulin in the colloid
      - (a) Only (1) and (2) and (5) are correct.
      - (b) Only (1) and (5) are correct.

(c) Only (1) and (2) are correct.
(d) Only (2) and (4) and (5) are correct.
(e) All are correct.

4. Once intravascularly, the vast majority of the thyroid hormones are bound to binding hormones with only 0.03% of total serum T4 and 0.3% of total serum T3 found in unbound forms. What are the most common hormone-binding proteins?
   1. Thyroglobulin
   2. Human serum albumin
   3. Thyroxine-binding hormone
   4. Thyroperoxidase
   5. Transthyretin
      (a) Only (1) and (2) and (5) are correct.
      (b) Only (1) and (5) are correct.
      (c) Only (1) and (2) are correct.
      (d) Only (2) and (3) and (5) are correct.
      (e) All are correct.
5. Several disease states and medications can alter the activity of deiodinase (DIO) enzymes. Which of the following statements are true?
   1. Deiodinase (DIO) enzymes can enhance the signaling and activation of T4 and T3.
   2. Deiodinase (DIO) enzymes can diminish the signaling and activation of T4 and T3.
   3. The signaling and activation of T4 and T3 is regulated by cell-specific iodothyronine (DIO) enzymes.
   4. T4 also exerts its action through ion flux regulation.
   5. T3 binds to thyroid hormone nuclear receptors, modulating gene expression and altering cellular function.
      (a) Only (1) and (2) and (5) are correct.
      (b) Only (1) and (5) are correct.
      (c) Only (1) and (2) are correct.
      (d) Only (2) and (3) and (5) are correct.
      (e) All are correct.
6. The hypothalamic-pituitary-thyroid axis is responsible for thyroid hormone regulation. Which of the following statements are correct?
   1. The major regulator of thyroid hormone production and secretion is synthesized and secreted by the thyrotroph cells of the anterior pituitary.
   2. Exposure to the thyrotrophs by circulating T4 and T3 stimulates the secretion of TSH and TRH.
   3. TSH secretion is pulsatile in nature.
   4. TSH secretion is affected by glucocorticoids, retinoids, somatostatin, and dopamine.
   5. TRH is not affected by glucocorticoids, retinoids, somatostatin, and dopamine.
      (a) Only (1) and (3) and (4) are correct.
      (b) Only (1) and (5) are correct.

(c) Only (1) and (2) are correct.
(d) Only (2) and (3) and (5) are correct.
(e) All are correct.

7. A TSH and free T4 panel is a preferred strategy for diagnosing thyroid dysfunction in ambulatory patients with which of the following conditions?
   1. Patients where central hypothyroidism is suspected
   2. Hashimoto's thyroiditis
   3. TSH-secreting pituitary tumor
   4. As a screening tool for thyroid dysfunction
   5. Patients suspected of having a subclinical hypothyroidism

   (a) Only (1) and (3) and (5) are correct.
   (b) Only (1) and (5) are correct.
   (c) Only (1) and (2) are correct.
   (d) Only (2) and (3) and (5) are correct.
   (e) All are correct.

8. Thyroglobulin assessment is particularly useful in the following scenarios.
   1. Presence of thyroglobulin antibodies
   2. Hashimoto's thyroiditis
   3. Surveillance following treatment for well-differentiated thyroid cancer
   4. Presence of interfering heterophile antibodies
   5. A circumstance of suspected excessive exogenous ingestion

   (a) Only (1) and (3) and (5) are correct.
   (b) Only (3) and (5) are correct.
   (c) Only (2) and (3) are correct.
   (d) Only (1) and (3) and (4) are correct.
   (e) All are correct.

9. The signs and symptoms of hypothyroidism include all of the following?
   1. Weight gain
   2. Impaired concentration
   3. Infertility
   4. Muscle cramps
   5. Cold intolerance

   (a) Only (1) and (3) and (5) are correct.
   (b) Only (3) and (5) are correct.
   (c) Only (2) and (3) are correct.
   (d) Only (1) and (3) and (4) are correct.
   (e) All are correct.

10. Ultrasonography (US) of the thyroid and neck has the following advantages?
    1. Provides great detail of the gland
    2. Allows real-time assessment of tissue mobility
    3. Assessment of cervical lymph node status
    4. Good screening tool for asymptomatic patients.
    5. Works well for the assessment of substernal extension of the thyroid

(a) Only (1) and (2) and (3) are correct.
(b) Only (3) and (5) are correct.
(c) Only (2) and (3) are correct.
(d) Only (1) and (2) and (4) are correct.
(e) All are correct.

11. There are distinctive ultrasonographic characteristics of thyroid malignancy that can be identified on US. Which of the following are these?
    1. Nodular echogenicity
    2. Irregular or blurred margins
    3. Microcalcifications
    4. Taller than wider shape
    5. Intranodular blood flow
       (a) Only (1) and (2) and (3) are correct.
       (b) Only (3) and (5) are correct.
       (c) Only (2) and (3) are correct.
       (d) Only (1) and (2) and (4) are correct.
       (e) All are correct.

1.1 Thyroid Physiology

1.1.1 Thyroid Cellular Physiology

The reason iodine is an essential human nutrient is due to its intrinsic role in the synthesis of two thyroid hormones, namely, triiodothyronine (T3) and tetraiodothyronine (T4 or thyroxine). The crucial first step for thyroid hormone biosynthesis is the active transport of iodine (I-) into the thyroid follicular cells. This is mediated by the Na/I symporter (NIS), an integral plasma membrane glycoprotein located on the basolateral membrane of the thyroid follicular cell [1]. The functional units of the thyroid are follicular structures that are formed by the thyroid epithelial cells orienting in a basal and apical direction. The apical membrane is adjacent to the follicular lumen, which is filled with colloid, and the basolateral membrane is in contact with capillaries and the circulatory system (◘ Fig. 1.1).

The proximity of the basolateral membrane to the circulatory system allows the thyroid-stimulating hormone (TSH) receptor to be activated by TSH, initiating the cascade of thyroid hormone synthesis and secretion. Upon binding of TSH to its receptor, there is activation of adenylyl cyclase with a subsequent increase in cyclic adenosine monophosphate (cAMP) formation, leading to phosphorylation of protein kinase A and to activation of targets in the cytosol and the nucleus of the thyroid cell [2]. Through this cAMP pathway, TSH stimulates the accumulation of iodide in the thyroid [3]. Consequently, the ability of the thyroid to accumulate iodide intracellularly has provided the basis for diagnostic scintigraphic imaging of the thyroid and served as an effective means for therapeutic doses of radioiodide to target and destroy hyperfunctioning

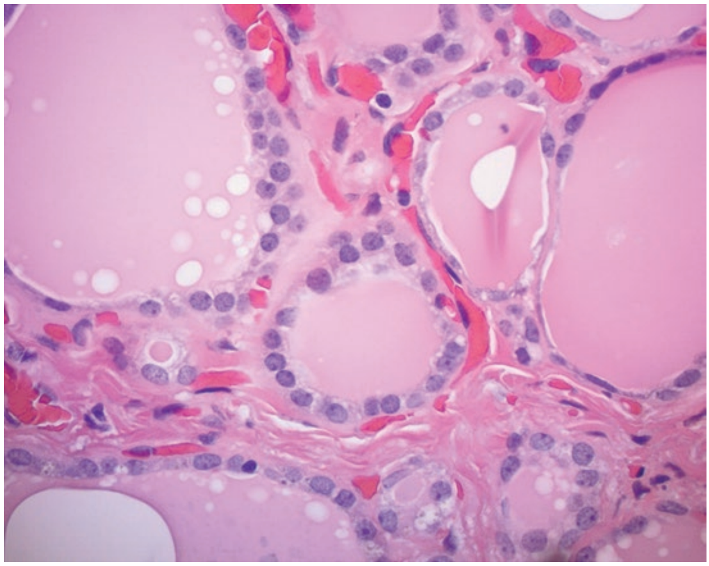


Fig. 1.1 Thyroid Follicles: The functional units of the thyroid are follicular structures that are formed by the thyroid epithelial cells orienting in a basal and apical direction. The apical membrane is adjacent to the follicular lumen, which is filled with colloid, and the basolateral membrane is in contact with capillaries and the circulatory system

thyroid tissue as well as differentiated malignant thyroid cells. The intracellularly accumulated iodide ion is then passively translocated across the apical membrane into the colloid via pendrin proteins and Cl- channels [4]. The effluxed iodide ion then becomes covalently attached to thyroglobulin, at the interface of the apical membrane and the follicular lumen, through an enzymatic reaction mediated by thyroperoxidase (TPO) [5]. Further iodinization (organification) of tyrosine molecules on the thyroglobulin glycoprotein then occurs via TPO facilitating the further incorporation of iodide onto the tyrosine residues. This process forms monoiodotyrosines (MITs) and diiodotyrosines (DITs), which are then coupled to create the bioactive thyroid hormones T4 and T3 again catalyzed via TPO [2]. It should be noted that this process of oxidation of iodide, organification, and coupling is dependent on the presence of hydrogen peroxide present intralumenally and truly occurs simultaneously. The formed thyroid hormones attached to thyroglobulin are then stored in the follicular lumen in the form of colloid. The majority of thyroid hormone stored in the colloid comes in the form of T4 versus T3 [5]. In response to demand for thyroid hormone, which requires further processing intracellularly, stimulation by TSH of its receptor commences the uptake of colloid into the follicular cell by micropinocytosis and subsequent vesicular internalization. These vesicles then fuse with lysosomes intracellularly. Through digestion of this thyroglobulin by lysosomal extracts and a resulting proteolytic breakdown of the thyroglobulin, T4 and T3 are released into

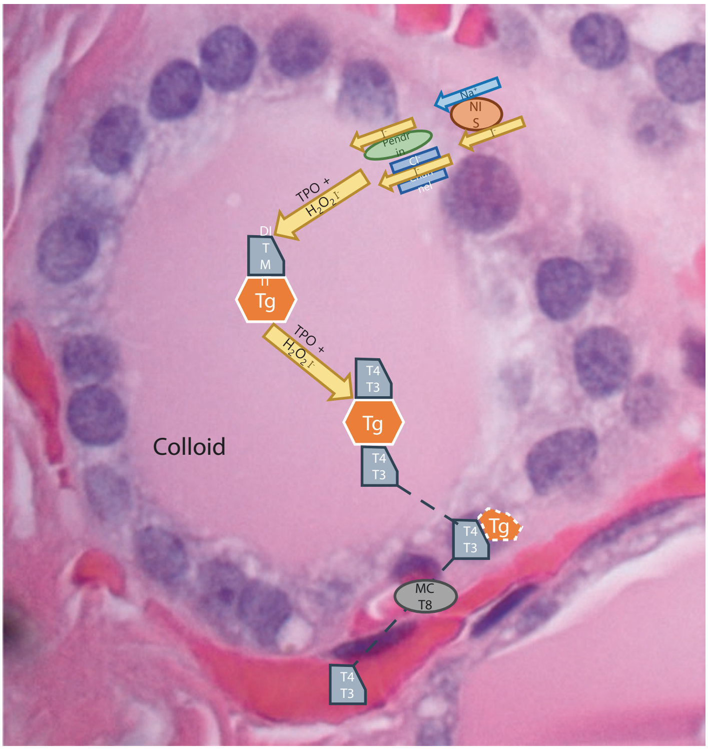


Fig. 1.2 Schematic of Thyroid Hormone Synthesis. Active transport of iodine (I-) into the thyroid follicular cells is mediated by the Na/I symporter (NIS). Intracellular accumulated iodide ion is then passively translocated across the apical membrane into the colloid via pendrin proteins and Cl-channels. The effluxed iodide ion becomes covalently attached to thyroglobulin mediated by thyroperoxidase (TPO). Further iodinization of tyrosine molecules on the thyroglobulin glycoprotein then occurs via TPO forming monoiodotyrosines (MIT) and diiodotyrosines (DIT) which are then coupled to create the bioactive thyroid hormones T4 and T3 again catalyzed via TPO. Colloid is taken up into the follicular cell by micropinocytosis Through digestion of this thyroglobulin by lysosomal extracts and a resulting proteolytic breakdown of the thyroglobulin, T4 and T3 are released into the cytoplasm. Finally T4 and T3 are transported into the circulation by a hormone transporter (monocarboxylate transporter 8 (MCT8))

the cytoplasm [6]. Finally, through a process likely involving the thyroid hormone transporter (monocarboxylate transporter 8 (MCT8)) expressed on the basolateral membrane of the thyroid cell, T4 and T3 are transported into the circulation (Fig. 1.2) [7].

Once intravascularly the vast majority of the thyroid hormones are bound to binding hormones with only 0.03% of total serum T4 and 0.3% of total serum T3 found in unbound forms [8]. The three major binding carriers of thyroid hormone are thyroxine-binding hormone (TBG), transthyretin (TTR), and albumin (HSA), while some minor carriers have also been identified [9]. Of the binding proteins, TBG binds approximately 75% of both T4 and T3 in circulation, while TTR binds approximately 20% of the circulating T4 and <5%

of T3; conversely, HSA binds 5% of the T4 and 20% of the T3 [8]. The physiological significance of this is that bound thyroid hormone is biologically inactive, while "free" T4 and T3 are biologically active and able to enter almost all target cells through transporters in the plasma membrane such as MCT8 [10]. An additional attribute of the extensive binding of thyroid hormone is a resulting long half-life and circulatory concentration [11]. Thyroid hormone receptors on target cells have a higher affinity to T3 than T4, binding for a greater duration and therefore regarded as the primary active thyroid hormone [5]. While T4 is exclusively synthesized by the thyroid gland, only 20% of T3 is produced in the thyroid cell, with the remaining majority being produced at the peripheral tissue level by the deiodination of circulating T4 [10]. Thyroid hormones exert a biological effect at the cellular level via the binding of free T3 to thyroid hormone nuclear receptors, modulating gene expression and altering cellular function. The signaling and activation of T4 and T3 is regulated by cell-specific iodothyronine deiodinase (DIO) enzymes, which can enhance or diminish the thyroid hormone effect once they are intracellular [10]. The clinical significance of this is that several disease states and medications can alter the activity of DIO enzymes [5]. Among the intracellular actions of thyroid hormone at the genomic level, T4 also exerts its action through ion flux regulation, resulting in actions and mechanisms with important effects of the hormone on brain function [12].

1.2 Hypothalamic-Pituitary-Thyroid Axis

A full appreciation of thyroid function and its testing is dependent on a thorough understanding of its axis of regulation. TSH, the major regulator of thyroid hormone production and secretion, is synthesized and secreted by the thyrotroph cells of the anterior pituitary. The main stimulator of TSH production by the anterior pituitary is thyrotropin-releasing hormone (TRH) via the hypothalamic-pituitary portal system [2]. Conversely, exposure to the thyrotrophs by circulating T4 and T3 inhibits the secretion of TSH and TRH via a negative feedback loop, decreasing gene expression of these hormones and therefore its activity. As with other pituitary hormones, TSH secretion is pulsatile in nature, with higher levels seen at night than during the day; however, despite this diurnal variation, serum TSH concentrations generally remain in the reference range when drawn during the day but may be elevated if drawn at night [13]. Among TRH and thyroid hormone itself, TSH secretion is also affected by glucocorticoids, retinoids, somatostatin, and dopamine [2]. Consequently, several disease states and medications can affect TSH levels such as pituitary or hypothalamic dysfunction, recent hyperthyroidism, critical illness, starvation, use of certain medications, interference with serum thyroid autoantibodies, and thyroid hormone resistance syndromes [14]. Given this, thyroid physiology can be affected in nonthyroidal illness (euthyroid sick syndrome) and it is important that the diagnosis of primary thyroid dysfunction not be established during severe illness based solely on an abnormal serum TSH. In these conditions, serum TSH concentrations may be low, normal, or high, due to the TSH-lowering effects of medications or from an acquired central hypothyroidism and therefore, when possible, assessment of thyroid function should be done after recovery from an acute illness [5].

1.3 Thyroid Function Testing

1.3.1 Serum TSH

The main diagnostic strategy for detecting euthyroidism, hypothyroidism, and hyperthyroidism is the measurement of serum TSH. TSH measurement is a more sensitive test than free T4 for identifying these conditions. A TSH-first strategy for diagnosing thyroid dysfunction in ambulatory patients suggests that a TSH within the reference range is evidence of normal thyroid function and requires no additional testing [15]. A TSH and free T4 panel approach more accurately assesses for central hypothyroidism, a TSH-secreting pituitary and allows for evaluations of interferences or detection of unusual conditions characterized by discordance in the ratio of TSH/FT4 [15]. If a TSH first strategy is adopted and an abnormal TSH is encountered, subsequent assessment of additional thyroid hormones levels should be assessed.

1.3.2 Total Thyroid Hormone

Recent increased accuracy of measurements of serum free T4 and free T3 has contributed to the decreased popularity of total thyroid hormone assessments. Total T4 and Total T3 concentrations are an assessment of both bound and free levels of T4 and T3. The clinical utility of this has been particularly impacted by the recognition that many conditions, commonly encountered in clinical practice during the assessment of thyroid function, affect the concentrations of thyroid-hormone-binding proteins and/or compete for binding and therefore do not accurately reflect bioactive free levels of the hormone [5]. Additionally, medications and thyroid hormone autoantibodies can also render total thyroid hormone measurements diagnostically unreliable [2]. The one general exception to this rule is during the assessment of the thyrotoxic patient when the clinician is attempting to differentiate stimulation-induced thyrotoxicosis (Graves' disease) from destruction-induced thyrotoxicosis (painless thyroiditis and subacute thyroiditis). The total T_3/T_4 ratio appears to be relatively useful in the differentiation of these thyrotoxic conditions where Graves' patients usually have a ratio >20, while a ratio of <20 was indicative of a destructive process [16, 17]. This assessment can be further augmented when TSH is considered as serum levels of TSH are generally suppressed in most untreated Graves' patients, whereas they usually were not completely suppressed in patients with painless thyroiditis or subacute thyroiditis [18].

1.3.3 Serum Free T4 and Free T3

The available free hormone fraction in the circulation is believed to be 0.03% for free T4 (FT4) and 0.3% for free T3 (FT3) and is responsible for the biological activity at the cellular level. The concentrations of free thyroid hormones are generally estimated using a variety of indirect (analog, immunometric, and two-step labeled hormone assays) or direct methods (equilibrium dialysis, ultrafiltration), with the concentrations of FT4 having the most clinical relevance [19]. FT3 is usually only measured in a small subset of patient with suspected T3 toxicosis and is not recommended for routine measurement [2].

As previously mentioned, although a TSH-first testing algorithm is sufficient for general screening, both FT4 and TSH assays are needed for diagnosing subclinical thyroid dysfunction, central hypothyroidism, and in the assessment of elderly and hospitalized patients, as well as for accurate assessment of treatment effects [20]. Guidelines from multiple thyroid and endocrine societies have also endorsed a TSH-first strategy in most clinical scenarios with FT4 testing when clinically indicated or TSH is found to be abnormal [15, 21–23]. Work by Henze et al. goes even further suggesting that a TSH-first strategy can be further perfected by widening the TSH reference range from 0.4–4.0 mIU/L to 0.2–6.0 mIU/L with minimal impact on case detection. They found that only 4.2% of TSH values between 0.2 mIU/L and 0.4 mIU/L would not have led to detection of a high FT4 and equally, only 2.5% of TSH values between 4.0 mIU/L and 6.0 mIU/L were associated with low FT4 level [24]. It is likely that this small additional group of patients outside the wider range with abnormal FT4 is clinically unimportant in most cases.

1.3.4 Serum Thyroid Autoantibodies

Autoimmune thyroid disease often accounts for a large proportion of patients with hyperthyroidism and hypothyroidism. Testing for autoantibodies, in particular anti-TSH receptor autoantibodies (TSHRabs), antithyroid peroxidase autoantibodies (TPOabs), and antithyroglobulin autoantibodies (Tgabs), is central to the diagnosis of autoimmune thyroid disease [2]. The evaluation of TSHRab is generally recommended when Graves' disease is suspected and can be done via a measurement of TSH receptor binding or in a functional bioassay of thyroid-stimulating immunoglobulin [5]. The suspected mechanism of action of these autoantibodies is believed to be via direct stimulation of the TSH receptor with increased metabolic activity of the thyroid gland. TSHRab are also believed to be responsible for metabolic changes in TSH receptor positive fibroblast cells in target orbital tissues leading to Graves' orbitopathy [2]. However, in some cases, TSHRabs act as antagonists competing with TSH for receptor binding and prevent the stimulating activity of TSH, resulting in hypothyroidism [25, 26].

The presence of TPOab is commonly associated with patients with hypothyroidism, but can be present in normal individuals who do not display any obvious symptoms of clinical thyroid disease. TPOabs are present in approximately 10% of normal individuals, while it was detected in almost 100% of samples of patients with autoimmune hypothyroidism [27, 28].

Antibodies to thyroglobulin can also be indicative of autoimmune hypothyroidism but are most clinically relevant in testing on patients with differentiated thyroid carcinomas. The presence of Tgab does not correlate with abnormal TSH levels and is not indicated in that assessment of thyroid autoimmunity screening [29]. However, its assessment with the assessment of TPOab may allow prediction of future hypothyroidism in some patients [30]. The most clinically relevant assessment of Tgab is made in conjunction with thyroglobulin, the primary tumor marker used to monitor patients with differentiated thyroid cancer. The presence of Tgab can compromise the accuracy and reliability of thyroglobulin as a tumor marker; however, Tgab trends can be used as a surrogate differentiated thyroid cancer tumor marker in preference to Tg [31].

In general, thyroid autoantibodies should not be measured in the setting of normal thyroid function except in special circumstances.

1.3.5 Serum Thyroglobulin

Thyroglobulin (Tg) represents the primary storage vehicle for precursor for thyroid hormone and serves as the main reservoir of iodine for thyroid hormone production. Tg is regularly released into the circulation as a consequence of thyroid hormone secretion and is present in all subjects with an intact thyroid gland. In view of this, its assessment in patients with intact thyroid glands has limited clinical utility. The caveat to this notion is in the circumstance of suspected excessive exogenous ingestion versus endogenous thyroid hormone release;

in the former scenario, TSH and Tg will be suppressed, while in the latter, only TSH levels will be decreased, while Tg will be increased [32].

The main clinical relevance of Tg testing is in differentiated thyroid carcinoma (DTC) as a tumor marker. Typically, papillary thyroid cancer cells and follicular thyroid cancer cells retain many characteristics of thyroid follicular cells including the expression of thyroid-specific proteins thyroglobulin (Tg). By leveraging this fact, the clinician is able to detect persistent or recurrent disease after treatment with surgery and/or radioactive iodine ablation [33]. Detection of Tg can be further augmented via conventional thyroid hormone withdrawal and subsequent endogenous TSH stimulation of any remaining thyroid cells or via the use of recombinant human thyrotropin stimulation, avoiding thyroid hormone withdrawal [34]. As previously mentioned, Tg serum measurements need to be assessed in conjunction with serum Tg Ab assays as unmeasurable Tg in the backdrop of positive Tg Ab does not eliminate the possibility of recurrent disease [29]. Additionally of note, undetectable Tg levels in the setting of rising Tg Ab are suggestive of recurrent/persistent disease in the setting of DTC [35].

Finally, when Tg levels appear discordant with clinical status or fail to change with TSH stimulation or suppression, the presence of interfering heterophile antibodies (antibodies against the animal-derived antibodies used in the immunometric assay) should be considered [5]. The most common heterophile antibody is human antimouse antibodies and can cause interference in accurate Tg measurements [2]. There is no entirely reliable method to avoid or detect heterophile antibody interference, but clinician awareness is critical and repeating the test using a heterophile-blocking tube (HBT) or measure Tg with an RIA assay should be considered [36, 37].

1.3.6 Hypothyroidism

There is extensive variation of symptoms and signs of hypothyroidism (◘ Table 1.1), and these can often be insidious and nonspecific and if left untreated can lead to serious morbidity and even mortality [38]. The biochemical presence of hypothyroidism is however often easily identified through laboratory testing. Hypothyroidism can be biochemically divided into clinical hypothyroidism and subclinical hypothyroidism. Clinical hypothyroidism can be defined as a TSH level above the reference range associated with a free T4 concentration below the reference range, while subclinical hypothyroidism is considered with a TSH above the reference range but a normal free T4 level.

Primary hypothyroidism, due to thyroid hormone deficiency, represents 99% of the cases while the remaining 1% of cases represent secondary (due to TSH deficiency), tertiary

Table 1.1 Signs and symptoms of hypothyroidism

System	Symptoms	Signs
General	Weight gain, fatigue, cold intolerance	Hyponatremia, hypothermia, increased BMI
Dermatological	Dry coarse skin and hair, hair loss	Pretibial myxedema
Otolaryngological	Hoarseness, tongue enlargement	Periorbital edema, goiter
Musculoskeletal	Myalgia, muscle cramps, muscle weakness	Carpal tunnel syndrome, elevation of serum creatine phosphokinase, Hoffman's syndrome
Neurological	Depression, impaired concentration, memory loss, changes in vision, hearing, and taste	Impaired cognitive function, neuropathy, cochlear dysfunction, decreased olfactory and gustatory sensitivity, delayed relaxation of tendon reflexes
Cardiovascular	Fatigue on exertion, shortness of breath	Dyslipidemia, bradycardia, hypertension, congestive heart failure, diastolic dysfunction, pericardial effusion, hyperhomocysteinemia, electrocardiogram changes, hyperlipidemia
Endocrinological	Infertility and subfertility, menstrual disturbance, galactorrhea, miscarriage	Goiter, glucose metabolism dysregulation, infertility, increased prolactin, pituitary hyperplasia
Hematological	Bleeding, fatigue	Mild anemia, acquired von Willebrand disease, decreased protein C and S, increased red cell distribution width, increased mean platelet volume
Gastrointestinal	Constipation	Reduced esophageal motility, nonalcoholic fatty liver disease

(due to thyrotropin-releasing hormone deficiency), and peripheral (consumptive hypothyroidism) [39, 40]. Environmental iodine deficiency continues to be the most common cause of all thyroid disorders, including hypothyroidism worldwide, but in areas of iodine sufficiency, the most common cause of primary hypothyroidism is chronic autoimmune thyroiditis (Hashimoto's disease) [41]. Hypothyroidism is also caused by various other etiologies listed on ◘ Table 1.2. When considering the diagnosis of hypothyroidism, it is important to differentiate the etiologies responsible for transient hypothyroidism from the clinical conditions presenting with long-term thyroid function failure. Examples of the transient etiologies of hypothyroidism include subacute, silent thyroiditis, postpartum thyroiditis among others, all with varying degrees of duration of biochemical thyroidal derangement. These conditions often follow a triphasic pattern with an initial thyrotoxic phase followed by a hypothyroid phase and an eventual return to a euthyroidism. Their management is generally directed toward controlling patient symptoms associated with the initial thyrotoxic phase with beta-blockers and the hypothyroid phase may or may not require thyroid hormone replacement [42].

1.3.7 Hyperthyroidism

The symptoms and signs of hyperthyroidism are also quite varied as with hypothyroidism but often more characteristic of the condition (◘ Table 1.3). The most common symptoms are palpitations, weakness, heat intolerance, and disturbed sleep with the most frequent physical findings being tachycardia, tremor of the extremities, and weight loss [43]. In clinical practice, the symptoms and signs of hyperthyroidism are often not necessarily correlated with the biochemical severity of the thyroid dysfunction and can be variable and less prevalent in the elderly [44].

As with hypothyroidism, hyperthyroidism can be biochemically defined as clinical (overt) or subclinical: With the former being characterized by low serum TSH with raised serum thyroid hormones while the later showing a low serum TSH associated with normal serum thyroid hormone levels [43]. The most common causes of hyperthyroidism are Graves' disease, followed by toxic multinodular goiter, while rarer causes include an autonomously functioning thyroid adenoma or thyroiditis [45]. Thyrotoxicosis itself can also occur without hyperthyroidism and is caused by extrathyroidal sources of thyroid hormone or by a release of preformed thyroid hormones into the circulation despite a low thyroid radioactive iodine uptake [43]. The underlying etiologies of hyperthyroidism and thyrotoxicosis are complex and varied (◘ Table 1.4). Hyperthyroidism and thyrotoxicosis have an increased risk of all-cause mortality with heart failure being the main cause of cardiovascular events [46]. Given this complexity and higher risk of mortality, identification of the underlying etiology is key prior to treatment. Generally, the diagnosis and management of hyperthyroidism and thyrotoxicosis is best initially deferred to an endocrinologist and, when surgical management is necessary, coordinated via a multidisciplinary team approach.

Table 1.2 Etiologies for hypothyroidism

	Etiology	Example
Primary hypothyroidism	Chronic autoimmune thyroiditis	Hashimoto's thyroiditis
	Dietary	Severe iodine deficiency, mild and severe iodine excess
	Medications	Amiodarone, lithium, tyrosine kinase inhibitors, interferon-alfa, thalidomide, monoclonal antibodies (ipilimumab and nivolumab), antiepileptic drugs (valproate), drugs for second-line treatment of multidrug-resistant tuberculosis
	Iatrogenic	Radioiodine ablation, thyroid surgery, radiotherapy or surgery in the neck or head region
	Transient thyroiditis	Subacute granulomatous (De Quervain's syndrome), postpartum, silent thyroiditis, destructive thyroiditis
	Thyroid gland infiltration	Infectious (mycoplasma), malignant (thyroid malignancy, lymphoma, metastasis), autoimmune (sarcoidosis), inflammatory (Riedel's thyroiditis)
	Genetic	Autoimmunity-related genes general and thyroid-specific genes
Central hypothyroidism	Pituitary tumors	Secreting or nonsecreting
	Pituitary dysfunction	Sheehan's syndrome
	Hypothalamic dysfunction	Posttraumatic
	Resistance to thyroid-stimulating hormone (TSH) or thyrotropin-releasing hormone	
	Medications	Dopamine, somatostatins, glucocorticosteroids, and retinoid X receptor selective ligands
Peripheral hypothyroidism	Consumptive hypothyroidism	
	Tissue-specific hypothyroidism due to decreased sensitivity to thyroid hormone	Mutations in MCT8

Adapted from Chaker et al. [38]

1

Table 1.3 Signs and Symptoms of hyperthyroidism

System	Symptoms	Signs
General	Weight loss, Increased appetite, heat intolerance, polydipsia	Weight loss
Dermatological	Diaphoresis	Warm skin, Palmer erythema
Ophthalmological	Diplopia; sense of irritation in the eyes; eyelid swelling; retro-orbital pain or discomfort	Proptosis; eyelid retraction and lag; periorbital edema; conjunctival injection and chemosis; ophthalmoplegia
Musculoskeletal	Tremor; muscle weakness; disturbed sleep; poor concentration	Tremor of the extremities; pelvic and girdle muscle weakness, osteoporosis
Neurological	Anxiety, nervousness, anxiety; fatigue, disturbed sleep; poor concentration	Hyperactivity, hyperreflexia, hyperkinesis
Cardiovascular	Palpitations, shortness of breath	Tachycardia; systolic hypertension; irregular heartbeat (atrial fibrillation), tachypnoea
Endocrinological	Irregular menstrual periods/amenorrhea	Irregular menstrual periods/amenorrhea Light menstrual flow Infertility Gynecomastia (males)
Gastrointestinal	Hyperdefecation, nausea, vomiting	Abdominal tenderness

Adapted from De Leo et al. [43]

1.4 Thyroid Anatomy

The foundation of performing safe and effective thyroid surgery is a clear and in-depth understanding of thyroid anatomy, its anatomical relationships, and congenital variations.

The thyroid gland consists of two lobes connected in the midline by a central isthmus. Under normal circumstances, each lobe is approximately 4 cm in length, 2 cm in width, and 2–3 cm in depth, with the majority of glands weighing 15–25 g in adults; however, these dimensions can be drastically different in thyroid disease processes [47].

Table 1.4 Etiologies of hyperthyroidism and thyrotoxicosis

	Etiology	Example
Primary hyperthyroidism	TSH receptor antibodies	Graves' disease
	Dietary	Excess exogenous thyroid hormone (iatrogenic or factitious), iodine-induced hyperthyroidism
	Medications	Amiodarone, lithium, interferon-alfa
	Autonomous thyroid function	Solitary hyperfunctioning adenoma, toxic multinodular goiter
	Transient thyroiditis	Subacute granulomatous (De Quervain's syndrome), postpartum, silent thyroiditis, destructive thyroiditis
	Thyroid gland infiltration	Bacterial or fungal infection with acute suppurative thyroiditis
	Genetic	Familial nonautoimmune hyperthyroidism
	Iatrogenic	Radiation-induced thyroiditis
Central hyperthyroidism	Pituitary tumors	TSH-secreting adenoma
	Pituitary dysfunction	Pituitary resistance to thyroid hormone
	Hypothalamic dysfunction	Posttraumatic
Peripheral hyperthyroidism	Excess hCG secretion	Trophoblastic tumors, hyperemesis gravidarum
	Ectopic thyroid hormone production	Struma ovarii, functional thyroid cancer metastasis

The anatomical boundaries of the normal thyroid gland lobes are the larynx and trachea medially, sternocleidomastoid muscle laterally and carotid sheath posterolaterally, the sternothyroid and sternohyoid muscles anteriorly, and the condensation of the deep cervical fascia forming the suspensory ligament of Berry affixing to the cornu of the cricoid cartilage extending inferiomedially onto the tracheal wall [47]. The isthmus of the thyroid glands is generally related anteriorly to the level of the second, third, and fourth tracheal rings. The superior pole of the thyroid lies lateral to the inferior constrictor muscle, and posterior to the sternothyroid muscle with the inferior pole extending to the level of the fifth or sixth tracheal ring [48]. The thyroid is enveloped by the layers of the deep cervical fascia, and the true thyroid capsule is tightly adherent to the gland and continues into the parenchyma to form fibrous septae often separating the gland into lobules. When a pyramidal lobe is present, it will be directed superiorly and may arise from the isthmus, or either lobe, occurring in 50% of cases.

1.4.1 Blood Supply and Lymphatics

The blood supply of the superior pole of the thyroid is derived from the superior thyroid artery, the first branch off the external carotid artery and less commonly the common carotid, and lies anterior to the external branch of the superior laryngeal nerve as it courses to supply the cricothyroid muscle [48]. Inferiorly, the thyroid is supplied by the inferior thyroid artery by way of the thyrocervical trunk from the subclavian artery. Furthermore, a thyroid ima artery may be additionally present or replace the inferior thyroid artery supplying the thyroid in the midline. The venous drainage is similar to the arterial supply with two or three pairs of veins traveling in association with their arterial pedicle along with a separate middle thyroid vein that drains directly into the internal jugular vein [49]. The lymphatic drainage of the thyroid gland is predominantly via the accompanying venous drainage with the superior and middle thyroid lymphatics draining into the upper and middle deep cervical chain and the inferior thyroid lymphatics draining into lower deep cervical chain nodes, the pretracheal, paratracheal, and supraclavicular nodes.

1.5 Surgical Thyroid Anatomy

1.5.1 External Branch of the Superior Laryngeal Nerve

The superior laryngeal nerve consists of two branches: the internal branch, which supplies sensory fibers to the pharynx, and the external laryngeal nerve (EBSLN), which innervates the cricothyroid muscle. The function of the cricothyroid muscle is to lengthen, stiffen, and thin the true vocal cord and therefore tense the vocal cords when they are approximated, providing timbre to the voice. There is also some evidence that the EBSLN may also be involved in reflex glottic closure, which prevents aspiration during deglutition [50]. The EBSLN is most commonly deep to the superior thyroid artery, but it can cross anterior, or between branches of the artery in 14–18% of cases

[51]. The external branch of the superior laryngeal nerve has highly variable anatomical patterns epitomized by the multiple classification schemes for its anatomy and consequently a thorough preoperative knowledge of its anatomy can be crucial in minimizing iatrogenic injury [52–55].

1.5.2 Recurrent Laryngeal Nerve

The recurrent laryngeal nerve (RLN) via its motor and sensory fibers supplies all of the intrinsic muscles of the larynx other than the cricothyroid while receiving sensory and secretomotor fibers from the glottis, subglottis, and trachea.

The left RLN arises off the vagus nerve at the level of the aortic arch, while the right RLN arises anterior to the right subclavian artery prior to their ascent into the neck. The right RLN generally courses more obliquely in the sagittal plane as it ascends the neck, while the left RLN ascends more vertically just anterior to the tracheal esophageal groove [56]. The terminal part of the RLN enters the larynx, underneath the thyroid gland, deep to the inferior border of the inferior pharyngeal constrictor, posterior to the cricothyroid joint making this a consistent surgical landmark. There have been multiple variations described as to the relationship of the RLN to inferior thyroid with three basic configurations including anterior to the artery, nerve between branches of the artery, and posterior to the artery [48].

The clinician must also be familiar with the occurrence of a nonrecurrent laryngeal nerve (NRLN). The NRLN is an anatomic variant and has been reported in 0.52% of cases on the right and 0.04% on the left by Henry et al. [57]. Almost invariably, this anatomic variant is also associated with the presence of an aberrant right subclavian artery when on the right and a situs inversus or right aortic arch when on the left [58, 59].

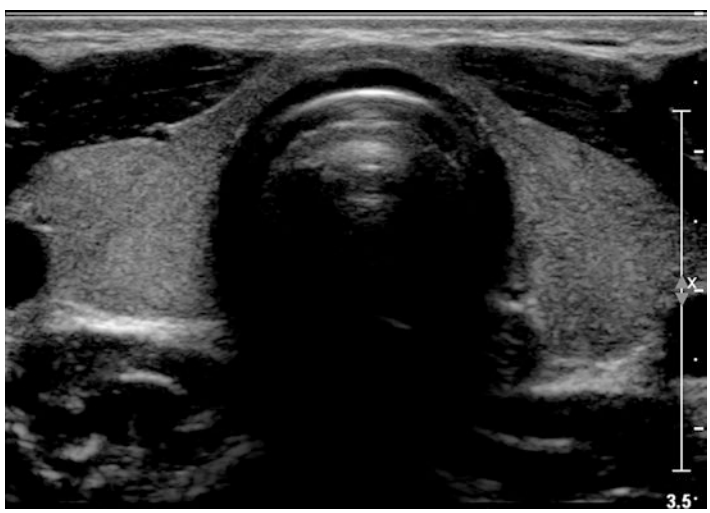
1.5.3 Parathyroid Glands

Typically, the inferior parathyroid glands are often found ventral to the plane of the RLN but deep to the thyroid gland [5]. However, 17% are found on or within the capsule of the thyroid gland, 26% are found within the cervical part of the thymus, and 2.8% found superior to the intersection of the recurrent nerve and the inferior thyroid artery [48] The superior parathyroid glands are typically found dorsal to the plane of the RLN. Due to its shorter embryological descent compared to the inferior parathyroid glands, its location is less variable. The superior parathyroid can often be found at the posterior aspect of the thyroid lobe in a 2-cm diameter area centered 1 cm above the junction of the inferior thyroid artery and the RLN [5].

1.6 Ultrasonography of the Thyroid Gland

Ultrasonography (US) is the modality of choice in the evaluation of the thyroid gland and its surrounding associated structures [33]. Given the gland's location, its distinct sonographic features, and signature echogenicity (◘ Fig. 1.3), ultrasound is a powerful tool in the assessment of the thyroid and its pathology, often providing greater detail of the gland than CT, MRI, or radionuclide studies [60]. The majority of thyroid ultrasounds are performed for thyroid nodules, many of which are discovered incidentally on other imaging studies. The current indications for US of the thyroid include evaluation of a palpable nodule, workup of incidentally found nodules, or assessment of suspected thyroid enlargement. Caution should be exercised in using thyroid US as a screening tool for the detection of nodules given the high prevalence rate (50%) [61]. US of the thyroid achieves multiple goals when imaging a nodule as it is also able to characterize its size, location, presence of benign or suspicious features, and evaluate for cervical lymphadenopathy [62]. It also permits greater accuracy when performing an ultrasound-guided fine-needle aspiration (USgFNA), if so indicated.

There are distinctive characteristics of thyroid malignancy that can be identified on US that not only offer high sensitivity, but when several of these characteristics are present, they increase sensitivity. The specific US features that have been recognized as suggestive of malignancy comprise namely hypoechogenicity, irregular or blurred margins, microcalcifications, taller than wider shape, and abnormal vascular signals (◘ Fig. 1.4) [63]. A hypoechoic nodule has a higher propensity for malignancy compared to an iso−/hyperechoic nodule



◘ **Fig. 1.3** Normal thyroid ultrasound image with signature thyroid echogenicity

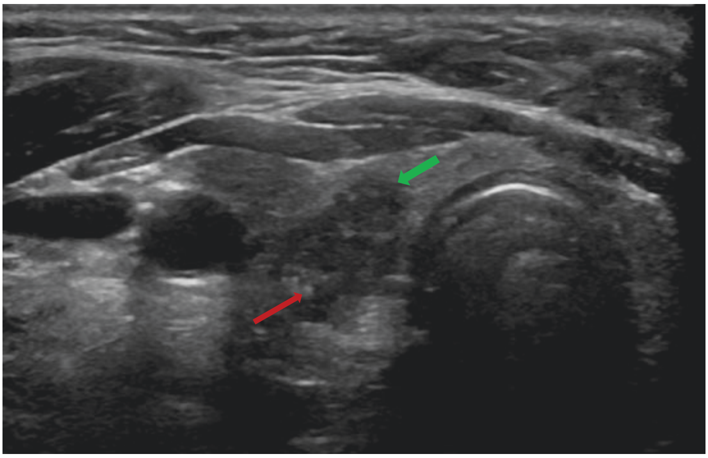


Fig. 1.4 Papillary thyroid cancer within the thyroid illustrating microcalcifications (red arrow), irregular boarders (green arrow), hypoechogenicity

Fig. 1.5 Spongioform thyroid nodule

[63, 64]. A solid composition of a nodule is more suggestive of malignancy when compared to a spongiform one (Fig. 1.5), and an increasingly cystic structure is more likely benign, with a completely cystic nodule being certainly benign [65]. Irregular or blurred margins are suggestive of malignancy via malignant extension of the carcinoma [64]. When concern for malignant extension is seen, an assessment of mobility of the nodule with respect to surrounding structures can be made, fixation suggests invasion of surrounding tissue [60]. Microcalcifications within the nodule have been shown to increase the risk of malignancy and have been corroborated by several studies (Fig. 1.6) [63, 64, 66]. These microcalcifications are thought to represent psammoma bodies, which are a histopathologic

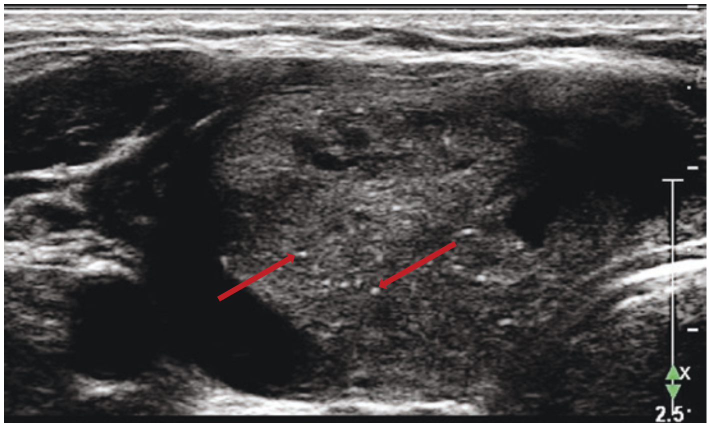


Fig. 1.6 Thyroid ultrasound image illustrating microcalcifications (red arrows)

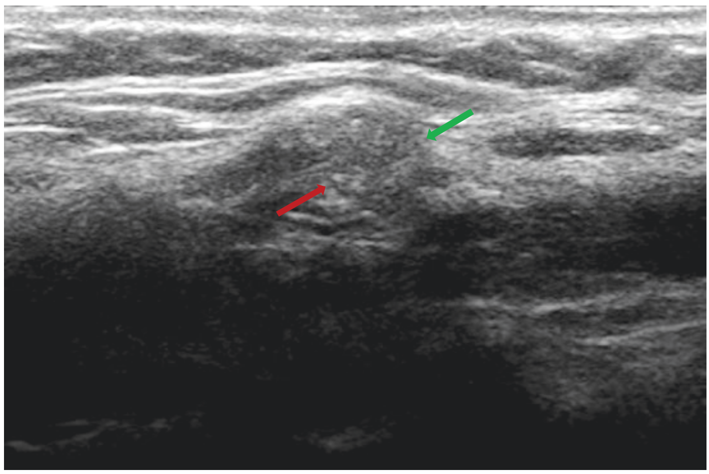


Fig. 1.7 Level V metastatic papillary carcinoma in a cervical lymph node. Illustrative of microcalcifications (red arrow) and ill-defined margins (green arrow)

feature considered pathognomonic of papillary thyroid cancer. The predictive value of the "taller than wider" nodular shape has been questioned by some authors with studies suggesting spherical nodules having a higher incidence of malignancy [60]. Finally, an intranodular blood flow pattern that becomes more dominant has been correlated with an increased risk of malignancy [67].

Ultrasound-guided fine-needle aspiration (USgFNA) is an integral part of ultrasonography of the thyroid in the assessment of suspicious lesions within the thyroid and in the neck (Fig. 1.7). USgFNA allows a greater sensitivity (83.3%), specificity (98.8%), positive predictive value (97.0%), and negative predictive value (92.5%) when compared to conventional FNA of thyroid nodules [62]. When considering the need for proceeding to FNA, it is useful to use one of the recognized guidelines for thyroid nodule classification. There are three main published and validated US classification criteria for stratifying risk of malignancy and determining the need for FNA. The American Thyroid Association (ATA) guidelines propose five levels of risk stratification ranging from benign, to very low, low, intermediate, and high suspicion for malignancy [33]. The American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE), and Associazione Medici Endocrinologi (AME) propose three risk categories: low (class 1), intermediate (class 2), and high (class 3) [61]. The American College of Radiology (ACR) Thyroid Imaging Reporting and Data System (TI-RADS) classification categorizes nodules as benign, minimally suspicious, moderately suspicious, or highly suspicious for malignancy depending on their US features [68]. All guidelines for the management of thyroid nodules couple the characteristics delineated above with nodule size thresholds to decide whether an FNA is warranted. The use of these classification systems improves communication among clinicians and helps in standardizing clinical practice [62]. It is also important not only to be knowledgeable of the various validated ultrasound classification systems but to be to be familiar with the Bethesda System for Reporting Thyroid Cytopathology. This is a well-established standardized, category-based cytological reporting system for thyroid fine-needle aspiration (FNA) specimens. The Bethesda system is broken down into six diagnostic categories: (I) nondiagnostic or unsatisfactory; (II) benign; (III) atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS); (IV) follicular neoplasm or suspicious for a follicular neoplasm; (V) suspicious for malignancy; and (VI) malignant. Each category has an implied risk of malignancy, ranging from 0% to 3% to virtually 100% with a corollary recommended clinical management strategy including observation, repeat biopsy, molecular testing, or surgical removal (◘ Table 1.5) [69].

Thyroid ultrasound can also be used to detect thyroid disease beyond nodularity including Graves' disease, thyroiditis, and subacute or de Quervain's thyroiditis. Graves' disease is characterized by heterogeneous thyroid tissue with diffuse hypoechogenicity and hypervascularity, while Hashimoto's thyroiditis includes ill-defined hypoechoic areas separated by echogenic septa, with increased (early) or decreased (late) vascularity [60]. Subacute or de Quervain's thyroiditis, though more often a clinical diagnosis, has US findings of an ill-defined hypoechoic area, without round or ovoid mass formation on the multiple planes of US, and no vascular flow on color doppler [70].

Finally, US is recommended for surveillance of thyroid nodules. Though malignant transformation of benign thyroid nodules is rare, the 3% or greater false-negative rate of FNA makes US surveillance advocated. The ATA and the AACE/

Table 1.5 The 2017 Bethesda System for Reporting Thyroid Cytopathology with corollary risk of malignancy and usual management strategy

	Bethesda category	Cytological findings	Risk of malignancy (%)	Usual management
I	Nondiagnostic or unsatisfactory	Cystic fluid Virtually acellular specimen Other (obscuring blood, clotting artifact, etc.)	5–10	Repeat FNA with ultrasound guidance
II	Benign	Benign follicular nodule Lymphocytic (Hashimoto) thyroiditis Granulomatous (subacute) thyroiditis	0–3	Clinical and sonographic follow-up
III	Atypia of undetermined significance or follicular lesion of undetermined significance		6–18	Repeat FNA, molecular testing or lobectomy
IV	Follicular neoplasm or suspicious for a follicular neoplasm		10–40	Molecular testing or lobectomy
V	Suspicious for malignancy	Suspicious for papillary carcinoma Suspicious for medullary carcinoma Suspicious for metastatic carcinoma Suspicious for lymphoma	45–60	Near-total thyroidectomy or lobectomy (dependent on the type of suspicious malignancy)
VI	Malignant	Papillary thyroid carcinoma Poorly differentiated carcinoma Medullary thyroid carcinoma Undifferentiated (anaplastic) carcinoma Squamous cell carcinoma Metastatic carcinoma Lymphoma	94–96	Near-total thyroidectomy or lobectomy (dependent on the type of suspicious malignancy)

Adapted from Cibas and Ali [69]

AME both recommend that cytologically benign thyroid nodules be followed every 6–18 months with palpation or with US if not easily palpable [33, 61]. Nodules should undergo repeat FNA if there is evidence of nodule growth, defined as more than 50% change in volume or >20% increase or greater than 2 mm in at least two nodule dimensions in solid nodules or in the solid portion of a mixed cystic solid nodule. If there is evidence of nodule growth either by palpation or sonographically, then an FNA should be repeated [33, 61].

Answers to the Questions

1. (c); 2. (b); 3. (e); 4. (d); 5. (e); 6. (a); 7. (a); 8. (b); 9. (e); 10. (a); 11. (e)

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