Anatomy and Physiology of the Thyroid Gland: Clinical Correlates to Thyroid Cancer

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Detailed knowledge of thyroid gland anatomy and physiology is extremely important for any physician that manages thyroid disorders, including thyroid malignancies. The thyroid gland is a relatively small butterfly-shaped organ located in the lower neck, anteriorly to the trachea. A large number of ectopic sites of thyroid tissue have been described, including thyroglossal duct cysts, lingual thyroid, or struma ovarii. The thyroid gland is in close proximity to several important structures, such as the recurrent laryngeal nerves, the parathyroid glands, as well as the large cervical blood vessels like the carotid artery and the jugular vein.

The function of the thyroid gland is to provide adequate amounts of thyroid hormone, a hormone with clinically important actions practically in every system in the human body. Its main functional unit is the thyroid follicle, a single cell-layered cystic unit that contains colloid. Thyroglobulin is the main component of colloid and it represents the large-molecular-weight protein in which the thyroid hormones, thyroxine (T4) and triiodothyronine, (T3) are stored.

The molecular biology of thyroid function has been studied extensively with identification of important cellular elements such as the thyroid-stimulating hormone receptor and the sodium–iodide symporter. These advances have significantly improved our understanding of thyroid physiology and have allowed us to identify potential therapeutic targets for diseases such as thyroid cancer.

To better understand the biology of thyroid malignancies, it is extremely important to have a thorough understanding of the thyroid's relationship to its surrounding structures, both anatomically and functionally. This would allow a clinician to understand the behavior of thyroid cancers in regard to issues of local invasion, regional spread to cervical lymph nodes, and distant metastasis. This short review focuses on some aspects of thyroid anatomy and physiology that are clinically relevant to the diagnosis and management of thyroid cancer.

Thyroid Anatomy, Histology, and Embryology

The thyroid gland is a butterfly-shaped organ located anteriorly to the trachea at the level of the second and third tracheal rings. Its name originates from the Greek term "thyreos," which means shield (named after the laryngeal thyroid cartilage). It consists of two lobes connected by the isthmus in the midline. Its bilaterality is important because the presence of malignant cells on one or both sides can significantly alter the management of the patient, e.g., requiring more extensive surgery, such as bilateral neck dissections if there is local extension of the tumor. Each lobe is about 3–4 cm long, about 2 cm wide, and only a few millimeters thick. Because of its very close anatomic relationship to the rounded trachea, nodules arising from the posterior aspect of the gland are usually inaccessible to the examining fingers and therefore often missed on a routine clinical examination. The isthmus is 12–15 mm high and connects the two lobes. Occasionally, a pyramidal lobe is located in the midline, superior to the isthmus (Fig. 1.1). It represents a remnant of the thyroglossal duct, as the primitive thyroid gland descends from the base of the tongue to its final location in the neck during embryonic development. Anatomic variations of the thyroid gland occur and are encountered in clinical practice; one of the more common is thyroid hemiagenesis [1], with only one lobe and an isthmus of the gland. Hemiagenetic thyroid lobes are susceptible to the same abnormalities as are normal thyroid glands, including nodules and thyroid cancer.

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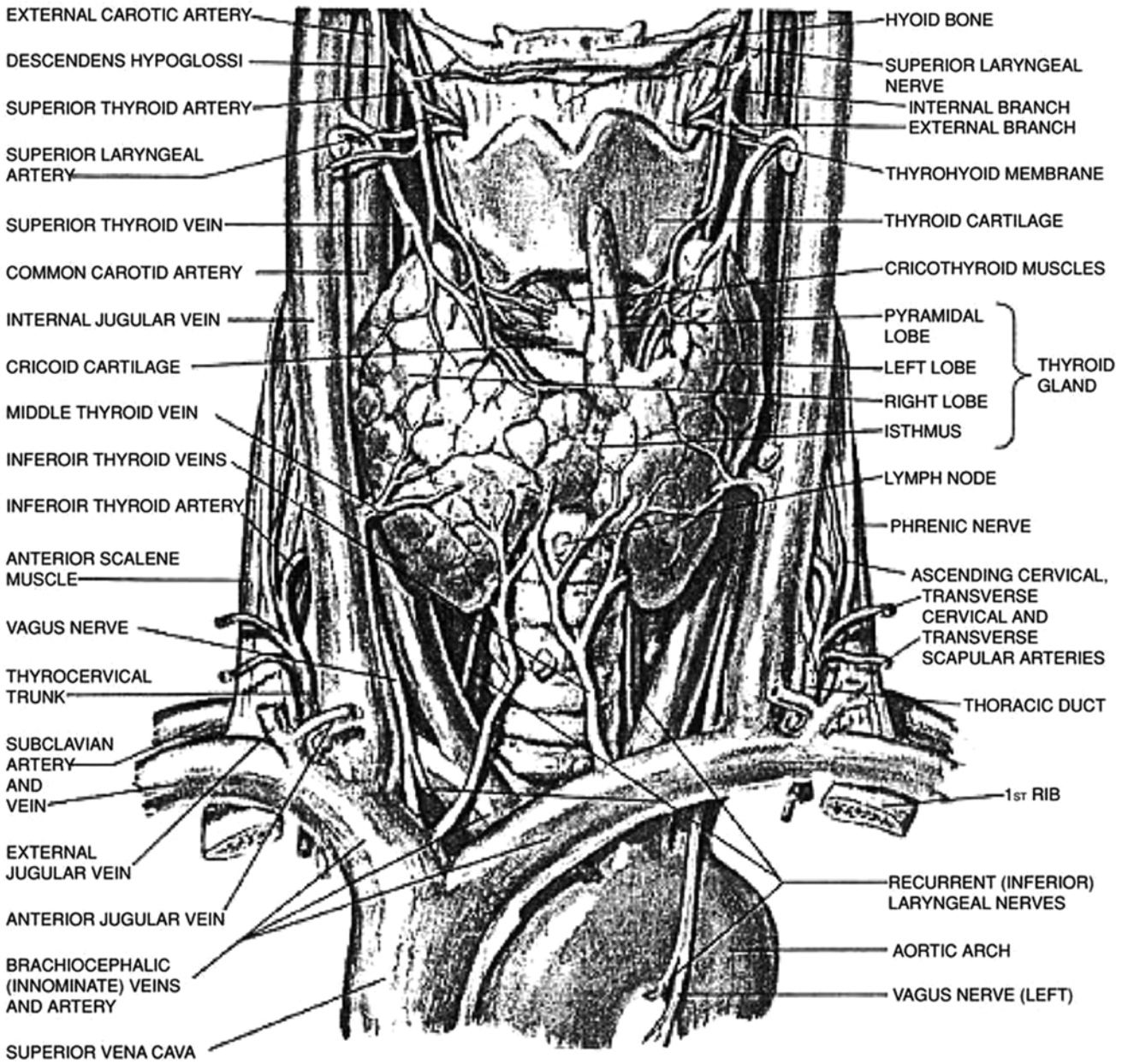

Fig. 1.1 Thyroid anatomy. Thyroid relations with surrounding cervical structures

A fibrous capsule covers the thyroid gland. Nodules within the parenchyma of the gland may also have a capsule or pseudocapsule. Surgical pathology reports may refer to tumor invasion "through the capsule," and for staging purposes, prognosis, and management, it is important to know if this represents extension through the capsule of the gland into the surrounding perithyroidal tissues. Several key structures are located in relation to the capsule and should be considered in the context of surgery on the thyroid gland, such as the parathyroid glands and the recurrent laryngeal nerve. This is particularly significant with total thyroidectomy in patients with thyroid cancer. The small parathyroid glands are located in the posterior aspect of this capsule. Their identification and preservation is critical during surgery and can be particularly difficult with invasive cancers that require extensive surgery for complete resection, including modified lymph node dissections. Also, close monitoring of their function by measurements of serum total and ionized calcium in the early postoperative period is important to avoid or adequately treat surgical hypoparathyroidism in a timely manner.

The recurrent laryngeal nerves provide an essential part of the innervation of the larynx, and any injury can result in symptoms that range from a hoarse voice to stridor and the need for a tracheostomy. They originate from the vagus

nerve at the level of the aortic arch and turn superiorly toward the tracheoesophageal groove. Several anatomic variations have been described; on the right side the recurrent laryngeal nerve runs laterally to the tracheoesophageal groove [2, 3]. It runs close to the inferior thyroid artery and can be found anteriorly, posteriorly, or in between the branches of the blood vessel. Several surgical approaches have been proposed to try to identify and preserve this nerve during surgery of the thyroid gland. Most investigators recommend identifying the nerve before ligating the artery to prevent inadvertent injury to the nerve, but there are variations in proposed methods to achieve this. As the nerve travels superiorly in or laterally to the tracheoesophageal groove, it is located directly posterior to the thyroid gland itself and can be adherent to it. This requires special attention by the thyroid surgeon to prevent damage to the nerve as the thyroid lobe is removed. Another variation is a division of the recurrent laryngeal nerve before entering the larynx [2, 3]. In less than 1 % of cases, an anomalous nonrecurrent nerve has been reported, originating from the cervical potion of the vagus nerve (also called the "inferior laryngeal nerve"), instead of the recurrent laryngeal nerve. This nerve is usually seen on the right side of the neck [4].

The gland's blood supply comes from two sets of arteries on each side. The superior thyroid arteries originate from the external carotid arteries. They descend to the superior poles of the thyroid gland and are accompanied by the superior laryngeal nerve. This nerve originates from the inferior vagus ganglion. As it approaches the larynx, it divides into the external and internal branches. The internal branch supplies sensory innervation to the supraglottic larynx, and the external branch innervates the cricothyroid muscle [5]. The surgeon should ligate the superior thyroid artery as close to the thyroid gland as possible to try to avoid damaging any branches of the superior laryngeal nerve. Clearly, the type of symptoms a patient will develop postoperatively is highly dependent on the experience and skill of the surgeon and the type of nerve injury. Unfortunately, it is not rare that the surgeon may have to sacrifice one of the recurrent laryngeal nerves in an en bloc resection because cancer has directly invaded the nerve.

Anatomy and Physiology

The inferior thyroid artery is a branch of the thyrocervical trunk, and as noted, this artery is in close proximity with the recurrent laryngeal nerve. Occasionally, the thyroidea ima artery also provides blood supply to the thyroid gland and may originate from either the thyrocervical trunk or the arch of the aorta. The venous drainage of the thyroid gland consists of three sets of veins: the superior, middle, and inferior. The superior and middle thyroid veins drain into the internal jugular veins, and the inferior veins anastomose with each other anteriorly to the trachea and drain into the brachiocephalic vein. The lymphatic drainage of the thyroid gland mainly involves the deep cervical lymph nodes in the central compartment. This area is usually dissected by the surgeons performing thyroidectomies for malignant disease to minimize the chance of residual malignancy in the neck. A few lymphatic vessels also drain to the paratracheal lymph nodes.

Another important aspect of thyroid anatomy is the potential presence of thyroid tissue at locations that are considered "ectopic." To better understand this, a short description of the embryonic development of the thyroid gland is necessary. The primitive thyroid gland develops in the first month of gestation in the pharyngeal floor and elongates caudally, forming the thyroglossal duct. As the duct descends to its final location in the neck, it comes in contact with the ultimobranchial pouch of the fourth pharyngeal pouch—the origin of the C cells that produce calcitonin. Their final resting place is at the lower part of the upper one third of the adult thyroid gland. Once the thyroid gland reaches its destination at the base of the neck, the thyroglossal duct regresses and usually disappears, leaving a remnant of only the foramen cecum at the base of the tongue. Sometimes, its distal part near the thyroid gland persists and forms the pyramidal lobe of the thyroid gland. Occasionally, the thyroglossal duct remains and presents (most often during childhood) as a neck mass. This mass usually represents a benign thyroglossal duct cyst, but cases of primary thyroid malignancy have been described at any place along the track of the duct's migration [6]. In addition to these ectopic sites for thyroid tissue and thyroid malignancy, benign ectopic thyroid tissue has been described in many different parts of the human body. These include the base of the tongue [7–10], intralaryngeal [11], intratracheal [12], submandibular [13], carotid bifurcation [14], intracardiac [15, 16], ascending aorta [17], gallbladder [18], porta hepatis [19], intramesenteric [20], and ovarian [21]. Thyroid cancer has been described in many of these sites as well, e.g., at the base of the tongue or in the ovary (struma ovarii) [16, 22–25], but whether some of these tumors are primary or secondary is a matter of debate.

Another aspect of ectopic thyroid tissue relates to the presence of thyroid follicular elements in cervical lymph nodes. Significant controversy exists in the literature about whether the thyroid tissue deposits are indeed benign or representative of metastatic disease [26]. Nevertheless, the presence of ectopic thyroid tissue—benign or malignant—can confuse the clinical perspective and may require a different therapeutic approach to adequately treat thyroid cancer and to follow the patient optimally.

The thyroid gland has a characteristic histology and distinctions between benign and malignant thyroid tissue are important to appreciate. The main histological structure is the thyroid follicle (Fig. 1.2), which consists of a single layer of epithelial cells—the thyroid follicular cells—surrounded by

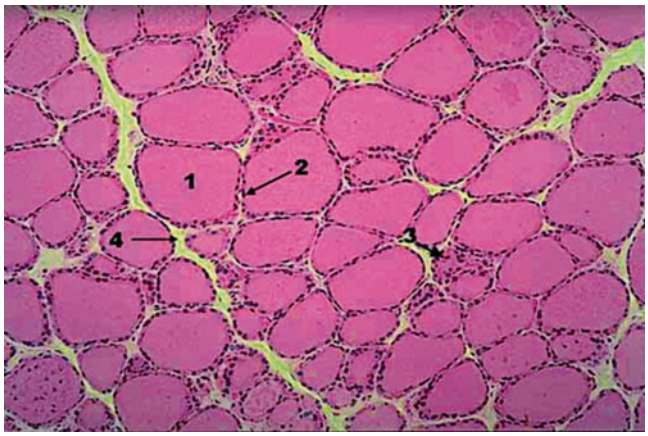

Fig. 1.2 Histology of normal adult thyroid gland: (*1*) colloid of a thyroid follicle; (*2*) follicular cells. Single-layer cells forming a follicle; (*3*) parafollicular cells (C cells); (*4*) connective tissue septum

a basement membrane. The follicle is filled with a colloid material that contains thyroglobulin, the precursor macromolecule and storage protein for the thyroid hormones: thyroxine (T4) and triiodothyronine (T3). The size of these follicles varies significantly—even within a single thyroid gland—but is usually about 200 μm. Every 20–40 follicles are separated from the rest by connective tissue septa. Although most authorities believe that the thyroid cells are monoclonal in origin, emerging evidence [27] suggests that different parts of the thyroid originate from different precursors, most interestingly with different malignant potentials. The differences could be reflected by those groups of thyroid follicles separated by the connective tissue septa. Blood vessels and supporting connecting tissue are seen in between the follicles, as well as groups of C cells (also called "parafollicular cells") that produce calcitonin. As mentioned above, these cells are concentrated in the lower part of the upper third of the thyroid gland and nodules in that part of the thyroid gland may be more suspicious for medullary thyroid cancer.

Thyroid Physiology

The main function of the thyroid gland is to provide adequate amounts of thyroid hormone for the proper regulation of a large number of bodily functions, e.g., energy expenditure and metabolic rate. Thyroid hormone is an iodinated hormone and thus requires the ability of the thyroid gland to concentrate iodine from the circulation and organify it for incorporation into the thyroid hormone molecules. The amount of thyroid hormone produced by the thyroid gland is tightly regulated in the human body under normal conditions. This process is very complex and requires several steps, both within and outside of the thyroid gland. Each step may have clinical relevance to thyroid cancer.

First, as thyroid cancer cells are derived from normal noncancerous thyroid cells, they use the same cellular mechanisms to function, depending on their level of differentiation. As a result, some of the physiologic functions of normal thyroid cells are used to identify, characterize, or ultimately treat thyroid cancer. For example, one of the most critical properties of a thyroid cell is its ability to trap iodine from the circulation, most often against a concentration gradient. Thus, radioactive iodine can be employed to destroy thyroid cancer cells. The uptake of iodine is accomplished by the sodium–iodide symporter (NIS), located at the basal membrane of the thyrocyte (Fig. 1.3). This active, energy-requiring process can concentrate iodide in the thyrocyte some 20–40-fold above its level in the circulation and is accomplished by the transport of sodium into the cell. Notably, similar iodide transport mechanisms are also present in other tissues, such as the salivary gland. Thus, because salivary tissue will actively transport radioactive iodine when administered, patients may suffer from radiation-induced sialadenitis or xerostomia when treated with radioactive iodine for thyroid cancer.

For organification of the iodide, the enzyme thyroid peroxidase (TPO), together with hydrogen peroxide, is required to organify the inorganic iodide and incorporate it into a tyrosine residue within thyroglobulin. This occurs in the apical membrane of the thyroid cell, facing the colloid (Fig. 1.3). Each tyrosine molecule can take up as many as four iodide atoms, forming the different types of thyroid hormone. Another important transporter in this system called pendrin has also been identified [28]. It is located at the apical membrane of thyrocytes (Fig. 1.3). It is an important regulator of inorganic iodide efflux into the lumen of the thyroid follicle where organification takes place as described above. Mutations of this gene have been described in the Pendred syndrome. A partial defect of iodide organification leads to the development of goiters in some of these patients [29].

Once the thyroid hormone has been synthesized, it is stored in linkage within the thyroglobulin molecule in the colloid of thyroid follicles. Under stimulation by thyrotropin (TSH), the gland receives the signal that thyroid hormone release is needed, and fragments of thyroglobulin enter the thyrocyte (pinocytosis) and are cleaved by endopeptidases in the endosomes and lysosomes. Thyroxine and triiodothyronine are produced and released into the circulation. Under normal conditions, the thyroid gland output consists of mainly thyroxine (~90 % or ~75–100 μg/day) and a small amount of triiodothyronine (~10 % or 6 μg/day).

Thus, the processes of iodide uptake and thyroid hormone synthesis are largely regulated by TSH, a pituitary hormone that stimulates both of these thyroid functions. As described in detail elsewhere in this volume, either endogenous TSH stimulation prompted by thyroid hormone withdrawal or exogenous recombinant human TSH is critical in the

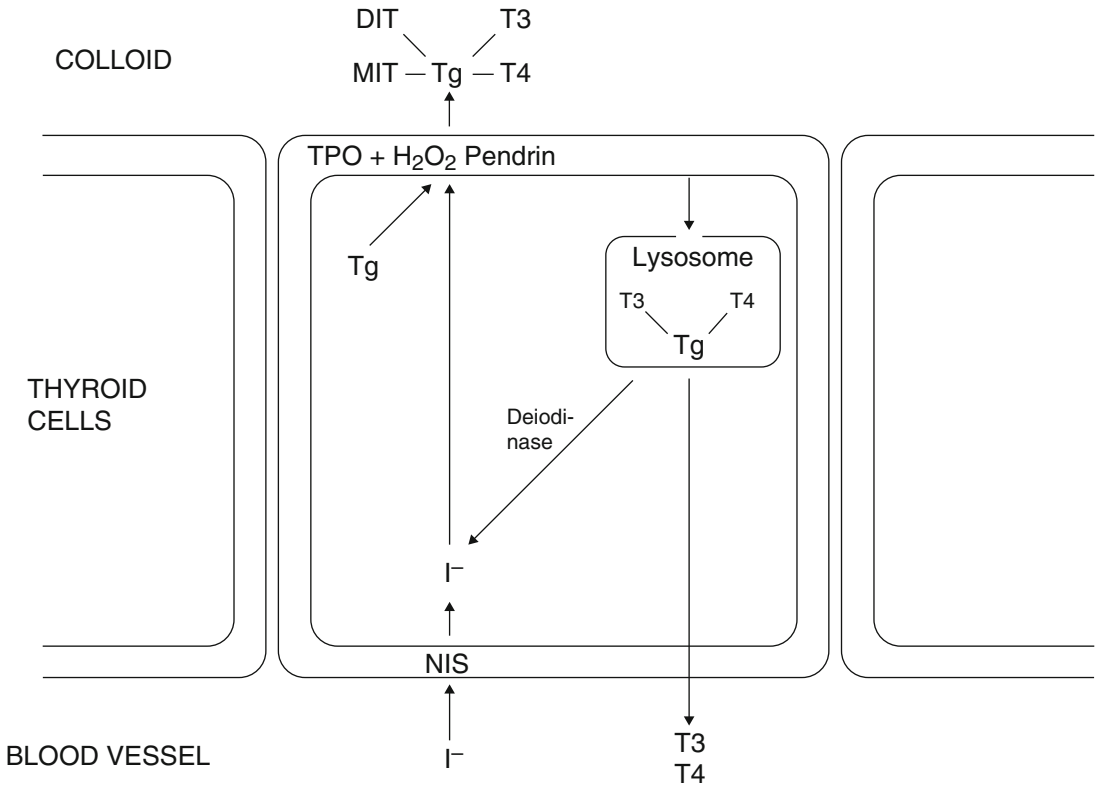

Fig. 1.3 Organification of iodide and synthesis and release of thyroid hormone. *NIS* sodium–iodide symporter, *Tg* thyroglobulin, *TPO* thyroid peroxidase, *MID* monoiodotyrosine, *DIT* diiodotyrosine, *H2O2* hydrogen peroxide, *T3* triiodothyronine, *T4* thyroxine, *I* iodide

diagnosis and treatment of thyroid cancer. On the contrary, as TSH has mitogenic activity, its chronic suppression by thyroxine therapy is critical to the prevention of thyroid cancer growth. Recent evidence suggests a potential role of TSH stimulation in thyroid oncogenesis. Higher TSH values, even within the normal range, are an independent predictor of malignancy for thyroid nodules [30, 31].

Another important aspect of molecular thyroid physiology is the effect that iodine has on thyroid function. As discussed previously, the thyroid gland actively concentrates iodine from the circulation which is used to synthesize thyroid hormone. It is a well-known that iodine deficiency causes goiters, and often when iodine-deficient patients are given iodine, production of excessive amounts of thyroid hormone, hyperthyroidism, is possible, at least transiently. This response is called the "Jod-Basedow phenomenon" [32]. The mechanism for this phenomenon is unclear, but it is thought that it is either because of rapid iodination of poorly iodinated thyroglobulin or the "fueling" of a subclinical autonomous functioning thyroid tissue, as in a "hot" nodule or in Graves' disease [33]. Alternatively, if there is an excess of iodine present in thyrocytes, the sodium–iodide symporter and TPO are inhibited to prevent excessive amounts of thyroid hormone from being synthesized. This inhibition is referred to as "the Wolff–Chaikoff phenomenon" [34]. A high concentration of inorganic iodide is needed for this effect. This inhibition of iodide organification is temporary because the inhibition of iodide transport by the NIS depletes intracellular iodine, allowing the system to reset with new iodide organification—this is called the "escape from the Wolff–Chaikoff effect."

Several molecules discussed have significant clinical utility in the daily management of thyroid cancer. Measurement of the TSH receptor, thyroglobulin, antithyroglobulin antibodies, and thyroperoxidase (TPO) can be used to determine if a neoplasm is of thyroid origin. Multiple other relevant molecules have been described, such as thyroid transcription factors (TTF) 1 and 2, galectin 3, and oncofetal fibronectin. Assessment of the presence of such proteins may be particularly important in the evaluation of material obtained by fine-needle aspiration of suspected metastatic lesions. See Chap. 3 for a more detailed description of molecular thyroid markers.

Finally, there are several elements of thyroid molecular physiology that are poorly understood but may play a significant role in thyroid cell function as well as in thyroid oncogenesis. One such element is the retinoid receptor system. Retinoids are vitamin A derivatives that regulate growth and differentiation of many cell types by binding to specific nuclear receptors. In thyroid cells, these molecules are involved in the regulation of important regulatory factors,

such as thyroglobulin and the NIS [35]. There is evidence to suggest that activation of these nuclear receptors may induce some degree of redifferentiation of thyroid cancer cells and make them more susceptible to conventional thyroid cancer treatments such as radioactive iodine [36].

References

1. Burman KD, Adler RA, Wartofsky L. Hemiagenesis of the thyroid gland. Am J Med. 1975;58(1):143–6.
2. Monfared A, Saenz Y, Terris DJ. Endoscopic resection of the submandibular gland in a porcine model. Laryngoscope. 2002;112(6):1089–93.
3. Moreau S, de Goullet Rugy M, Babin E, Salame E, Delmas P, Valdazo A. The recurrent laryngeal nerve: related vascular anatomy. Laryngoscope. 1998;108(9):1351–3.
4. Abboud B, Aouad R. Non-recurrent inferior laryngeal nerve in thyroid surgery: report of three cases and review of the literature. J Laryngol Otol. 2004;118(2):139–42.
5. Miller FR, Netterville JL. Surgical management of thyroid and parathyroid disorders. Med Clin N Am. 1999;83(1):247–59, xi.
6. Naghavi SE, Jalali MM. Papillary carcinoma of thyroglossal duct cyst. Med Sci Monit: Int Med J Exp Clin Res. 2003;9(7):CS67–70.
7. Tang ZH, Li WY. Diagnosis of ectopic thyroid in the tongue root by 99mTcO4(-) and 131I radionuclide thyroid imaging: report of one case. Di 1 jun yi da xue xue bao = Acad J First Med Coll PLA. 2003;23(10):1041–2.
8. Thomas G, Hoilat R, Daniels JS, Kalagie W. Ectopic lingual thyroid: a case report. Int J Oral Maxillofac Surg. 2003;32(2):219–21.
9. Boer A, Polus K. Lingual thyroid: a rare disease resembling base of tongue neoplasm. Magy Onkol. 2002;46(4):347–9.
10. Chiu TT, Su CY, Hwang CF, Chien CY, Eng HL. Massive bleeding from an ectopic lingual thyroid follicular adenoma during pregnancy. Am J Otolaryngol. 2002;23(3):185–8.
11. Jimenez Oliver V, Ruiz Rico R, Davila Morillo A, Fernandez Ruiz E, del Ruiz Portal JM, Perez Arcos JA, Rodriguez Baro G. Intralaryngeal ectopic thyroid tissue. Report of one case and review of the literature. Acta Otorrinolaringol Esp. 2002;53(1):54–9.
12. Byrd MC, Thompson LD, Wieneke JA. Intratracheal ectopic thyroid tissue: a case report and literature review. Ear Nose Throat J. 2003;82(7):514–8.
13. Ulug T, Ulubil SA, Alagol F. Dual ectopic thyroid: report of a case. The J Laryngol Otol. 2003;117(7):574–6.
14. Hollander EJ, Visser MJ, van Baalen JM. Accessory thyroid gland at carotid bifurcation presenting as a carotid body tumor: case report and review of the literature. J Vasc Surg. 2004;39(1):260–2.
15. Larysz B, Jedrzychowska-Baraniak J, Nikodemska I, Sell M. Ectopic thyroid tissue in the heart – a case report. Kardiol Pol. 2003;59(8):149–51.
16. Chosia M, Waligorski S, Listewnik MH, Wiechowski S. Ectopic thyroid tissue as a tumour of the heart – case report and review of the literature. Pol J Pathol. 2002;53(3):173–5.
17. Williams RJ, Lindop G, Butler J. Ectopic thyroid tissue on the ascending aorta: an operative finding. Ann Thorac Surg. 2002;73(5):1642–3.
18. Ihtiyar E, Isiksoy S, Algin C, Sahin A, Erkasap S, Yasar B. Ectopic thyroid in the gallbladder: report of a case. Surg Today. 2003;33(10):777–80.
19. Ghanem N, Bley T, Altehoefer C, Hogerle S, Langer M. Ectopic thyroid gland in the porta hepatis and lingua. Thyroid. 2003;13(5):503–7.
20. Gungor B, Kebat T, Ozaslan C, Akilli S. Intra-abdominal ectopic thyroid presenting with hyperthyroidism: report of a case. Surg Today. 2002;32(2):148–50.
21. Ribeiro-Silva A, Bezerra AM, Serafini LN. Malignant struma ovarii: an autopsy report of a clinically unsuspected tumor. Gynecol Oncol. 2002;87(2):213–5.
22. Perez JS, Munoz M, Naval L, Blasco A, Diaz FJ. Papillary carcinoma arising in lingual thyroid. J Craniomaxillofac Surg. 2003;31(3):179–82.
23. Massine RE, Durning SJ, Koroscil TM. Lingual thyroid carcinoma: a case report and review of the literature. Thyroid. 2001;11(12):1191–6.
24. Kao SY, Tu H, Chang RC, Yang AH, Chang KW, Lee CH. Primary ectopic thyroid papillary carcinoma in the floor of the mouth and tongue: a case report. Br J Oral Maxillofac Surg. 2002;40(3):213–5.
25. Klubo-Gwiezdzinska J, Manes RP, Chia SH, Burman KD, Stathatos NA, Deeb ZE, Wartofsky L. Clinical review: ectopic cervical thyroid carcinoma – review of the literature with illustrative case series. J Clin Endocrinol Metab. 2011;96(9):2684–91.
26. Meyer JS, Steinberg LS. Microscopically benign thyroid follicles in cervical lymph nodes. Serial section study of lymph node inclusions and entire thyroid gland in 5 cases. Cancer. 1969;24(2):302–11.
27. Jovanovic L, Delahunt B, McIver B, Eberhardt NL, Grebe SK. Thyroid gland clonality revisited: the embryonal patch size of the normal human thyroid gland is very large, suggesting X-chromosome inactivation tumor clonality studies of thyroid tumors have to be interpreted with caution. J Clin Endocrinol Metab. 2003;88(7):3284–91.
28. Scott DA, Wang R, Kreman TM, Sheffield VC, Karniski LP. The Pendred syndrome gene encodes a chloride-iodide transport protein. Nat Genet. 1999;21(4):440–3.
29. Bizhanova A, Kopp P. Genetics and phenomics of Pendred syndrome. Mol Cell Endocrinol. 2010;322(1–2):83–90.
30. Boelaert K, Horacek J, Holder RL, Watkinson JC, Sheppard MC, Franklyn JA. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. J Clin Endocrinol Metab. 2006;91(11):4295–301.
31. Zafon C, Obiols G, Baena JA, Castellvi J, Dalama B, Mesa J. Preoperative thyrotropin serum concentrations gradually increase from benign thyroid nodules to papillary thyroid microcarcinomas then to papillary thyroid cancers of larger size. J Thyroid Res. 2012;2012:530721.
32. Stanbury JB, Ermans AE, Bourdoux P, Todd C, Oken E, Tonglet R, Vidor G, Braverman LE, Medeiros-Neto G. Iodine-induced hyperthyroidism: occurrence and epidemiology. Thyroid. 1998;8(1):83–100.
33. Ermans AM, Camus M. Modifications of thyroid function induced by chronic administration of iodide in the presence of "autonomous" thyroid tissue. Acta Endocrinol. 1972;70(3):463–75.
34. Wolff J, Chaikoff IL. Plasma inorganic iodide as a homeostatic regulator of thyroid function. J Biol Chem. 1948;174(2):555–64.
35. Kurebayashi J, Tanaka K, Otsuki T, Moriya T, Kunisue H, Uno M, Sonoo H. All-trans-retinoic acid modulates expression levels of thyroglobulin and cytokines in a new human poorly differentiated papillary thyroid carcinoma cell line, KTC-1. J Clin Endocrinol Metab. 2000;85(8):2889–96.
36. Van Herle AJ, Agatep ML, Padua 3rd DN, Totanes TL, Canlapan DV, Van Herle HM, Juillard GJ. Effects of 13 cis-retinoic acid on growth and differentiation of human follicular carcinoma cells (UCLA R0 82 W-1) in vitro. J Clin Endocrinol Metab. 1990;71(3):755–63.