Objectives

- Recap the basic function of the thyroid gland and the broad principles of regulation of thyroid hormone synthesis
- Recap the main anatomical relations of the thyroid gland
- Understand the main clinical manifestations of thyroid disease: functional and physical
- Understand the pathology of simple and nodular goitre
- Understand the pathology of immune-related thyroid conditions
- Understand the pathology of common thyroid neoplasms

Outline

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g. **Lymphoma**

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Pathweb: https://medicine.nus.edu.sg/pathweb/normal-histology/thyroid/

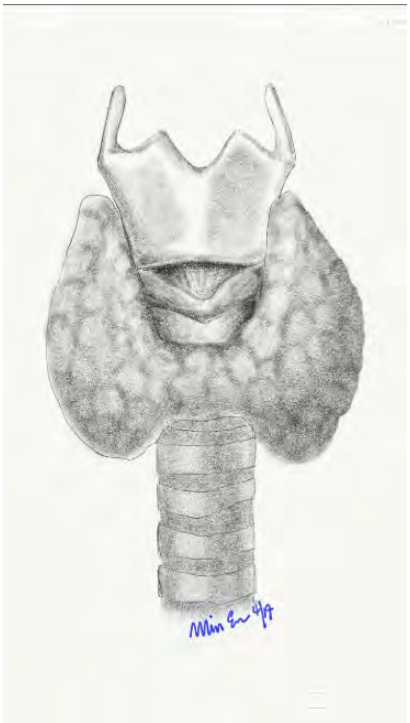
***Note**: Pathweb Study Notes are based on the key topics covered in the lectures in the Yong Loo Lin School of Medicine, as well as additional topics covered in major texts. For more comprehensive discussion on specific pathology topics, readers are advised to refer to the recommended texts in your respective courses.*

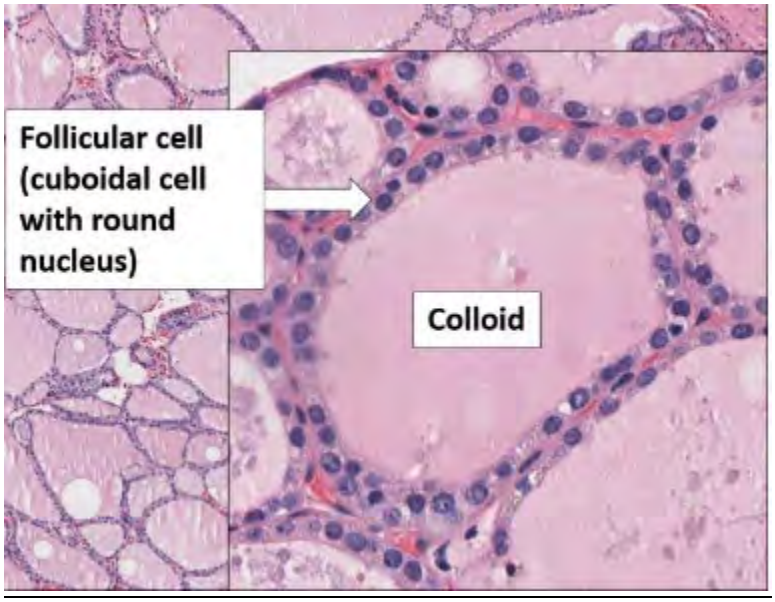
I. ANATOMY, PHYSIOLOGY AND CLINICAL PRESENTATION

a. Normal Anatomy

The thyroid gland comprises 2 lateral lobes, an isthmus and, sometimes, a pyramidal lobe, which is usually attached to the isthmus.

- Weight 20-25g
- Embryology: Descends from an evagination of the pharyngeal epithelium starting from the foramen caecum
- Histologically, it comprises lobules, which are filled with thyroid follicles lined by follicular cells. The follicles contain thyroglobulin, which appears as a pink homogenous material known as colloid.
- There is a much smaller population of parafollicular C cells within the thyroid follicles that produce calcitonin.





b. Physiology and Regulation

Thyroid hormones T3 and T4

- The thyroid follicular cells convert thyroglobulin into peptide hormones thyroxine (T4) and triiodothyronine (T3), the latter in smaller amounts. In the peripheral circulation, these are bound to plasma proteins, which helps to regulate proportions of unbound (“free”) vs bound T3 and T4.

- In peripheral (target) tissues, most of free T4 is deiodinated to T3, which then binds to thyroid hormone nuclear receptors, causing increased transcription of target genes.
- Effects of T3 and T4 include stimulation of carbohydrate and lipid catabolism and protein synthesis, resulting in an overall increase in the basal metabolic rate (BMR). Also, these hormones are important to brain development in the fetus and neonate. Congenital deficiency thus may result in growth and mental retardation.

Regulation of T3 and T4 production

- Hypothalamus-pituitary axis. The hypothalamus releases thyrotropin-releasing hormone (TRH) which cause thyrotroph cells in the anterior pituitary to release thyroid stimulating hormone (TSH).
- TSH binds to receptors on thyroid follicular cells, triggering events that increase intracellular cAMP and stimulate thyroid growth and hormone production and release
- If T3 and T4 levels are decreased, a feedback loop is triggered, causing release of TSH and thus action on the thyroid gland to increase plasma levels of thyroid hormones.
- Conversely, raised levels of T3 and T4 suppress TRH and TSH release, thereby attempting to normalize thyroid hormone levels.
- Thus, a pituitary (secondary) cause of raised thyroid hormones gives rise to high TSH *and* thyroid hormone levels, while a thyroid (primary) cause will give rise to low TSH levels due to the negative feedback mechanism from the presence of raised thyroid hormone levels. Similarly, in secondary hypothyroidism, TSH levels are low, whilst in primary hypothyroidism, TSH is high.

Function of calcitonin

- Involved in calcium regulation – produced in response to raised serum calcium
- Calcitonin reduces osteoclastic activity in bone and renal tubular reabsorption of calcium

c. Clinical Presentations of Thyroid Disease

There are two main ways in which thyroid disease can manifest clinically, and both can occur concurrently.

i. Goitre

- Goitre = Enlargement of the thyroid gland. It can be **diffuse** (i.e. whole gland symmetrically enlarged without discrete masses); or **discrete**, i.e. a nodule or several nodules with some normal-appearing gland in between; see section III. Below.
- Multinodular goitre is the commonest thyroid disease overall. It is a non-neoplastic condition.
- Functional abnormalities, e.g. hyper- or hypothyroidism can also be associated with goitre.

ii. Functional abnormality

There are 2 main abnormal functional states:

- Hyperthyroidism (excessive release of thyroid hormones - this term is now used interchangeably with "thyrotoxicosis" – although, traditionally, "hyperthyroidism" was used to refer to primary thyroid causes of thyrotoxicosis).
  - Primary hyperthyroidism – caused by intrinsic thyroid overproduction of thyroid hormones
    - Causes:
      - Graves disease,
      - Toxic (hyperfunctioning) multinodular goitre
      - Toxic follicular adenoma
    - Lab results: high free T4 and low TSH (note: T3 toxicosis shows raised T3 levels while free T4 may be decreased)
  - Secondary hyperthyroidism – caused by non-thyroidal pathology, e.g. TSH-producing pituitary adenoma
    - Lab results: free T4 high, TSH normal/raised (pituitary cause)
  - Clinical manifestations of thyrotoxicosis/hyperthyroidism:
    - Signs and symptoms arising from increased basal metabolic rate: Heat intolerance, sweating, loss of weight despite increased appetite
    - Manifestations from increased cardiac contractility/output: Tachycardia, palpitation, atrial fibrillation, potentially congestive cardiac failure, potential left ventricular dysfunction (so-called thyrotoxic or hyperthyroid cardiomyopathy, leading to low output heart failure)
    - Overactive sympathetic nervous system: Tremor, emotional lability, anxiety, irritability, insomnia, increased frequency of defecation (hyperdefecation), proximal myopathy; staring gaze and lid lag (note: this is distinct from proptosis which occurs in thyroid ophthalmopathy, specifically in Graves disease)
    - Increased bone resorption leading to osteoporosis
    - Thyroid storm: A state of abrupt, severe hyperthyroidism (e.g. during an infection or period of stress; on cessation of antithyroid medication), characterised by fever and tachycardia. This may be potentially fatal due to cardiac arrhythmias.
- Hypothyroidism (thyroid hormone deficiency)
  - Caused by a deficiency anywhere in the hypothalamic-pituitary-thyroid axis
  - Females 10X more frequently affected than males
  - Primary hypothyroidism (commonest type)
    - Causes:
      - Autoimmune (Hashimoto thyroiditis - #1 cause in iodine-sufficient areas)
      - Iatrogenic (previous thyroidectomy, irradiation, drugs – lithium, iodides etc)
      - Congenital (dietary iodine deficiency, dyshormonogenetic goitre, genetic defects in thyroid development)
    - Lab results: Raised TSH, decreased T4
  - Secondary hypothyroidism (less common), due to hypopituitarism (TSH deficiency) or TRH deficiency.
    - Causes:

        - Pituitary pathology e.g. tumours, postpartum pituitary necrosis, trauma
        - Hypothalamus pathology e.g. tumours, trauma, radiation therapy, infiltrative disease
    - Lab results: Normal/low TSH, decreased T4
- Clinical manifestations of hypothyroidism:
    - Cretinism – hypothyroidism that develops in infancy or early childhood.
        - Growth and mental developmental abnormalities - short stature, severe intellectual disability, coarse facial features with protruding tongue, umbilical hernia.
    - Myxedema – hypothyroidism that develops in an older child or during adulthood.
        - Fatigue, mental and physical sluggishness, apathy
        - Cold intolerance and decreased sweating, cool and pale skin (decreased blood flow)
        - Weight gain, despite depressed appetite
        - Constipation (due to decreased sympathetic activity)
        - Shortness of breath and decreased exercise capacity (due to decreased cardiac output, secondary to decreased thyroid hormone-mediated transcription of several sarcolemmal genes)
        - Raised total cholesterol and LDL due to abnormal lipid metabolism
        - Changes in appearance due to deposition of glycosaminoglycans and hyaluronic acid in skin and subcutis → coarsening of facial features and tongue enlargement.

II. CONGENITAL ANOMALIES

a. Thyroglossal Duct Cyst

Common congenital anomaly; arises from a vestigial sinus tract from embryonal development of the thyroid, from the thyroglossal duct.

- Clinical presentation is a midline neck cyst, anywhere from the foramen caecum to the suprasternal notch (thyrohyoid location > suprahyoid > intralingual)
- Often connected to the hyoid bone
- Complications: Infection and abscess formation, rarely malignant change
- Grossly: Cystic lesion containing watery to mucoid, viscous fluid, clear to brownish
- Microscopy: Cyst lined by ciliated pseudostratified columnar epithelium, or non-keratinising stratified squamous epithelium (if closer to the tongue), or stratified cuboidal epithelium. Thyroid follicles sometimes present in cyst wall, as well as lymphocytic infiltrates.
- Treatment: Complete surgical excision together with excision of the hyoid bone (Sistrunk procedure)

b. Congenital Hypothyroidism

Commonest cause of congenital hypothyroidism globally is dietary iodine deficiency.

Other causes are rare:

- Dyshormonogenetic goitre - inborn errors of thyroid metabolism e.g. defective iodide transport into thyrocytes, defective binding of iodine to tyrosine residues.
- Genetic defects (germline mutations) in the developmental of the thyroid gland - thyroid hypoplasia or agenesis

III. DIFFUSE AND MULTINODULAR GOITRE

A condition in which a goitre (enlargement of the thyroid gland) arises due to impaired thyroid hormone synthesis. Mechanism: Deficiency in dietary iodine → reduced thyroid hormone production → compensatory increase in serum TSH → **hypertrophy** and **hyperplasia** of thyroid follicular cells → thyroid gland enlargement → restoration of euthyroid state (usually)

2 main types of non-neoplastic goitres:

a. Diffuse (Simple) Nontoxic Goitre
b. Multinodular Goitre

a. Diffuse (Simple) Nontoxic Goitre

Diffuse enlargement, non-nodular, also known as “colloid goitre” because follicles contain abundant colloid

2 main types:
1. Endemic goitre (more common)
    - Caused by dietary iodine deficiency, which can be reduced by iodine supplementation.
    - In locales where iodine levels are low (e.g. landlocked areas such as the Himalayas, Andes), and in which >10% of the population develop goitres.
    - Dietary factors e.g. increased or limited diet high in goitrogens which interfere with thyroid hormone synthesis (e.g. Cruciferae family vegetables such as cabbage, cauliflower, Brussels sprouts, cassava)

2. Sporadic goitre (less common)
    - Female preponderance, in adolescence or young adulthood
    - Causes: Ingestion of goitrogens; dyshormonogenetic goitre; sometimes idiopathic

- Clinical features:
    - Clinically euthyroid
    - Diffuse goitre, +/- mass effects
    - Hormone levels usually normal, but TSH may be at upper end of normal

- Morphology:
  - Hyperplastic phase – Grossly, symmetrical enlargement. Microscopically, follicular cells columnar, crowded, forming projections into follicular lumina. Follicles may vary in size.
  - Colloid involution phase – (usually when demand for thyroid hormones decreases) Grossly, glassy, translucent cut surface because of abundant colloid. Microscopically, large, distended colloid-filled follicles lined by flattened cuboidal cells.

b. Multinodular Goitre

Commonest cause of thyroid nodule, which may appear to be solitary on clinical examination.

Usually evolve from a simple diffuse goitre; because of follicular cells responding differently to trophic thyroid hormones e.g. due to acquired genetic abnormalities, for example in the TSH signalling pathway, which allow increased proliferation.

Secondary changes may occur due to differently sized follicles → fibrosis, cystic change, calcifications and increased nodularity.

- Clinical features:
  - Goitre, which may be large; or may present as a single nodule clinically (dominant nodule)
  - Mass effects – airway obstruction, dysphagia, compression of large vessels (e.g. superior vena cava syndrome)
  - Functional status – usually euthyroid, or subclinical hyperthyroidism (raised TSH); rarely clinical hyperthyroidism from autonomous toxic nodule (Plummer syndrome)
  - Low risk of malignancy (<5%)

- Morphology:
  - Asymmetrically enlarged thyroid, up to 2000g
  - Occasionally grows retrosternally – plunging goitre
  - Cut section – multiple nodules of varying sizes, some containing gelatinous, glistening colloid. Haemorrhage, fibrosis, calcifications, cystic change may be present.
  - Microscopically – areas of hyperplasia, with intervening areas of involution, with large, distended, colloid-filled follicles lined by flattened cuboidal cells. Fibrosis and calcifications may be present.

IV. THYROIDITIS AND IMMUNE-RELATED DISORDERS

The main pathology of thyroiditis is inflammation of the thyroid gland, while immune-related disorders may give rise to inflammatory infiltrates and also functional or growth-related effects. Five conditions are discussed below:

a. Graves Disease

b. Hashimoto Thyroiditis (Autoimmune disorder)
c. Subacute Lymphocytic Thyroiditis
d. Granulomatous Thyroiditis (DeQuervain thyroiditis)
e. IgG4-related Thyroiditis

a. Graves Disease

Commonest endogenous cause of hyperthyroidism. Autoimmune disorder, with autoantibodies against a variety of thyroid antigens.

- Epidemiology:
  - Women 10 > Men
  - Most frequent age 20 – 40y, but may occur in childhood
  - Association with *HLA-B8* and *HLA-DR3*
  - Increased susceptibility with polymorphisms in some immune-regulation genes e.g. cytotoxic T lymphocyte-associated antigen-4 (*CTLA4*), protein tyrosine phosphatase-22 (*PTPN22*), and interleukin-2 receptor α chain (*IL2RA)*
  - Increased risk of other autoimmune conditions e.g. SLE, pernicious anaemia, type 1 diabetes, Addison disease
- Pathogenesis:
  - Autoimmune disease – breakdown of self-tolerance, with production of autoantibodies to thyroid autoantigens. Main autoantigen involved is TSH (thyrotropin) receptor → main autoantibody is anti-TSH receptor antibodies (there are several subtypes) → increased thyroid hormone synthesis and increased thyroid gland growth
  - Anti-TSH receptor antibodies subtypes:
    - Thyroid-stimulating immunoglobulin (TSI) which is quite specific for Graves disease – binds to TSH receptor and mimics its actions → increased release of thyroid hormones; stimulation of protein C kinase pathway → cell proliferation
    - TSH-receptor blocking antibodies → may cause hypothyroidism in a minor subset of patients
  - Other less specific autoantibodies e.g. anti-thyroglobulin, anti-TPO (thyroid peroxidase)
  - Thyroid ophthalmopathy: activated CD4+ Th cells secrete cytokines → stimulate fibroblast proliferation and extracellular matrix synthesis (glycosaminoglycans). Increased lymphocyte infiltration, oedema and swelling of extraocular muscles, increased amounts of ECM and fatty infiltration → increased volume of retro-orbital tissues → exophthalmos (forward protrusion of eyeballs)

- Clinical features
  - Clinical triad of:
    - **Hyperthyroidism** associated with **diffuse** goitre
    - Infiltrative ophthalmopathy with **exophthalmos**

        - Localised, infiltrative dermopathy (**pretibial myxedema**) – infrequent; seen in shins as scaly thickening and induration
    - Symptoms of thyrotoxicosis and sympathetic overactivity (e.g. tachycardia, palpitations, tremulousness, anxiety)
    - May have compressive symptoms if goitre is large
    - Thyroid examination – diffuse goitre, +/- audible bruit
    - Ocular abnormalities – wide, staring gaze with lid lag (sympathetic overactivity); exophthalmos (infiltrative ophthalmopathy)
    - Thyroid function tests: High T3 and free T4, low TSH
    - Radioiodine scans show diffuse increase in iodine uptake
    - May have coexisting autoimmune conditions (see "Epidemiology" above)

- Morphology:
    - Diffusely, usually symmetrically enlarged thyroid, larger than in Hashimoto thyroiditis
    - Meaty, reddish, soft cut surface
    - Microscopy:
        - Follicles featuring pseudopapillae (finger-like projections into follicle lumen, without true fibrovascular cores) due to proliferation of follicular cells
        - Follicular cells taller, crowded
        - Colloid is pale and shows scalloped margins
        - Lymphoid infiltrates and some plasma cells; germinal centres may be present
        - Orbital tissues – oedema, lymphoid infiltrates, increased ECM deposition, fibrosis and fatty infiltration
- Treatment:
    - Sympathetic blockage – β-blockers
    - Suppress thyroid hormone synthesis – thionamides, radioiodine ablation, thyroidectomy

b. Hashimoto thyroiditis

- Commonest cause of hypothyroidism in geographic areas in which dietary iodine is sufficient
- Epidemiology:
    - Women 10-20X > Men
    - Most frequent age 45 – 65y , but may occur in childhood
    - Increased susceptibility with HLA-DR5, HLA-DR3 and polymorphisms in some immune-regulation genes e.g. cytotoxic T lymphocyte-associated antigen-4 (*CTLA4*), (*PTPN22*), and (*IL2RA)* ; similar to Graves disease
    - May be associated with other autoimmune diseases e.g. Type 1 diabetes
- Pathogenesis:

  - Autoimmune disease – breakdown of self-tolerance to thyroid autoantigens – specific cause is uncertain (possibly abnormalities of regulatory T cells; exposure of usually sequestered thyroid antigens)
  - Circulating antibodies: anti-thyroglobulin, anti-TPO (thyroid peroxidase)
  - Immune-mediated progressive destruction and failure of thyroid gland, with replacement by lymphocytic infiltrates and fibrosis. Mechanisms of tissue destruction:
    - CD8+ cytotoxic cell-mediated follicular cell death
    - Cytokine-mediated cell death – activated CD4+ Th1 cells produce cytokines (e.g. IFNγ) → macrophage recruitment and activation → damage to follicular cells
    - Antibody-dependent cell-mediated cytotoxicity (anti-TGB, anti-TPO antibodies)
- Clinical features
  - Painless goitre (usually symmetrical, but may be asymmetrical or nodular)
  - Often symptoms and signs of hypothyroidism (low T3 and free T4, raised TSH)
  - Occasionally: Preceding thyrotoxicosis ("hashitoxicosis") due to thyroid hormone release from disruption of follicles
  - Increased risk of thyroid lymphoma (e.g. extranodal marginal zone B-cell lymphoma) – recently enlarging mass raises concern for lymphoma
- Morphology:
  - Diffusely, sometimes asymmetrically, enlarged firm gland
  - Pale yellow-tan cut surface
  - Microscopy:
    - Infiltration by lymphocytes and plasma cells, with lymphoid follicles featuring well-developed germinal centres.
    - Thyroid follicles atrophic, lining cells exhibit oncocytic change (metaplastic response – cells contain abundant eosinophilic, granular cytoplasm)
    - May have increased interstitial fibrosis

c. Subacute Lymphocytic (Painless) Thyroiditis

Sometimes also referred to as "painless thyroiditis".

- Epidemiology:
  - Women > Men
  - Most frequent during middle-age
  - Similar condition may be seen in postpartum women (postpartum thyroiditis)
  - May have family history of other autoimmune disorders
- Pathogenesis:
  - Presumed autoimmune disease
  - Circulating antibodies: anti-TPO (thyroid peroxidase)
- Clinical features
  - Mild, transient hyperthyroidism; sometimes progressing to hypothyroidism (self-limiting or progressive)

and/or
    - Painless goitre
    - May progress to overt hypothyroidism over years (similar features to Hashimoto thyroiditis)
- Morphology:
    - Grossly normal to mildly enlarged thyroid
    - Microscopy:
        - Infiltration by lymphocytes with lymphoid follicles featuring germinal centres.
        - Thyroid follicles show patchy disruption

d. Granulomatous Thyroiditis (DeQuervain Thyroiditis)

- Less common than Hashimoto thyroiditis
- Self-limiting condition, usually resolves over 6 – 8 weeks, even if untreated
- Epidemiology:
    - Women 4X > Men
    - Most frequent age 40 – 50y
    - Seasonal occurrence, peaking in summer (linked to prevalence of viral infections) – case clusters reported in association with coxsackievirus, mumps, measles, adenovirus etc infections
- Pathogenesis:
    - Virus-induced cytotoxic T-lymphocyte response to thyroid antigen(s) → host thyroid follicle damage
    - Triggered by viral infection – precedes thyroiditis
    - Self-limiting course – transient inflammation of thyroid gland
- Clinical features
    - Commonest cause of *thyroid pain*
    - Variable enlargement
    - Transient hyperthyroidism (may be subclinical), usually with high T3 and T4 and low TSH; often resolves in 2 – 8 weeks
    - Radioiodine uptake is reduced (in contrast to hyperthyroid conditions e.g. Graves disease)
- Morphology:
    - Diffusely or asymmetrically (unilaterally) enlarged gland
    - Capsule may be adherent to adjacent structures
    - Cut surface is firm, with yellow-white areas (paler than usual brown colour)
    - Microscopy:
        - Findings depend on phases of activity, which may vary in different areas throughout the gland
        - Early (active) phase – neutrophil microabscesses causing disruption to thyroid follicles
        - Later – lymphoid aggregates, activated macrophages, variably well-formed epithelioid granulomas, plasma cells; with thyroid follicle damage and collapse
        - Large multinucleated giant cells engulfing colloid

- May progress to fibrosis

e. IgG4-related Thyroiditis

- Rare condition characterised by progressive fibrosis, hardening and enlargement of the thyroid, with adherence to neck structures – this may mimic malignancy clinically. Uncommonly may cause airway obstruction.
- May be associated hypothyroidism.
- Recent literature favours close association with the condition previously known as "Riedel thyroiditis", which is now considered by some to be part of the spectrum of IgG4-related diseases.
- Characterised by infiltration of increased numbers of lymphocytes and IgG4-producing plasma cells, with accompanying fibrosis and obliterative thrombophlebitis.
- Serology:
  - In some cases of Riedel thyroiditis, anti-thyroglobulin and anti-TPO antibodies are present.
  - Serum IgG4 is raised
- Generally responds to corticosteroid therapy.
- Patients also may present with extra-thyroidal manifestations of IgG4-related fibrosclerotic disease e.g. retroperitoneal or mediastinal fibrosis, sclerosing cholangitis, lacrimal or salivary gland disease.

IV. THYROID NEOPLASMS

- Most thyroid nodules are benign and often not neoplastic – e.g. dominant nodule in multinodular goitre, cysts etc.
- Amongst neoplastic nodules, benign neoplasms (10X) > malignant neoplasms.
- Only approximately 1% of solitary thyroid nodules are malignant. Amongst malignancies, most are indolent (slow growing), with a 90% 20-year survival rate in the USA.
- Higher risk of nodules being malignant:
  - Younger patient
  - Solitary nodules
  - Nodule in a male patient
  - History of radiation treatment to head and neck
  - Nonfunctional nodules (i.e. do not take up radioactive iodine)

- Pathogenesis of thyroid neoplasms:
  - Driver mutations (see Table 1) – Four main groups of tumours and sets of mutations, many converging on the receptor tyrosin kinase (RTK) pathway
  - Prior exposure to ionizing radiation (e.g. Chernobyl nuclear disaster in 1986 → increased incidence of PTC in exposed children – rearrangements are the predominant genetic aberration)
  - Dietary deficiency leading to goitre is a potential risk factor for follicular lesions

a. Genetics: Overview

Table 1. Specific sets of driver mutations are associated with specific groups of thyroid neoplasms. Looking from the viewpoint of main tumour groups

Tumour group	Tumour types	Main mutation	Grade	Overall prognosis	Remarks
1. Conventional papillary thyroid carcinoma (PTC)	Conventional PTC; some follicular variant PTCs (infiltrative FVPTC)	- *RET* or *NTRK* gene fusions (e.g. *RET/PTC* fusion*)* - *BRAF* mutation (usually $BRAF^{V600E}$ mutation), in 50-80% of conventional PTC	Low grade	Good	PTC is by far the commonest thyroid malignancy
2. Follicular-patterned neoplasms (Benign to malignant)	Benign: Follicular adenoma (FA) Low risk tumours: Non-invasive follicular thyroid neoplasm with papillary-like nuclear features [NIFTP] Malignant: Follicular carcinoma (FC), some follicular variant PTCs	- *RAS* gain-of-function mutations (30- 50% of FC; 20-40% of FA) - *PAX8/PPARG* translocation (fusion); 20-50% of FC - *PI3K* gain-of-function mutation or *PTEN* loss-of-function mutation (10% follicular carcinoma)	Low grade (includes benign neoplasms too)	Good	Both benign follicular neoplasms (e.g. follicular adenoma) and malignant neoplasms can share mutation profiles
3. High grade carcinoma	- Poorly differentiated carcinoma (PDTC) - Anaplastic/ Undifferentiated thyroid carcinoma (ATC)	- Driver mutations in low grade neoplasms and additional genetic aberrations: - *TP53* mutations	High grade	- Intermediate (PDTC) - Very poor (ATC)	

		- Beta-catenin (*CTNNB1*) mutation and – *TERT* mutation			
4. Medullary thyroid carcinoma (MTC)		- *RET* activating point mutations (germline mutations in MEN-2 syndrome; sporadic mutations in nonfamilial MTC)		Intermediate	

b. Thyroid Adenomas

Benign neoplasms that arise from follicular cells. Commonest type is the follicular adenoma, and less commonly, oncocytic adenoma (formerly also known as "Hurthle cell adenoma").

Most of the time, follicular adenomas do not progress to follicular carcinoma, although a small percentage harbour oncogenic *RAS* mutations or gene fusions similar to those seen in follicular carcinoma.

A complete and intact capsule is an essential diagnostic criterion for follicular adenoma (see below).

- Clinical features
    - Solitary painless thyroid nodule
    - Occasionally causing obstructive symptoms (larger adenomas) e.g. dysphagia
    - Mostly non-functioning – less radioiodine uptake than normal thyroid parenchyma ("cold nodule")
    - Rare – functioning/toxic adenoma – increased secretion of thyroid hormones due to mutations that give rise to autonomous hormone secretion (without TSH stimulation)

- Morphology:
    - Solitary, spherical, nodule with an intact capsule
    - Tumour bulges out from the cut surface; colour ranges from whitish to reddish brown
    - Secondary change e.g. haemorrhage, cystic change, fibrosis and calcification may also occur
    - Microscopy:

- Follicular architecture that appears distinct from surrounding thyroid parenchyma, often with microfollicles predominating, containing scant colloid. There may be a mixture of micro, normal-sized and macrofollicles.
- Follicular cells are uniform and usually cuboidal.
- No necrosis is seen; and mitoses are very rare.
- Oncocytic adenoma: The follicular cells have abundant eosinophilic granular cytoplasm.
- A well-formed, completely intact fibrous capsule is present around the whole nodule, with no evidence of capsular invasion or vascular invasion (only vessels within or outside the capsule are included).

- Treatment:
  - Complete excision, with complete microscopic examination of the capsule, to confirm the absence of invasion

c. Well-differentiated (Low grade) Thyroid Carcinoma: *Papillary carcinoma, Follicular carcinoma*

Two commonest thyroid malignancies are well differentiated, and they are:

1. Papillary thyroid carcinoma (PTC)
2. Follicular carcinoma (FC)

These have an excellent prognosis (>95% 5-year survival).

1. Papillary thyroid carcinoma

Commonest thyroid cancer (85% of cases in USA), increasing incidence because of increased detection of incidental tumours

Many subtypes, e.g. Classic PTC, Encapsulated classic PTC; follicular variant PTC (FVPTC – infiltrative subtype vs invasive encapsulated FVPTC); tall cell PTC etc.

- Epidemiology:
  - Most frequent age 25 – 50y, and may occur in childhood
  - May be associated with exposure to ionizing radiation

- Clinical features:
  - Usually thyroid nodule (self-palpated or incidental) – move with swallowing
  - Sometimes present with an enlarged cervical lymph node (harboring metastatic disease, which may be cystic) – PTC metastasizes via lymphatics preferentially rather than via the haematogenous route
  - Advanced disease may present with hoarseness, dysphagia, cough or dyspnoea

- Morphology:

- Solitary or multifocal
- May be well-circumscribed/encapsulated or infiltrative with ill-defined margins
- Gross cut surface often whitish, may have visible papillary foci
- Microscopy:
  - Classic PTC: Branching finger-like papillae with fibrovasculare cores, covered by cuboidal to columnar cells with classical nuclear features
  - Diagnostic nuclear features: enlarged, oval nuclei with finely dispersed, ground-glass chromatin (called "Orphan Annie eye nuclei"); longitudinal nuclear grooves and nuclear pseudoinclusions (infoldings of the nuclear membrane)
  - Occasional psammoma bodies (within cores of papillae) – concentric calcifications
  - Lymphatic invasion may be present, with nodal metastases
- Subtypes:
- Encapsulated classic PTC: Features of classic PTC but surrounded by a thick fibrous capsule, which may be intact or show invasion by tumour (excellent prognosis)
- Follicular variant PTC (FVPTC): 2 subtypes
  - Infiltrative FVPTC: Follicular architecture, but with classical nuclear features of PTC (mutation profile and behaviour similar to classic PTC)
  - Invasive encapsulated FVPTC: Encapsulated tumour with capsular or vascular invasion, with follicular architecture and nuclear features of PTC (mutation profile and behaviour similar to FC rather than PTC)
- Tall cell PTC: Tall columnar cells with eosinophilic cytoplasm; associated with higher incidence of extrathyroidal extension, lymphovascular invasion and distant metastases (often harbour both *BRAF* mutations and *RET/PTC* translocations)

- Prognosis:
  - Excellent, 10-year survival rate >95%
  - Even presence of isolated regional nodal metastases does not adversely impact prognosis
  - 5 – 20% develop regional recurrence
  - 10 – 15% have distant metastases
  - Less favorable prognosis: 40y age, extrathyroidal extension and distant metastases

2. Follicular carcinoma

5 – 15% of primary thyroid malignancies; higher incidence in areas with dietary iodine deficiency.

Three subtypes: Minimally invasive FC (MIFC) (commonest subtype); encapsulated angioinvasive FC (EAFC); widely invasive FC (WIFC)

- Epidemiology:
  - Women 3X > Men
  - Most frequent age 40 – 60y

- Clinical features:

  - Slowly enlarging painless nodule (cold nodule on scintigram usually; rarely warm)
  - Metastasizes preferentially via bloodstream (not lymphatics), hence may present with distan metastases to bone, lungs etc, rather than nodal metastases

- Morphology:
  - Solitary nodule – most often well-circumscribed and encapsulated (MIFC, EAFC), and occasionally widely infiltrative without clear cut original capsule (WIFC)
  - WIFC may also be adherent to and invade surrounding neck structures
  - Cut surface is tan or pinkish; secondary changes may be seen (e.g. haemorrhage, fibrosis, calcification)
  - Microscopy:
    - Small follicular structures lined by uniform cells that appear similar to normal follicular cells
    - Nuclei do not show features of PTC
    - Note: Architectural and nuclear features may be identical to FA – the only difference being the presence of capsular or vascular invasion in MIFC and EAFC
    - WIFC: obvious infiltrative growth beyond capsular of tumour into thyroid and often into extrathyroidal tissues

- Prognosis:
  - Depends on subtype – MIFC has the best prognosis (no angioinvasion)
  - MIFC: Excellent, 10-year survival rate >90%; WIFC: up to 50% die of disease within 10 years

- Treatment:
  - Total thyroidectomy most often, followed by radioactive iodine

d. Poorly Differentiated Thyroid Carcinoma

Aggressive behaviour, but uncommon.

- Epidemiology:
  - Older age group, mean age 65y
  - Past history of well differentiated (low grade) thyroid carcinoma (e.g. PTC, FC) may be present

- Clinical features:
  - Enlarging thyroid nodule
  - May have obstructive symptoms e.g. hoarseness, dysphagia, cough or dyspnoea
  - Sometimes present with metastatic disease

- Morphology:
  - Solid mass, usually large, may have irregular borders and necrosis

- Microscopy:
  - Histologic diagnosis is based on Turin criteria
  - Architecture often trabecular/**insular** (large solid islands)
  - Increased **mitotic cou**nts or **tumour necrosis**
  - Some have features of well differentiated thyroid carcinoma, but with increased mitoses or necrosis

- Prognosis:
  - Overall 5 year survival 60- 70%

e. Anaplastic Thyroid Carcinoma

Uncommon, with very poor prognosis, progressing to death within 1 year.

- Epidemiology:
  - Elderly patients, mean age 65y
  - May be associated with past history of well differentiated thyroid carcinoma

- Clinical features:
  - Rapidly enlarging thyroid mass
  - Hoarseness, dysphagia, cough or dyspnoea
  - May present with metastatic disease

- Morphology:
  - Usually large bulky tumour, infiltrating into surrounding tissues in neck
  - May have necrosis
  - Microscopy:
    - Highly pleomorphic cells (not recognisable as follicular cells), usually no longer forming follicular structures; no papillary architecture
    - Cells may be spindle (resembling high grade sarcoma); giant pleomorphic cells or squamous-appearing
    - Heterologous differentiation may be present (e.g. bone, cartilage differentiation)
    - Necrosis, vascular invasion, frequent mitoses including abnormal mitoses

- Prognosis:
  - Very poor, median survival several months (usually < 1y)
  - Some tumours respond to targeted therapy e.g. tumours with *BRAF* V600E mutation may respond to BRAF and MEK inhibitors

f. Medullary Carcinoma

Malignancy arising from parafollicular C cells, and hence cells secrete calcitonin. Tumour cells sometimes also secrete serotonin, ACTH and vasoactive intestinal peptide (VIP)

- Epidemiology:
  - Approximately 5% of thyroid neoplasms
  - 70% sporadic – peak incidence 40 – 50y
  - 30% familial, associated with MEN-2A or MEN-2B syndrome – younger patients, including children <10y

- Clinical features:
  - Thyroid mass, +/- obstructive symptoms
  - Paraneoplastic manifestations may be present – e.g. diarrhoea (VIP secretion), Cushing syndrome (ACTH secretion)
  - Raised serum calcitonin (helpful in diagnosis and post-operative follow-up), but usually not associated with hypocalcaemia
  - CEA level may also be raised
  - Familial MTC – other endocrine neoplasms e.g. parathyroid or adrenal neoplasms
  - Spread both via lymphatics (regional lymph nodes) and bloodstream (distant metastases)

- Morphology:
  - Solitary (sporadic) or multifocal (familial)
  - Firm, grey-tan cut surface, infiltrative
  - Larger tumours – may exhibit necrosis, haemorrhage, extrathyroidal extension
  - Microscopy:
    - Cells arranged in nests, trabeculae, follicle-like structures
    - Polygonal to spindle cells with round to ovoid nuclei containing stippled “salt and pepper” chromatin (granular chromatin with both fine and coarse granularity)
    - Amyloid (glassy eosinophilic extracellular material) may be present in some tumours
    - Familial MEN-syndrome associated MTC – there may be multicentric C cell hyperplasia in the surrounding thyroid parenchyma

- Prognosis:
  - MTC in MEN-2B are more aggressive, metastasize more frequently than MEN-2A or sporadic tumours
  - Some RET tyrosine kinase inhibitors may be effective in treatment

g. Lymphoma (Primary lymphoma of the thyroid)

Approximately 4-5% of all thyroid malignancies. Usually B cell lymphomas – most commonly diffuse large B cell lymphoma and marginal zone/MALT (mucosa-associated lymphoid tissue) lymphoma.

Thyroid glands may also infrequently be the site of secondary involvement of lymphoma originating outside the thyroid.

- Epidemiology:
  - Elderly patients
  - Predominantly women (75%)
  - Frequently history of longstanding Hashimoto thyroiditis and sometimes lymphocytic thyroiditis

- Clinical features:
  - Progressively enlarging thyroid mass, +/- obstructive symptoms
  - Background history of Hashimoto thyroiditis frequently present
  - Hypothyroidism may be present

- Morphology:
  - Pale whitish areas in enlarged thyroid gland, soft, ill-defined
  - Fish-flesh appearance
  - Microscopy:
    - Sheets of lymphocytes infiltrating into thyroid parenchyma – specific appearance depends on which lymphoma type

- Prognosis:
  - Depends on type of lymphoma – MALT lymphoma has better prognosis than diffuse large B cell lymphoma