Thyroid

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The Thyroid Gland

Named after the thyroid cartilage

(Greek: Shield-shaped)
The Thyroid Gland

- Vercelloni 1711: “a bag of worms” whose eggs pass into the esophagus for digestive purposes

- Parry 1825: “a vascular shunt” to cushion the brain from sudden increases in blood flow
Thyroid Embryology

- Medial portion of thyroid gland
  - Arises from the endodermal tissue of the base of tongue posteriorly, the foramen cecum - **lack of migration results in a retrolingual mass**
  - Attached to tongue by the thyroglossal duct - lack of atrophy after thyroid descent results in midline cyst formation (thyroglossal duct cyst)
  - Descent occurs about fifth week of fetal life - remnants may persist along track of descent

- Lateral lobes of thyroid gland
  - Derived from a portion of ultimobranchial body, part of the fifth branchial pouch from which C cells are also derived (calcitonin secreting cells)
Lingual Thyroid (failure of descent)

Verification that lingual mass is thyroid by its ability to trap I^{123}

Significance: May be only thyroid tissue in body (~70% of time), removal resulting in hypothyroidism; treatment consists of TSH suppression to shrink size
Anatomy, physiology and pathology of the thyroid gland
Anatomy
Thyroid Anatomy

Brownish-red and soft during life Usually weighs about 25-30g (larger in women)
Surrounded by a thin, fibrous capsule of connective tissue
External to this is a “false capsule” formed by pretracheal fascia

Right and left lobes
United by a narrow isthmus, which extends across the trachea anterior to second and third tracheal cartilages

In some people a third “pyramidal lobe” exists, ascending from the isthmus towards hyoid bone
Position and relations

- Clasps anterior and lateral surface of *pharynx, larynx, oesophagus and trachea* “like a shield”
- Lies deep to *sternothyroid* and *sternohyoid* muscles
- *Parathyroid glands* usually lie between posterior border of thyroid gland and its sheath (usually 2 on each side of the thyroid), often just lateral to anastomosis between vessel joining superior and inferior thyroid arteries
- *Internal jugular vein* and *common carotid artery* lie postero-lateral to thyroid
**Position and relations**

- **Recurrent laryngeal nerve** is an important structure lying between trachea and thyroid
  - may be injured during thyroid surgery → ipsilateral VC paralysis, hoarse voice
- Each lobe
  - pear-shaped and ~5cm long
  - extends inferiorly on each side of trachea (and oesophagus), often to level of 6th tracheal cartilage
- Attached to arch of cricoid cartilage and to oblique line of thyroid cartilage
  - moves up and down with swallowing and oscillates during speaking
Arterial supply

- highly vascular
- main supply from *superior and inferior thyroid arteries*
  - lie between capsule and pretracheal fascia (false capsule)
- all thyroid arteries anastomose with one another on and in the substance of the thyroid, but little anastomosis across the median plane (except for branches of superior thyroid artery)
Arterial supply

- **superior thyroid artery**
  - first branch of ECA
  - descends to superior pole of gland, pierces pretracheal fascia then divides into 2-3 branches

- **inferior thyroid artery**
  - branch of thyro-cervical trunk
  - runs superomedially posterior to carotid sheath
  - reaches posterior aspect of gland
  - divides into several branches which pierce pretracheal fascia to supply inferior pole of thyroid gland
  - intimate relationship with recurrent laryngeal nerve
  - in ~10% of people the **thyroid ima artery** arises from aorta, brachiocephalic trunk or ICA, ascends anterior to trachea to supply the isthmus
Venous drainage

- usually 3 pairs of veins drain venous plexus on anterior surface of thyroid
  - superior thyroid veins drain superior poles
  - middle thyroid veins drain lateral parts
    - superior and middle thyroid veins empty into internal jugular veins
  - inferior thyroid veins drain inferior poles
    - empty into brachio-cephalic veins
    - often unite to form a single vein that drains into one or other brachio-cephalic vein
Lymphatic drainage

- Lymphatics run in the interlobular connective tissue, often around arteries
- Communicate with a capsular network of lymph vessels
- Pass to prelaryngeal LN’s → pretracheal and paratracheal LN’s
- Lateral lymphatic vessels along superior thyroid veins pass to deep cervical LN’s
- Some drainage directly into brachio-cephalic LN’s or directly into thoracic duct
Lymph nodes of the neck
Innervation

- nerves derived from superior, middle and inferior cervical sympathetic ganglia – reach thyroid through cardiac and laryngeal branches of vagus nerve which accompany arterial supply
- postganglionic fibres and vasomotor – indirect action on thyroid by regulating blood vessels
Histology
The thyroid gland is composed of 2 lobes connected by an **isthmus**.

It is surrounded by a dense irregular collagenous connective tissue capsule, in which (posteriorly) the **parathyroid glands** are embedded.

The thyroid gland is subdivided by capsular septa into lobules containing **follicles**.

These septa also serve as conduits for blood vessels, lymphatic vessels, & nerves.
Thyroid follicles are spherical structures filled with colloid, a viscous gel consisting mostly of iodinated thyroglobulin.

- Thyroid follicles are enveloped by a layer of epithelial cells, called follicular cells, which in turn are surrounded by parafollicular cells. These 2 parenchymal cell types rest on a basal lamina, which separates them from the abundant network of fenestrated capillaries in the connective tissue.

- **Function.** Thyroid follicles synthesize & store thyroid hormones.
Follicular cells are normally **cuboidal** in shape but become **columnar** when stimulated & **squamous** when inactive.

Follicular cells contain many small **apical vesicles**, involved in transport & release of thyroglobulin & into the colloid.
Follicles: the Functional Units of the Thyroid Gland

Follicles Are the Sites Where Key Thyroid Elements Function:
- Thyroglobulin (Tg)
- Tyrosine
- Iodine
- Thyroxine ($T_4$)
- Triiodothyronine ($T_3$)
**Follicular Cells**

- **Synthesis & release** of the thyroid hormones throxine ($T_4$) & triiodothyronine ($T_3$)

  - Thyroglobulin is synthesized like other secretory proteins.
  
  - Circulating iodide is actively transported into the cytosol, where a thyroid peroxidase oxidizes it & iodinates tyrosine residues on the thyroglobulin molecule; iodination occurs mostly at the apical plasma membrane.
  
  - A rearrangement of the iodinated tyrosine residues of thyroglobulin in the colloid produces the iodothyronines $T_4$ & $T_3$. 
Follicular Cells

- Binding of thyroid-stimulating hormone to receptors on the basal surface stimulates follicular cells to become columnar & to form apical pseudopods, which engulf colloid by endocytosis.

- After the colloid droplets fuse with lysosomes, controlled hydrolysis of iodinated thyroglobulin liberates $T_3$ & $T_4$ into the cytosol.

- These hormones move basally & are released basally into the bloodstream & lymphatic vessels.

- These processes are promoted by **TSH**, which binds to G-protein-linked receptors on the basal surface of follicular cells.
Parafollicular Cells

- **Parafollicular cells** are also called **clear (C) cells** because they stain less intensely than thyroid follicular cells.

- They synthesize & release **calcitonin**, a polypeptide hormone, in response to high blood calcium levels.
Thyroid Physiology
The Thyroid Produces and Secretes 2 Metabolic Hormones

- Two principal hormones
  - Thyroxine ($T_4$) and triiodothyronine ($T_3$)
    - Required for homeostasis of all cells
    - Influence cell differentiation, growth, and metabolism
    - Considered the major metabolic hormones because they target virtually every tissue
TRH

- Produced by Hypothalamus
- Release is pulsatile, circadian
- Downregulated by $T_3$
- Travels through portal venous system to adenohypophosphysis
- Stimulates TSH formation
Thyroid-Stimulating Hormone (TSH)

- Upregulated by TRH
- Downregulated by T4, T3
- Travels through portal venous system to cavernous sinus, body.
- Stimulates several processes
  - Iodine uptake
  - Colloid endocytosis
  - Growth of thyroid gland
- Produced by Adenohypophysis Thyrotrophs
Hypothalamic-Pituitary-Thyroid Axis
Negative Feedback Mechanism
Biosynthesis of $T_4$ and $T_3$

The process includes:

- Dietary iodine (I) ingestion
- Active transport and uptake of iodide (I⁻) by thyroid gland
- Oxidation of I⁻ and iodination of thyroglobulin (Tg) tyrosine residues
- Coupling of iodotyrosine residues (MIT and DIT) to form $T_4$ and $T_3$
- Proteolysis of Tg with release of $T_4$ and $T_3$ into the circulation
Iodine Sources

- Available through certain foods (eg, seafood, bread, dairy products), iodized salt, or dietary supplements, as a trace mineral
- The recommended minimum intake is 150 µg/day
Active Transport and $I^-$ Uptake by the Thyroid

- Dietary iodine reaches the circulation as iodide anion ($I^-$).
- The thyroid gland transports $I^-$ to the sites of hormone synthesis.
- $I^-$ accumulation in the thyroid is an active transport process that is stimulated by TSH.
Oxidation of I\(^-\) and Iodination of Thyroglobulin (Tg) Tyrosyl Residues

- I\(^-\) must be oxidized to be able to iodinate tyrosyl residues of Tg
- Iodination of the tyrosyl residues then forms monoiiodotyrosine (MIT) and diiodotyrosine (DIT), which are then coupled to form either T\(_3\) or T\(_4\)
- Both reactions are catalyzed by TPO
Thyroperoxidase (TPO)

- TPO catalyzes the oxidation steps involved in I⁻ activation, iodination of Tg tyrosyl residues, and coupling of iodotyrosyl residues
- TPO has binding sites for I⁻ and tyrosine
- TPO uses H₂O₂ as the oxidant to activate I⁻ to hypoiiodate (OI⁻), the iodinating species
Proteolysis of Tg With Release of T₄ and T₃

- T₄ and T₃ are synthesized and stored within the Tg molecule.
- Proteolysis is an essential step for releasing the hormones.
- To liberate T₄ and T₃, Tg is resorbed into the follicular cells in the form of colloid droplets, which fuse with lysosomes to form phagolysosomes.
- Tg is then hydrolyzed to T₄ and T₃, which are then secreted into the circulation.
Conversion of T₄ to T₃ in Peripheral Tissues
Production of $T_4$ and $T_3$

- $T_4$ is the primary secretory product of the thyroid gland, which is the only source of $T_4$.
- The thyroid secretes approximately 70-90 $\mu$g of $T_4$ per day.
- $T_3$ is derived from 2 processes:
  - The total daily production rate of $T_3$ is about 15-30 $\mu$g.
  - About 80% of circulating $T_3$ comes from deiodination of $T_4$ in peripheral tissues.
  - About 20% comes from direct thyroid secretion.
T₄: A Prohormone for T₃

- T₄ is biologically inactive in target tissues until converted to T₃
  - Activation occurs with 5' iodination of the outer ring of T₄
- T₃ then becomes the biologically active hormone responsible for the majority of thyroid hormone effects
Sites of $T_4$ Conversion

- The liver is the major extrathyroidal $T_4$ conversion site for production of $T_3$
- Some $T_4$ to $T_3$ conversion also occurs in the kidney and other tissues
T₄ Disposition

• Normal disposition of T₄
  – About 41% is converted to T₃
  – 38% is converted to reverse T₃ (rT₃), which is metabolically inactive
  – 21% is metabolized via other pathways, such as conjugation in the liver and excretion in the bile

• Normal circulating concentrations
  – T₄ 4.5-11 µg/dL
  – T₃ 60-180 ng/dL (~100-fold less than T₄)
Hormonal Transport
Carriers for Circulating Thyroid Hormones

• More than 99% of circulating T<sub>4</sub> and T<sub>3</sub> is bound to plasma carrier proteins
  – Thyroxine-binding globulin (TBG), binds about 75%
  – Transthyretin (TTR), also called thyroxine-binding prealbumin (TBPA), binds about 10%-15%
  – Albumin binds about 7%
  – High-density lipoproteins (HDL), binds about 3%

• Carrier proteins can be affected by physiologic changes, drugs, and disease
Free Hormone Concept

• Only unbound (free) hormone has metabolic activity and physiologic effects
  – Free hormone is a tiny percentage of total hormone in plasma (about 0.03% T₄; 0.3% T₃)
• Total hormone concentration
  – Normally is kept proportional to the concentration of carrier proteins
  – Is kept appropriate to maintain a constant free hormone level
Changes in TBG Concentration Determine Binding and Influence $T_4$ and $T_3$ Levels

- **Increased TBG**
  - Total serum $T_4$ and $T_3$ levels increase
  - Free $T_4$ ($FT_4$), and free $T_3$ ($FT_3$) concentrations remain unchanged

- **Decreased TBG**
  - Total serum $T_4$ and $T_3$ levels decrease
  - $FT_4$ and $FT_3$ levels remain unchanged
Drugs and Conditions That Increase Serum $T_4$ and $T_3$ Levels by Increasing TBG

- **Drugs that increase TBG**
  - Oral contraceptives and other sources of estrogen
  - Methadone
  - Clofibrate
  - 5-Fluorouracil
  - Heroin
  - Tamoxifen

- **Conditions that increase TBG**
  - Pregnancy
  - Infectious/chronic active hepatitis
  - HIV infection
  - Biliary cirrhosis
  - Acute intermittent porphyria
  - Genetic factors
Drugs and Conditions That Decrease Serum $T_4$ and $T_3$ by Decreasing TBG Levels or Binding of Hormone to TBG

- **Drugs that decrease serum $T_4$ and $T_3$**
  - Glucocorticoids
  - Androgens
  - L-Asparaginase
  - Salicylates
  - Mefenamic acid
  - Antiseizure medications, eg, phenytoin, carbamazepine
  - Furosemide

- **Conditions that decrease serum $T_4$ and $T_3$**
  - Genetic factors
  - Acute and chronic illness
Wolff-Chaikoff Effect

- Increasing doses of I\(^-\) increase hormone synthesis initially.
- Higher doses cause cessation of hormone formation.
- This effect is countered by the Iodide leak from normal thyroid tissue.
- Patients with autoimmune thyroiditis may fail to adapt and become hypo-thyroid.
Jod-Basedow Effect

- Opposite of the Wolff-Chaikoff effect
- Excessive iodine loads induce hyperthyroidism
- Observed in hyperthyroid disease processes
  - Graves’ disease
  - Toxic multinodular goiter
  - Toxic adenoma
- This effect may lead to symptomatic thyrotoxicosis in patients who receive large iodine doses from
  - Dietary changes
  - Contrast administration
  - Iodine containing medication (Amiodarone)
Perchlorate

- $\text{ClO}_4^-$ ion inhibits the $\text{Na}^+ / \text{I}^-$ transport protein.
- Normal individuals show no leak of $\text{I}^{123}$ after $\text{ClO}_4^-$ due to organification of $\text{I}^-$ to MIT / DIT
- Patients with organification defects show loss of RAIU.
- Used in diagnosis of Pendred syndrome
Thyroid Hormone Action
Thyroid Hormone Plays a Major Role in Growth and Development

- Thyroid hormone initiates or sustains differentiation and growth
  - Stimulates formation of proteins, which exert trophic effects on tissues
  - Is essential for normal brain development
- Essential for childhood growth
  - Untreated congenital hypothyroidism or chronic hypothyroidism during childhood can result in incomplete development and mental retardation
Thyroid Hormones and the Central Nervous System (CNS)

• Thyroid hormones are essential for neural development and maturation and function of the CNS

• Decreased thyroid hormone concentrations may lead to alterations in cognitive function
  – Patients with hypothyroidism may develop impairment of attention, slowed motor function, and poor memory
  – Thyroid-replacement therapy may improve cognitive function when hypothyroidism is present
Thyroid hormone influences cardiovascular hemodynamics. Thyroid hormone mediated thermogenesis (Peripheral Tissues) leads to release of metabolic endproducts. This results in local vasodilation, decreased systemic vascular resistance, and increased cardiac output. Elevated blood volume further contributes to increased cardiac output. T3 influences cardiac chronotropy and inotropy, leading to decreased diastolic blood pressure.

Thyroid Hormone Influences the Female Reproductive System

- Normal thyroid hormone function is important for reproductive function
  - Hypothyroidism may be associated with menstrual disorders, infertility, risk of miscarriage, and other complications of pregnancy

Thyroid Hormone is Critical for Normal Bone Growth and Development

- $T_3$ is an important regulator of skeletal maturation at the growth plate
  - $T_3$ regulates the expression of factors and other contributors to linear growth directly in the growth plate
  - $T_3$ also may participate in osteoblast differentiation and proliferation, and chondrocyte maturation leading to bone ossification
Thyroid Hormone Regulates Mitochondrial Activity

- $T_3$ is considered the major regulator of mitochondrial activity
  - A potent $T_3$-dependent transcription factor of the mitochondrial genome induces early stimulation of transcription and increases transcription factor (TFA) expression
  - $T_3$ stimulates oxygen consumption by the mitochondria
Thyroid Hormones Stimulate Metabolic Activities in Most Tissues

- Thyroid hormones (specifically T<sub>3</sub>) regulate rate of overall body metabolism
  - T<sub>3</sub> increases basal metabolic rate
- Calorigenic effects
  - T<sub>3</sub> increases oxygen consumption by most peripheral tissues
  - Increases body heat production
Metabolic Effects of T₃

- Stimulates lipolysis and release of free fatty acids and glycerol
- Induces expression of lipogenic enzymes
- Effects cholesterol metabolism
- Stimulates metabolism of cholesterol to bile acids
- Facilitates rapid removal of LDL from plasma
- Generally stimulates all aspects of carbohydrate metabolism and the pathway for protein degradation
Evaluation Of Thyroid

[Diagram of thyroid gland with annotations:]
- Isthmus
- 4 cm long
- 2 cm wide
- ~2 cm thick
History

- Age
- Gender
- Exposure to Radiation
- Signs/symptoms of hyper- / hypo-thyroidism
- Rapid change in size
  - With *pain* may indicate hemorrhage into nodule
  - Without pain may be bad sign
History

- **Gardner Syndrome** (familial adenomatous polyposis)
  - Association found with thyroid ca
  - Mostly in young women (94%) (RR 160)
  - Thyroid ca preceded dx of Garners 30% of time

- **Cowden Syndrome**
  - Mucocutaneous hamartomas, keratoses, fibrocystic breast changes & GI polyps
  - Found to have association with thyroid ca (8/26 patients in one series)
History

- Familial h/o medullary thyroid carcinoma
  - Familial MTC vs MEN II
- Family hx of other thyroid ca
- H/o Hashimoto’s thyroiditis (lymphoma)
History

- History elements suggestive of malignancy:
  - Progressive enlargement
  - Hoarseness
  - Dysphagia
  - Dyspnea
  - High-risk (fam hx, radiation)

- Not very sensitive / specific
Disorders of the Thyroid Gland

Physical Examination of the Thyroid Gland

- **Inspection**
  - Glass of water for swallowing

- **Palpation**
  - Anteriorly
  - From behind

*Each lobe measures: vertical dimension – 2 cm*
*horizontal dimension – 1 cm*
FEELING THE ISTMUS

FEELING THE LATERAL LOBES
Thyroid Palpation

- Texture - soft / firm / hard
- Surface - smooth / seedy / lumpy
- Shape - diffuse / nodular
- Presence of regional adenopathy
Physical

- Complete Head & Neck exam
- Vocal cord mobility (?Strobe)
- Palpation thyroid
- Cervical lymphadenopathy
- Ophthalmopathy
Physical

- Physical findings suggestive of malignancy:
  - Fixation
  - Adenopathy
  - Fixed cord
  - Induration
  - Stridor

- Not very sensitive / specific
Graves Ophthalmopathy
Neck Bruising

- Suggests hemorrhage into nodule
Lingual Thyroid
Workup
Serum Testing

- **TSH** – first-line serum test
  - Identifies subclinical thyrotoxicosis
- **T4, T3**
- **Calcium**
- **Thyroglobulin**
  - Post-treatment good to detect recurrence
- **Calcitonin** – only in cases of medullary
- **Antibodies** – Hashimoto’s
- **RET proto-oncogene**
Flow Chart

Serum TSH

- High
  - R/I Hypothyroidism
    - T₄ (FT₄I)
      - Normal
      - Low
        - Subclinical Hypothyroidism
        - Hypothyroidism

- Normal
  - Euthyroid

- Low
  - R/I Hyperthyroidism
    - T₄ (T₃), FT₄I (FT₃I)
      - Normal
      - High
        - Subclinical Hyperthyroidism
        - Hyperthyroidism
Imaging
Plain Films

- Not routinely ordered
- May show:
  - Tracheal deviation
  - Pulmonary metastasis
  - Calcifications (suggests papillary or medullary)
Tracheal Deviation
Thyroid ultrasound uses high frequency sound waves to make a picture of the thyroid gland.
Thyroid ultrasound
Ultrasonography

- Thyroid vs. non-thyroid
  - Good screen for thyroid presence in children
- Cystic vs. solid
- Localization for FNA or injection
- Serial exam of nodule size
  - 2-3 mm lower end of resolution
- May distinguish solitary nodule from multinodular goiter
  - Dominant nodule risks no different
Ultrasonography

- Findings suggestive of malignancy:
  - Presence of halo
  - Irregular border
  - Presence of cystic components
  - Presence of calcifications
  - Heterogeneous echo pattern
  - Extrathyroidal extension

- No findings are definitive
Nuclear Medicine

- Concept
- Uses
  - Metabolic studies
  - Imaging
- Iodine is taken up by gland and *organified*
- Technetium trapped but not organified
- Usually only for papillary and follicular
- Rectilinear scanner (historical interest) vs. scintillation camera
Nuclear Medicine

Diagram:
- Uptake Probe Assembly
- Cable to electronics
- Shielding
- Photomultiplier tube
- Scintillating crystal
- Level of crystal surface
- Collimator
- 30 cm (11.8 in)
- Surface of phantom or patient's neck
- Phantom or patient's neck
- 20 cm (7.9 in)
- Penumbra

Image: A medical professional holding a nuclear medicine equipment over a patient.
Rectilinear Scan

- Provided life-size images
- Not common today
Nuclear Medicine

- Radioisotopes:
  - I-131
  - I-123
  - I-125
  - Tc-99m
  - Thallium-201
  - Gallium 67
Nuclear Medicine

- **Technetium 99m**
  - Most commonly used isotope (some authors)
  - 99m: “m” refers to metastable nuclide
    - Decay product of Molybdenum-99
    - Long half-life before decaying into Tc-99
  - Administered as pertechnate (TcO4⁻)
  - Images can be obtained quickly
    - “One-Stop” evaluation
  - Hot nodules need f/u Iodine scan
    - Discordant nodules higher risk of malignancy
Nuclear Medicine

- **Iodine**
  - **127** – only stable isotope of iodine
  - **123** – cyclotron product
    - Half-life 13.3 hr
    - Expensive, limited availability
    - Low radiation-exposure to patient
  - **131** – fission product
    - Half-life 8 days
    - Cheap, widely available
    - Better for mets (diagnostic and therapeutic) (high radiation exposure)
  - **125** – no longer used
    - Long half-life (60 days); high radiation exposure with poor visualization
Radioactive iodine uptake and scan

- Radio labeled Iodine (I-123) is given to the patient which is actively trapped and concentrated by the thyroid gland.

- It can assess:
  - Function → Uptake
  - Morphology → Scan
Radioactive iodine “uptake”

- **Uptake:**
  - Measurements of % of the administered dose localizing to the gland at a fixed time.
  - Reflects gland function.
  - Normal 24 hour uptake is ~10 to 30%.
Tc-99m versus I-123
Radioactive iodine "scan"
Combining “uptake” and “scan”

Any nodules can be “Hot”, “Warm”, or “Cold” depending on the intensity of the uptake.
Hot Nodule
Hot nodule

- Left lobe
- Right lobe
- Isthmus
- 'Hot' nodule
Cold nodule
Multinodular Goiter

Nuclear Medicine Thyroid Scan

Abnormally Decreased Uptake

Enlarged Thyroid Gland

Abnormally Increased Uptake
Radioactive iodine uptake and scan

- “Hot” nodules (autonomously functioning thyroid nodules) are usually not malignant, for practical purposes.
- “Cold” nodules (either hypofunctioning or nonfunctioning) can be malignant in approximately 5-8% of cases.
Nuclear Medicine

- **Thallium-201**
  - Expensive, role poorly defined
  - Can detect (but not treat) mets
  - Not trapped or organified – mechanism unclear
    - Potassium analogue
  - Potential advantages:
    - Not necessary to be off thyroid replacement
    - Patients with large body iodine pool (ex: recent CT with contrast) or hypofunctioning gland
    - Can sometimes image medullary
Nuclear Medicine

- **Gallium-67**
  - Generally lights up inflammation
    - Hashimoto’s
  - Uses in thyroid imaging limited
    - Anaplastic
    - Lymphoma
Nuclear Medicine

- Other imaging agents
  - Tc-99m sestamibi
  - Tc-99m pentavalent DMSA
  - Radioiodinated MIBG
    - Developed for medullary (APUD derivative)
  - Radiolabeled monoclonal antibodies
Nuclear Medicine

- Hurthle-cell neoplasms
  - Better imaged with Technetium sestamibi
    - Concentrates in mitochondria
  - Poorly imaged with iodine
Other Imaging Modalities

- CT
  - Keep in mind iodine in contrast
- MRI
- PET

- Not first-line, but may be adjunctive
MRI
Fine Needle Aspiration (FNA)
US Guided FNA
Fine-Needle Aspiration Biopsy

- Technique:
  - 25-gauge needle
  - Multiple passes
  - Ideally from periphery of lesion
  - Reaspirate after fluid drawn
  - Immediately smeared and fixed
  - Papanicolaou stain common
Fine-needle aspiration (FNA) biopsy
FNA biopsy

Source: Thyroid Disease Manager
FNA biopsy

Source: Thyroid Disease Manager
FNA results

- Inadequate specimen
- Adequate specimen
  - Benign
  - Malignant
  - Suspicious
Fine-Needle Aspiration Biopsy

- Emerged in 1970s – has become standard first-line test for diagnosis
- Concept
- Results comparable to large-needle biopsy, less complications
- Safe, efficacious, cost-effective
- Allow preop diagnosis and therefore planning
- Some use for sclerosing nodules
Fine-Needle Aspiration Biopsy

- **Problems:**
  - Sampling error
    - Small (<1 cm)
    - Large (>4 cm)
  - Hashimoto’s versus lymphoma
  - Follicular neoplasms
  - Fluid-only cysts
  - Somewhat dependent on skill of cytopathologist
FNA of Papillary Ca

- NG: nuclear grooves
- IC: intranuclear inclusions
Disorders of the Thyroid Gland

- Abnormal thyroid function
  - Hypothyroidism
  - Hyperthyroidism

- Thyroid enlargement

  Structural Thyroid Disease
Abnormal thyroid function

- Hypothyroidism
- Hyperthyroidism
Hypothyroidism

- Hypothyroidism is a disorder with multiple causes in which the thyroid fails to secrete an adequate amount of thyroid hormone.
  - The most common thyroid disorder
  - Usually caused by primary thyroid gland failure
  - Also may result from diminished stimulation of the thyroid gland by TSH
Hyperthyroidism

- Hyperthyroidism refers to excess synthesis and secretion of thyroid hormones by the thyroid gland, which results in accelerated metabolism in peripheral tissues.
## Typical Thyroid Hormone Levels in Thyroid Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>TSH</th>
<th>T&lt;sub&gt;4&lt;/sub&gt;</th>
<th>T&lt;sub&gt;3&lt;/sub&gt;</th>
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<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Low</td>
<td>High</td>
<td>High</td>
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</tbody>
</table>
Clinical Features of Hypothyroidism

- Tiredness
- Forgetfulness/Slower Thinking
- Moodiness/ Irritability
- Depression
- Inability to Concentrate
- Thinning Hair/Hair Loss
- Loss of Body Hair
- Dry, Patchy Skin
- Weight Gain
- Cold Intolerance
- Elevated Cholesterol
- Family History of Thyroid Disease or Diabetes
- Puffy Eyes
- Enlarged Thyroid (Goiter)
- Hoarseness/ Deepening of Voice
- Persistent Dry or Sore Throat
- Difficulty Swallowing
- Slower Heartbeat
- Menstrual Irregularities/ Heavy Period
- Infertility
- Constipation
- Muscle Weakness/ Cramps
Hypothyroidism
Hypothyroid Face

Notice the apathetic facies, bilateral ptosis, and absent eyebrows
Faces of Clinical Hypothyroidism
Hypothyroidism

Clinical Presentations

- Easy fatigability
- Coldness
- Weight gain
- Constipation
- Menstrual irregularities
- Muscle cramps
- Hair loss
- Difficulty concentrating

Clinical Findings

- Skin – cool, rough, dry, yellowish color (carotenemia)
- Face – puffy
- Voice – hoarse
- Reflexes – slow
- Bradycardia
- Peripheral nonpitting edema
Hypothyroidism

- **CVS**:
  - Impaired muscular contraction
  - EKG - bradycardia, low voltage of QRS complexes and P and T waves
  - Echo - cardiac enlargement, pericardial effusion

![EKG and Echo Images]
Hypothyroidism

- **Pulmonary function**:
  - Respirations – shallow and slow
  - Impaired ventilatory response to hypercapnia

- **Anemia**:
  - Impaired Hb synthesis
  - Iron and folate deficiency
  - Pernicious anemia

- **Renal function**:
  - Decreased GFR
  - Impaired ability to excrete water load
Hypothyroidism

- **Neuromuscular system**: 
  - Muscle cramps and weakness
  - Paresthesias
  - Carpal tunnel syndrome

- **CNS symptoms**: 
  - Lethargy
  - Inability to concentrate
  - Depression
Hypothyroidism

Diagnostic Studies

- **Thyroid function tests**
  - TSH, fT4, TT3

- **Thyroid autoantibodies**
  - Anti TPO, Anti Tg

- **Ultrasonography**
  - Enlarged thyroid gland with a diffusely hypoechochogenic pattern

- **Other Laboratory Studies**: Elevated cholesterol and TG, anemia, elevated CPK
Causes of Hypothyroidism

- **Primary** \((\text{fT}_4 \downarrow; \text{TSH} \uparrow)\)
  - **Autoimmune** (Hashimoto’s) thyroiditis
  - **Iatrogenic:** \(^{131}\text{I}\) treatment, ionizing external irradiation, subtotal or total thyroidectomy
  - **Drugs:** Amiodarone, Lithium, Interferon-\(\alpha\), Interleukin-2
  - **Congenital:** absent or ectopic thyroid gland, dyshormonogenesis, TSH-R mutation
  - **Iodine deficiency**
  - **Infiltrative disorders:** amyloidosis, sarcoidosis, hemochromatosis, scleroderma, cystinosis
Causes of Hypothyroidism

- **Central - Hypothalamic-pituitary dysfunction**
  \[ fT_4 \downarrow; \ TSH \ N/ \downarrow \]
  - Tumors
  - Pituitary surgery or irradiation
  - Infiltrative disorders
  - Trauma
  - Genetic forms of CPHD or isolated TSH deficiency

- **Transient** (fT$_4$ N/↓/↑; TSH ↑/N/↓)
  - Silent thyroiditis including post-partum thyroiditis
Autoimmune (Hashimoto’s) Thyroiditis

- Prevalence
  - 5% - 15% of women
  - 1% - 5% of men

- Sex ratio (F:M) - 8-9:1

- Diagnostic criteria
  - Positive test for thyroid autoantibodies
  - Presence of lymphocytic infiltration of thyroid
  - Goiter
  - Thyroid functions: 50%-75% - euthyroid
    25%-50% - subclinical hypothyroidism
  - 5%-10% - overt hypothyroidism
Autoimmune (Hashimioto’s) Thyroiditis

Associations with other diseases

IDDM (Insulin dependent diabetes mellitus)

Autoimmune polyendocrinopathy diseases

- Type 1: mucocutaneous candidiasis, hypoparathyroidism, Addison’s disease, alopecia, primary hypogonadism …

- Type 2: Addison’s disease, thyroiditis, IDDM …

Pernicious anemia  Turner syndrome (50%)  
Addison’s disease  Down syndrome (20%)  
Myasthenia gravis  Klienfelter syndrome  
Vitiligo  
Celiac disease
Hashimoto’s (Chronic, Lymphocytic)

- Most common cause of hypothyroidism
- Usually non-tender and asymptomatic
- Bossalated
Antibodies in Hashimoto’s

- **Antimicrosomal abys**
  - Against peroxidase

- **Antithyroglobulin abys**
  - Against thyroglobulin

- **Autoantibodies against TSH receptor**
  - Net effect is prevent TSH stimulation of gland
Hashimoto’s Thyroiditis

**Treatment**

- Levothyroxine if hypothyroid
- Triiodothyronine (for myxedema coma)
- Thyroid suppression (levothyroxine) to decrease goiter size
- Surgery for compression or pain or suspicious of malignant
Gross and Microscopic Pathology of Chronic Thyroiditis
Subacute Thyroiditis
DeQuervain’s, Granulomatous

- Most common cause of painful thyroiditis
- Often follows a URI
- FNA may reveal multinucleated giant cells or granulomatous change.
- Course
  - Pain and thyrotoxicosis (3-6 weeks)
  - Asymptomatic euthyroidism
  - Hypothyroid period (weeks to months)
  - Recovery (complete in 95% after 4-6 months)
Subacute Thyroiditis

- **Diagnosis**
  - Elevated ESR
  - Anemia (normochromic, normocytic)
  - Low TSH, Elevated T4 > T3, Low anti-TPO/Tgb
  - Low RAI uptake (same as silent thyroiditis)

- **Treatment**
  - NSAID’s and salicylates.
  - Oral steroids in severe cases
  - Beta blockers for symptoms of hyperthyroidism, Iopanoic acid for severe symptoms
  - PTU not indicated since excess hormone results from leak instead of hyperfunction
  - Symptoms can recur requiring repeat treatment
  - Graves’ disease may occasionally develop as a late sequellae
Histopathology of Subacute Thyroiditis
Silent Thyroiditis

- Silent thyroiditis is termed painless Subacute Thyroiditis Clinical
  - Hyperthyroid symptoms at presentation
  - Progression to euthyroidism followed by hypothyroidism for up to 1 year.
  - Hypothyroidism generally resolves
- Diagnosis
  - May be confused with post-partum Graves’ relapse
- Treatment
  - Beta blockers during toxic phase
  - No anti-thyroid medication indicated
  - Iopanoic acid (Telopaque) for severe hyperthyroidism
  - Thyroid hormone during hypothyroid phase. Must withdraw in 6 months to check for resolution.
Postpartum Thyroiditis

- Underlying autoimmune thyroid disease
- Up to 5% of women 3-6 months after pregnancy
- Transient
- Goiter - painless, small, non-tender, firm, diffuse
- Hyperthyroidism followed by hypothyroidism and resolution within 12 weeks
- Positive antithyroid antibodies; Thyroid scan – no uptake
Postpartum Thyroiditis

- May occur in 5% of women with no known thyroid disease

- Clinically
  - 44% hypothyroid
  - 33% thyrotoxicosis
  - 33% thyrotoxicosis followed by hypothyroidism

- Treatment
  - Thyrotoxic phase – not necessary
  - Hypothyroid phase – levothyroxine
Acute Thyroiditis

- **Causes**
  - 68% Bacterial (S. aureus, S. pyogenes)
  - 15% Fungal
  - 9% Mycobacterial

- **May occur secondary to**
  - Pyriform sinus fistulae
  - Pharyngeal space infections
  - Persistent Thyroglossal remnants
  - Thyroid surgery wound infections (rare)

- **More common in HIV**
Acute Thyroiditis

**Diagnosis**
- Warm, tender, enlarged thyroid
- FNA to drain abscess, obtain culture
- RAI U normal (versus decreased in DeQuervain’s)
- CT or US if infected TGDC suspected

**Treatment**
- High mortality without prompt treatment
- IV Antibiotics
  - Nafcillin / Gentamycin or Rocephin for empiric therapy
- Search for pyriform fistulae (BA swallow, endoscopy)
- Recovery is usually complete
Riedel’s Thyroiditis

- Rare disease involving fibrosis of the thyroid gland

- **Diagnosis**
  - Thyroid antibodies are present in 2/3
  - Painless goiter **“woody”**
  - Open biopsy often needed to diagnose
  - Associated with focal sclerosis syndromes (retroperitoneal, mediastinal, retroorbital, and sclerosing cholangitis)

- **Treatment**
  - Resection for compressive symptoms
  - Chemotherapy with Tamoxifen, Methotrexate, or steroids may be effective
  - Thyroid hormone only for symptoms of hypothyroidism
Histopathology of Riedel’s Thyroiditis
Hypothyroidism

Treatment

- **Overt hypothyroidism**
  - Thyroxine 1.6 mcg/kg/day (100-150 mcg/day)
  - (elderly patients – lower dose)
  - Adjustment: on the basis of TSH levels

- **Sub-clinical / mild hypothyroidism**
  - Thyroxine
    - Symptoms attributable to hypothyroidism
    - TSH > 8 – 10 mU/L
    - Strongly positive thyroid autoantibodies
    - Goiter
  - Surveillance – TSH measurements q 6mo

- **Euthyroid goiter and positive thyroid autoantibodies**
  - Thyroxine
Hypothyroidism

Toxic Effects of Levothyroxine Therapy

- Cardiac symptoms
  (Paroxysmal atrial tachycardia or fibrillation)
- Restlessness and insomnia
- Tremor
- Excessive warmth
- Osteopenia
Hypothyroidism

Course and Prognosis

Treatment of hypothyroidism

Thyroxine - aiming to normalise the serum TSH concentration

Before

After

NB - always check for angina and perform an ECG
Hypothyroidism

Complications

- Myxedema and heart disease
- Neuropsychiatric disease – myxedema madness
- Myxedema coma
- Thyroid lymphoma or carcinoma
Myxedema
Long-standing hypothyroidism

- Stress & starvation decrease thyroid function
  - provoked by sedatives, opioids, illness

- Periorbital edema, facial puffiness, masklike affect
  - also, intense cold intolerance, profound lethargy

- Can progress coma: *a medical emergency*
  - Monitor vital signs & LOC
  - Respiratory support
  - Cardiac monitoring
  - Administer medications IV (Thyroid hormone)
Myxedema Characteristics

- Described as;
- Face is expression less when at rest, puffy, pale, heavy
- Skin of the face is parchment-like.
- In spite of the swelling it may be traced with fine wrinkles,
- Swelling sometimes gives face a round or moonlike appearance
- When spoken to, usually responds with a smile, which spreads after a latent period very slowly over the face.
Myxedema Coma

- The progression of hypothyroid if remained
  - Decreasing mental ability
  - Cardiovascular collapse
  - Severe electrolyte imbalance
  - Cerebral hypoxia (elevated CO2 levels)
  - Comatose
  - Severe hypothermia

- Monitor airway, breathing, circulation
Sick Euthyroid Syndrome

- Background – Acute and severe illness
  No underlying thyroid disease

- Pathogenesis – Release of cytokines

- Thyroid function tests – reduced TT3 and fT3
  increased rT3
  normal TSH and fT4

An adaptive state in order to limit catabolism
Mild Thyroid Failure
Definition of Mild Thyroid Failure

- Elevated TSH level (>4.0 μIU/mL)
- Normal total or free serum $T_4$ and $T_3$ levels
- Few or no signs or symptoms of hypothyroidism
Causes of Mild Thyroid Failure

- **Exogenous factors**
  - Levothyroxine underreplacement
  - Medications, such as lithium, cytokines, or iodine-containing agents (eg, amiodarone)
  - Antithyroid medications
  - $^{131}$I therapy or thyroidectomy

- **Endogenous factors**
  - Previous subacute or silent thyroiditis
  - Hashimoto thyroiditis
Prevalence and Incidence of Mild Thyroid Failure

- **Prevalence**
  - 4% to 10% in large population screening surveys
  - Increases with increasing age
  - Is more common in women than in men

- **Incidence**
  - 2.1% to 3.8% per year in thyroid antibody-positive patients
  - 0.3% per year in thyroid antibody-negative patients

Populations at Risk for Mild Thyroid Failure

- Women
- Prior history of Graves disease or postpartum thyroid dysfunction
- Elderly
- Other autoimmune disease
- Family history of
  - Thyroid disease
  - Pernicious anemia
  - Type 1 Diabetes mellitus

Mild Thyroid Failure Affects Cardiac Function

- Cardiac function is subtly impaired in patients with mild thyroid failure
- Abnormalities can include
  - Subtle abnormalities in systolic time intervals and myocardial contractility
  - Diastolic dysfunction at rest or with exercise
  - Reduction of exercise-related stroke volume, cardiac index, and maximal aortic flow velocity
- The clinical significance of the changes is unclear

Mild Thyroid Failure May Increase Cardiovascular Disease Risk

- Mild thyroid failure has been evaluated as a cardiovascular risk factor associated with
  - Increased serum levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels
  - Reduced high-density lipoprotein cholesterol (HDL-C) levels
  - Increased prevalence of aortic atherosclerosis
  - Increased incidence of myocardial infarction
Four Stages in the Development of Hypothyroidism

<table>
<thead>
<tr>
<th>Stage</th>
<th>FT$_4$</th>
<th>FT$_3$</th>
<th>Consensus for Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Earliest</td>
<td>Normal</td>
<td>Within population reference range</td>
<td>None</td>
</tr>
<tr>
<td>Second</td>
<td>Normal</td>
<td>High (5-10 µIU/mL)</td>
<td>Controversial</td>
</tr>
<tr>
<td>Third</td>
<td>Normal</td>
<td>High (&gt;10 µIU/mL)</td>
<td>Treat with LT$_4^*$</td>
</tr>
<tr>
<td>Fourth</td>
<td>Low</td>
<td>High (&gt;10 µIU/mL)</td>
<td>Uniform: Treat with LT$_4^*$</td>
</tr>
</tbody>
</table>

* Treat if patient falls into predefined categories.

The Rate of Progression of Mild Thyroid Failure to Overt Hypothyroidism

- Mild thyroid failure is a common disorder that frequently progresses to overt hypothyroidism
  - Progression has been reported in about 3% to 18% of affected patients per year
  - Progression may take years or may rapidly occur
  - The rate is greater if TSH is higher or if there are positive antithyroid antibodies
  - The rate may also be greater in patients who were previously treated with radioiodine or surgery
Hyperthyroidism
### Causes of Hyperthyroidism

**Most common causes**
- Graves disease
- Toxic multinodular goiter
- Autonomously functioning nodule

**Rarer causes**
- Thyroiditis or other causes of destruction
- Thyrotoxicosis factitia
- Iodine excess (Jod-Basedow phenomenon)
- Struma ovarii
- Secondary causes (TSH or βHCG)
Causes of Thyrotoxicosis

Primary Hyperthyroidism

- Diffuse toxic goiter (Graves’ disease) – 60%-80%
- Hashitoxicosis – hyperthyroid phase
- Toxic multinodular goiter
- Toxic adenoma
- Activating mutation of TSH receptor
- Ovarian struma
- Iodine excess
Causes of Thyrotoxicosis

Secondary Hyperthyroidism

- TSH secreting pituitary adenoma
- Pituitary resistance to $T_3$ and $T_4$
- Chorionic gonadotropin-secreting tumors (hydatiform mole)
- Gestational thyrotoxicosis

Thyrotoxicosis without Hyperthyroidism

- Subacute thyroiditis
- Silent thyroiditis
- Thyrotoxicosis factitia
Signs and Symptoms of Hyperthyroidism

- Nervousness/Tremor
- Mental Disturbances/Irritability
- Difficulty Sleeping
- Hoarseness/Deepening of Voice
- Persistent Dry or Sore Throat
- Difficulty Swallowing
- Bulging Eyes/Unblinking Stare/Vision Changes
- Palpitations/Tachycardia
- Impaired Fertility
- Enlarged Thyroid (Goiter)
- Weight Loss or Gain
- Heat Intolerance
- Increased Sweating
- Menstrual Irregularities/Light Period
- Sudden Paralysis
- Warm, Moist Palms
- First-Trimester Miscarriage/Excessive Vomiting in Pregnancy
- Family History of Thyroid Disease or Diabetes
- Difficulty Swallowing
- Difficulty Sleeping
- Bulging Eyes/Unblinking Stare/Vision Changes
- Enlarged Thyroid (Goiter)
- Menstrual Irregularities/Light Period
- Warm, Moist Palms
- First-Trimester Miscarriage/Excessive Vomiting in Pregnancy
- Family History of Thyroid Disease or Diabetes
Thyrotoxicosis

**Symptoms**
- Palpitations
- Nervousness
- Easy fatigability
- Excessive sweating
- Intolerance to heat
- Diarrhea
- Weight loss / gain (5%)
- Oligomenorrhea
- Atypical symptoms:
  - Hypokalemic periodic paralysis
  - Pruritus
  - Atrial fibrillation
  - Apathetic hyperthyroidism

**Signs**
- Goiter
- Thyrotoxic eye signs
- Tachycardia
- Tremor
- Warm, moist skin
- Muscle weakness/ loss of muscle mass
- Thickening of the pre-tibial skin
- Onycholysis
- Clubbing
- Gynecomastia
Diagnosis of Graves Disease

- TSH ↓, free T4 ↑
- Thyroid auto antibodies
- Nuclear thyroid scintigraphy ($I_{123}$, $Te_{99}$)
Graves Disease

• Autoimmune disorder
• $\text{Ab}^s$ directed against TSH receptor with intrinsic activity. Thyroid and fibroblasts
• Responsible for 60-80% of Thyrotoxicosis
• More common in women
Graves’ Disease

- Autoimmune with over activity of thyroid gland
- HLA-DR3 association
- Defect in suppressor T cells
- B cells synthesize thyroid-stimulating immunoglobulin (TSI)
  - Autoantibody against TSH receptor
  - Gland becomes over stimulated and loses negative feedback to T₃ and T₄
Graves' Disease

- Goiter
- Thyrotoxicosis
- Exophthalmos
- pretibial myxedema
- Thyroid acropachy
- Thyroid stimulating immunoglobulins
Graves’ Disease

Associations with other diseases

- IDDM (Insulin dependent diabetes mellitus)
- Addison’s disease
- Vitiligo
- Pernicious anemia
- Myasthenia gravis
- Celiac disease
- Other autoimmune diseases associated with the HLA-DR3 haplotype
Clinical Characteristics of Goiter in Graves’ Disease

- Diffuse increase in thyroid gland size
- Soft to slightly firm
- Non-nodular
- Bruit and/or thrill
- Mobile
- Non-tender
- Without prominent adenopathy
Graves’ Gross and Microscopic Pathology

Fig. 10-13. Graves disease. A. The thyroid gland is symmetrically enlarged. B. On cut section the thyroid gland appears moist and hyperemic and lacks normal colloidal appearance.
Graves’ Ophthalmopathy

- **Class one:** spasm of upper lids with thyrotoxicosis
- **Class two:** periorbital edema and chemosis
- **Class three:** proptosis
- **Class four:** extraocular muscle involvement
- **Class five:** corneal involvement
- **Class six:** loss of vision due to optic nerve involvement
Graves Disease Eye Signs

N - no signs or symptoms
O – only signs (lid retraction or lag) no symptoms
S – soft tissue involvement (periorbital oedema)
P – proptosis (>22 mm)(Hertl’s test)
E – extra ocular muscle involvement (diplopia)
C – corneal involvement (keratitis)
S – sight loss (compression of the optic nerve)
Clinical Characteristics of Exophthalmos

- Proptosis
- Corneal Damage
- Periorbital edema
- Chemosis
- Conjunctival injection
- Extraocular muscle impairment
- Optic neuropathy
Clinical Differentiation of Lid Retraction from Proptosis

- Measurement using prisms or special ruler (exophthalmometer)
  OR with sclera seen above iris:
- Observing position of lower lid (sclera seen below iris = proptosis, lid intersects iris = lid retraction)
Lid Lag in Thyrotoxicosis

Normal

Lid Lag
Graves Disease Other Manifestations

- Pretibial mixoedema
- Thyroid acropachy
- Onycholysis
Graves’…Dermopathy
Clinical Characteristics of Localized Myxedema

- Raised surface
- Thick, leathery consistency
- Nodularity, sometimes
- Sharply demarcated margins
- Prominent hair follicles
- Usually over pretibial area
- Non-tender
Graves’ Disease - Localized Myxedema

- Margins sharply demarcated
- Nodularity
- Thickened skin
- Margins sharply demarcated
Thyroid Acropachy

- Clubbing of fingers
- Painless
- Periosteal bone formation and periosteal proliferation
- Soft tissue swelling that is pigmented and hyperkeratotic
Onycholysis of Thyrotoxicosis

Distal separation of the nail plate from nail bed (Plummer’s nails)
Thyrotoxicosis

Diagnostic Studies

• Thyroid function tests:
  TSH - suppressed
  fT₄ and/or TT₃ / fT₃ - elevated

• TSI
• Antithyroid antibodies
• Thyroid scan
Thyrotoxicosis – Thyroid Scan

Normal Thyroid Scan

Nuclear Medicine Thyroid Scan

Abnormally Decreased Uptake

Enlarged Thyroid Gland

Abnormally Increased Uptake
Thyrotoxicosis

**Increased Uptake**
- Graves’ disease
- Toxic adenoma
- Toxic multinodular goiter
- Hashitoxicosis
- TSH producing pituitary tumor

**Decreased Uptake**
- Subacute thyroiditis
- Painless thyroiditis
- Iodine induced hyperthyroidism
- Thyroid hormone therapy
Graves’ Disease

Treatment

• Symptomathic treatment
  *(Beta-adrenergic blocking agents)*

• Antithyroid drug therapy

• Radioiodine therapy

• Surgical therapy
Graves’ Disease

Antithyroid Drug Therapy - Thionamides

*(Carbimazole, Mercaptizole, Propylthiouracil)*

- Inhibit the synthesis of thyroid hormones (suppression of TPO; interference with T4 → T3)

- Method of therapy
  - Titration regimen
  - “Block-replace” regimen
Antithyroid Drug Therapy - Thionamides

(Carbimazole, Mercaptizole, Propylthiouracil)

**Side effects**

- **Minor (5%)** – rash, urticaria, arthralgia, abnormalities of smell and taste, increased liver enzymes, fever, lymphadenopathy

- **Major (<1%)** – agranulocytosis, thrombocytopenia, DIC, hepatitis, vasculitis, nephrotic syndrome, SLE-like syndrome
Considerations with Thionamides

- Both PTU and Methimazole may be used in pregnancy
- PTU and Methimazole are considered safe in breastfeeding
  - Methimazole appears in higher concentrations
- Watch for agranulocytosis
  - Fever
  - Sore throat
Thionamides Cont…

- Measure FT$_4$ and FTI every 2-4 weeks and titrate accordingly
- Goal is high normal range
- 90% see improvement in 2-4 weeks
Graves’ Disease

Surgical treatment

- Subtotal thyroidectomy
- Preoperative preparation
  - antithyroid drugs
  - Inderal
  - lugol’s iodoine
Surgery
Subtotal Thyroidectomy

• **Complications**
  – Laryngeal nerve damage
  – Hemorrhage
  – Hypo calcemia –Tetany (tingling) usually in & around mouth. Does pt c/o numbness?
  – Resp distress
  – Dehiscence
Thyroidectomy
Post-operative Management

• **Maintain patent airway**
  – monitor respirations, color, O2 saturation
  – tracheostomy kit, O2, Suctioning- at bedside

• **Monitor for complications**
  – hemorrhage
    • Check VS
    • check back of neck & supraclavicular hollows
  – tetany (laryngospasm and seizures) – does pt deny numbness
  – injury to laryngeal nerve – can pt speak clearly

• **Decrease strain on suture line, HOB up**
Monitor for complications

**Tetany** - from accidental removal of parathyroid (monitor calcium levels, assess for tingling, twitching, muscle cramps)
- **Chvostek’s sign**: contraction of facial muscles in response to light tap over facial nerve in front of the ear
- **Trousseau’s sign**: inflate BP cuff above systolic pressure. Carpal spasms occur within 3 minutes if hypocalcemia is present
- Treatment: Calcium Gluconate IV,

**Thyroid storm** (Monitor vital signs for tachycardia & hyperthermia)

**Injury to laryngeal nerve** (bedside trach)

**Decrease strain on suture line**
- Semi-fowlers position
- No hyperextension of neck
Thyroid Storm

• Medical Emergency
• Occurs in ~ 1% of pregnant pts with hyperthyroidism
• Diagnostic signs and symptoms:
  – Fever
  – Tachycardia
  – Altered mental status
  – Vomiting and diarrhea
  – Cardiac arrhythmia
Thyrotoxicosis and Thyroid Storm

- Acute thyrotoxicosis: beta-blockers, barbiturates, cholestyramine
- Thyroid storm: manage aggressively with beta-blockers, calcium channel blockers, PTU, methimazole, sodium iodide, digitalis or diuretics for heart failure, fluid and electrolyte management
Iodine 131

- Contraindicated in pregnancy
- Avoid pregnancy for 4 months after $^{131}\text{I}$ treatment
- Avoid breastfeeding for 120 days after $^{131}\text{I}$ treatment
- Gestational age key when counseling pregnant women exposed to $^{131}\text{I}$
Graves’ Disease

Radioactive Iodine Treatment

Side-effects

• Worsening of ophthalmopathy
• Hypothyroidism
• Radiation thyroiditis
Exophthalmos
Medical Management

**Eye Care**

- Continuous eye care is required until condition resolves.

- Blinking & closing eyelid helps move tears across eye and into drainage channels.

- Tears are continuously produced to maintain moisture in the eye, remove metabolic waste products & environmental debris (dust, ash, etc) keep the eyes outer surface smooth, & deliver nutrients to underlying tissues.
Exophthalmos
Medical Management

Corneal protection
• with an artificial tears solution (keep eye moist & debris out),

• sunglasses (help protect from injury & dryness by exposure to wind),

• an eye patch at night (heavy lubricant placed in eye, eyelid taped shut to dryness & risk for injury)
Graves’ Disease

Course and Prognosis

• 45%-55% - Remission and exacerbation over a protracted period of time
• 30%-40% - Euthyroidism
• 15% - Hypothyroidism

Graves’ ophthalmopathy is independent on thyroid status
Toxic Nodular Goiter

- Develops from multinodular goiter
- Nodules become autonomous
- Plummer’s disease
- Cardiac symptoms

**Treatment**

- Antithyroid drug therapy
- Surgery
Toxic Adenoma

• Thyrotoxicosis
  – Hyperfunctioning nodules <2 cm rarely lead to thyrotoxicosis
  – Most nodules leading to thyrotoxicosis are >3 cm.

• Treatment Indications
  – Post-menopausal female
    • Due to increased risk of bone loss
  – Patients over 60
    • Due to high risk of atrial fibrillation
  – Adenomas greater than 3 cm (?)
Toxic Adenoma

• Treatments
  – Antithyroid medications
    • Not used due to complications of long-term treatment
  – Radioiodine
    • Cure rate > 80% (20 mCi I131)
    • Hypothyroidism risk 5% - 10%
    • Second dose of I131 needed in 10% - 20%
    • Patients who are symptomatically toxic may require control with thionamide medications before RAI to reduce risk of worsening toxicity.
Toxic Adenoma

– **Surgery**
  - Preferred for children and adolescents
  - Preferred for very large nodules when high I131 doses needed
  - Low risk of hypothyroidism

– **Ethanol Injection**
  - Rarely done in the US
  - May achieve cure in 80%
# Differential Diagnosis of a Painful Thyroid

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subacute granulomatous thyroiditis</td>
<td>Most</td>
</tr>
<tr>
<td>Hemorrhage into a goiter, tumor or cyst with or without demonstrable trauma</td>
<td>Less</td>
</tr>
<tr>
<td>Acute suppurative thyroiditis</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Anaplastic (inflammatory) thyroid carcinoma</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>TB, atypical TB, amyloidosis</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Metastatic carcinoma</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
Structural Thyroid Disease
Benign Thyroid Disease

- **Benign Simple Conditions**
  - Diffuse (Physiological, colloid)
  - Nodular Goiter (Multi, Solitary)

- **Benign Toxic Conditions**
  - Toxic Multinodular Goiter
  - Graves’ Disease
  - Toxic Adenoma

- **Inflammatory Conditions**
  - Chronic (Hashimoto’s) Thyroiditis
  - Subacute (De Quervain’s) Thyroiditis
  - Riedel’s Thyroiditis
History

- **Goiter**
  - Fist described in China in 2700 BC

- **Thyroid Function**
  - Roman physicians – thyroid enlargement is a sign of puberty
Surgical advances

- **500 AD**
  - *Abdul Kasan Kelebis Abis* performed the first goiter excision in Baghdad.
  - Procedure: unknown
1870’s–80’s – **Billroth** – emerges as leader in thyroid surgery (Vienna)
- Mortality 8%
- Shows need for RLN preservation
- Defines need for parathyroid preservation (von Eiselberg)
- Emphasis on speed
History of Thyroid Surgery

- **Kocher** – emerges as leader in thyroid surgery (Bern)
  - Mortality:
    - 1889 – 2.4%
    - 1900 – 0.18%
  - Emphasis on meticulous technique
  - Performed 5000 cases by death in 1917
  - Awarded 1909 Nobel Prize for efforts
History of Thyroid Surgery

- **Halstead**
  - Studied under Kocher and Billroth
  - Returned to US 1880
  - Worked at Hopkins with Cushing, Osler, Welch
  - Laid groundwork for thyroid specialists Mayo, Lahey, Crile
Goiter

- **Goiter**: Chronic enlargement of the thyroid gland not due to neoplasm
- **Endemic goiter**
  - Areas where > 5% of children 6-12 years of age have goiter
  - Common in China and central Africa
- **Sporadic goiter**
  - Areas where < 5% of children 6-12 years of age have goiter
  - *Multinodular goiter* in sporadic areas often denotes the presence of multiple nodules rather than gross gland enlargement
- **Familial**
Simple Goiter

- Physiological
- Colloid
- Nodular
Enlarged Thyroid Gland - Goiter

**Diffuse**
- Physiological
- Simple/Colloid goiter
- Iodine deficiency
- Endemic - > 5% of the population in the endemic region
  (iodine deficiency or exposure to environmental goitrogens)
- Biosynthetic defects

**Nodular**
- Single Or multiple
A woman in Viet Nam, 1970
A woman in Switzerland, 1874
Simple Goiter

Etiology

- **Physiological**
  - Increase demand
- **Pathological**

**Defects In Synthesis**

- **Dyshormonegenesis**
- **Goitergens**
  - Lithium, ca++, vit A, Fluoride, Antithyroid, PASA, Iodine excess

Vegetables----Brassica family (cabbage, turnips, cauliflower, rape)
- **Iodine Deficiency**
  - Intake
  - Absorption
Pathogenesis

- Hyperplasia, Hypertrophy
- Involution
- Hyperinvolution excess iodide (Colloid)
- Active & Inactive lobule
- Hage, Necrosis
- Nodular Goiter
Clinical picture

- Swelling
- pressure symptom
  - Trachea, Esophagus, Recurrent laryngeal nerve, carotid
- complication
  - cystic degeneration
  - Hemorrhage
  - calcification
  - 2nd toxic goiter
  - Reterosternal goiter
  - malignant
Tracheal Compression
Retrosternal Goiter
Diagnostic tools

- History and examination
- Thyroid function tests
  - T3, T4, TSH
- Tumour markers
  - Thyroglobulin
  - Anti-TG antibodies
- Iodine-123 or 131 scan
- Ultrasound
- Biopsy
MNG

- **Cancer screening in MNG**
  - Longstanding MNG has a risk of malignancy identical to solitary nodules (<5%)
  - MNG with nodules < 1.5 cm may be followed clinically
  - MNG with non-functioning nodules > 4cm should be excised
    - No FNA needed due to poor sensitivity
    - Incidence of cancer (up to 40%)

- **FNA in MNG**
  - Sensitivity 85% - 95%
  - Specificity 95%
  - Negative FNA can be followed with annual US
  - Insufficient FNA’s should be repeated
  - Incocclusives FNA or papillary cytology warrants excision

- **Hyperfunctioning nodules** may mimic follicular neoplasm on FNA
Diffuse Goiter

- Treatment options
  - Iodoine (Salt, Oil)
  - Thyroid hormones therapy
MNG Goiter

- **Treatment options** (no compressive symptoms)
  - US follow-up to monitor for progression

- **Thyroid hormone therapy**
  - May be used for progressive growth
  - May reduce gland volume up to 50%
  - Goiter regrowth occurs rapidly following therapy cessation

- **Surgery**
  - Suspicious neck lymphadenopathy
  - History of radiation to the cervical region
  - Rapid enlargement of nodules
  - Papillary histology
  - Microfollicular histology (?)
Non-Toxic Goiter

- **Treatment options** *(compressive symptoms)*
  - **RAI ablation**
    - Volume reduction 33% - 66% in 80% of patients
    - Improvement of dysphagia or dyspnea in 70% - 90%
    - Post RAI hypothyroidism 60% in 8 years
    - Post RAI Graves’ disease 10%
    - Post RAI lifetime cancer risk 1.6%
  - **Surgery**
    - Most commonly recommended treatment for healthy individuals
Gross and Microscopic Pathology
Multinodular Goiter
## Classification of Malignant Thyroid Neoplasm

- **Papillary carcinoma**
  - Tall cell
  - Diffuse sclerosing
  - Follicular variant
  - Encapsulated
- **Follicular carcinoma**
  - Overtly invasive
  - Minimally invasive
- **Hurthle cell carcinoma**
- **Anaplastic carcinoma**
  - Giant cell
  - Small cell

- **Medullary Carcinoma**
- **Miscellaneous**
  - Sarcoma
  - Lymphoma
  - Squamous cell carcinoma
  - Mucoepidermoid carcinoma
  - Clear cell tumors
  - Plasma cell tumors
  - Metastatic
    - Direct extension
    - Kidney
    - Colon
    - Melanoma
Thyroid Mets

- Breast
- Lung
- Renal
- GI
- Melanoma
Well-Differentiated Thyroid Carcinomas (WDTC) - Papillary, Follicular, and Hurthle cell

Pathogenesis - unknown

- Papillary has been associated with the RET proto-oncogene but no definitive link has been proven (Geopfert, 1998)
- Certain clinical factors increase the likelihood of developing thyroid cancer
  - Irradiation - **papillary carcinoma**
  - Prolonged elevation of TSH (iodine deficiency) - **follicular carcinoma** (Goldman, 1996)
    - relationship not seen with papillary carcinoma
    - mechanism is not known
RISK FACTORS

Radiation exposure

External:
- Treatment for benign conditions
- Treatment for malignancies
- Nuclear weapons/accidents

Internal:
- Medical treatment with I131
- Diagnostic tests with I131
- Environmental- nuclear weapons

Other factors

- Diet- Iodine deficiency, goitrogens
- Hormonal factors- female gender predominance
- Benign thyroid disease
- Alcohol
SIGNS AND SYMPTOMS

- Lump / Nodule In Neck
- Hoarseness
- Swollen Lymph Node
- Difficulty Swallowing
- Difficulty Breathing
- Pain In Throat / Neck
DIAGNOSIS

1. Physical Examination
2. TSH Level
3. Thyroid Scan
4. Ultrasound
5. Fine Needle Biopsy
6. Coarse Needle Biopsy
7. Surgical Biopsy

COLD NODULE
WDTC - Papillary Carcinoma

- 60%-80% of all thyroid cancers (Geopfert, 1998, Merino, 1991)
- Histologic subtypes
  - Follicular variant
  - Tall cell
  - Columnar cell
  - Diffuse sclerosing
  - Encapsulated
- Prognosis is 80% survival at 10 years (Goldman, 1996)
- Females > Males
- Mean age of 35 years (Mazzaferri, 1994)
Lymph node involvement is common

- Major route of metastasis is lymphatic
- 46%-90% of patients have lymph node involvement (Goepfert, 1998, Scheumann, 1984, De Jong, 1993)
- Clinically undetectable lymph node involvement does not worsen prognosis (Harwood, 1978)
Microcarcinomas - a manifestation of papillary carcinoma

- Definition - papillary carcinomas smaller than 1.0 cm
- Most are found incidentally at autopsy
- Usually clinically silent
- Most agree that the morbidity and mortality from microcarcinoma is minimal and near that of the normal population
- One study showed a 1.3% mortality rate (Hay, 1990)
WDTC - Papillary Carcinoma (continued…)

• Pathology

  □ Gross - vary considerably in size
    - often multi-focal
    - unencapsulated but often have a pseudocapsule

  □ Histology - closely packed papillae with little colloid
    - psammoma bodies
    - nuclei are oval or elongated, pale staining with ground glass appearance - Orphan Annie cells
Papillary Thyroid Carcinoma
dark staining colloid in the FVPCA on right
nuclear clearing / colloid scalloping / irregularly shaped follicles
irregularly shaped, overlapping nuclei with clearing and grooving
psammoma bodies / ground glass nuclei / nuclear pseudoinclusion
nuclear pseudoinclusion
Papillary Carcinoma

- “Orphan Annie” nuclei
- Psamomma bodies
Papillary carcinoma
WDTC - Follicular Carcinoma

- 20% of all thyroid malignancies
- Mean age of 39 years (Mazzaferri, 1994)
- Prognosis - 60% survive to 10 years (Geopfert, 1994)
- Metastasis - angioinvasion and hematogenous spread
  - 15% present with distant metastases to bone and lung
- Lymphatic involvement is seen in 13% (Goldman, 1996)
WDTC - Follicular Carcinoma
(Continued…)

• Pathology

  □ Gross - encapsulated, solitary

  □ Histology - very well-differentiated (distinction between follicular adenoma and carcinoma is difficult)

    - Definitive diagnosis - evidence of vascular and capsular invasion

  □ FNA and frozen section cannot accurately distinguish between benign and malignant lesions
Follicular Thyroid Carcinoma
capsular invasion / suspicious vascular invasion
Follicular Carcinoma
WDTC - Hurthle Cell Carcinoma

• Variant of follicular carcinoma
• First described by Askanazy
  "Large, polygonal, eosinophilic thyroid follicular cells with abundant granular cytoplasm and numerous mitochondria" (Goldman, 1996)
• Definition (Hurthle cell neoplasm) - an encapsulated group of follicular cells with at least a 75% Hurthle cell component
• Carcinoma requires evidence of vascular and capsular invasion
WDTC - Hurthle Cell Carcinoma

(Continued…)

• Women > Men
• Lymphatic spread seen in 30% of patients (Goldman, 1996)
• Distant metastases to bone and lung is seen in 15% at the time of presentation
WDTC - Hurthle Cell Carcinoma
Medullary Thyroid Carcinoma

- 10% of all thyroid malignancies
- 1000 new cases in the U.S. each year
- Arises from the parafollicular cell or C-cells of the thyroid gland
  - derivatives of neural crest cells of the branchial arches
  - secrete calcitonin which plays a role in calcium metabolism
Medullary Thyroid Carcinoma (MTC)

- Tumor of the para-follicular cells (C cells)
- Tumor markers: calcitonin and CEA
Medullary Thyroid Carcinoma
(Continued…)

• Developes in 4 clinical settings:
  - Sporadic MTC (SMTC)
  - Familial MTC (FMTC)
  - Multiple endocrine neoplasia IIa (MEN IIa)
  - Multiple endocrine neoplasia IIb (MEN IIb)
Medullary Thyroid Carcinoma
(continued…)

• **Sporadic MTC:**
  - 70%-80% of all MTCs Mean age of 50 years
    (Russell, 1983)
  - 75% 15 year survival (Alexander, 1991)
  - Unilateral and Unifocal (70%)
  - Slightly more aggressive than FMTC and MEN IIa
  - 74% have extrathyroid involvement at presentation (Russell, 1983)
Medullary Thyroid Carcinoma
(Continued…)

- **Familial MTC:**
  - Autosomal dominant transmission
  - Not associated with any other endocrinopathies
  - Mean age of 43
  - Multifocal and bilateral
  - Has the best prognosis of all types of MTC
  - 100% 15 year survival
Medullary Thyroid Carcinoma (continued…)

- **Multiple endocrine neoplasia IIa (Sipple’s Syndrome):**
  - MTC, Pheochromocytoma, parathyroid hyperplasia
  - Autosomal dominant transmission
  - Mean age of 27
  - 100% develop MTC (Cance, 1985)
  - 85%-90% survival at 15 years (Alexander, 1991, Brunt, 1987)
Medullary Thyroid Carcinoma (continued…)

- *Multiple endocrine neoplasia IIb (Wermer’s Syndrome, MEN III, mucosal syndrome):*
  - Pheochromocytoma, multiple mucosal neuromas, marfanoid body habitus
  - 90% develop MTC by the age of 20
  - Most aggressive type of MTC
  - 15 year survival is <40%-50%
Medullary Thyroid Carcinoma
(continued…)

• Diagnosis

  - Labs: 1) basal and pentagastrin stimulated serum calcitonin levels (>300 pg/ml)
    2) serum calcium
    3) 24 hour urinary catecholamines (metanephrines, VMA, nor-metanephrines)
    4) carcinoembryonic antigen (CEA)

  - Fine-needle aspiration

  - Genetic testing of all first degree relatives
    – RET proto-oncogene
Anaplastic Carcinoma

- Highly lethal form of thyroid cancer
- Median survival <8 months (Jereb, 1975, Junor, 1992)
- 1%-10% of all thyroid cancers (Leeper, 1985, LiVolsi, 1987)
- Affects the elderly (30% of thyroid cancers in patients >70 years) (Sou, 1996)
- Mean age of 60 years (Junor, 1992)
- 53% have previous benign thyroid disease (Demeter, 1991)
- 47% have previous history of WDTC (Demeter, 1991)
Anaplastic Carcinoma of the Thyroid

• Pathology
  □ Classified as large cell or small cell
  □ Large cell is more common and has a worse prognosis
  □ Histology - sheets of very poorly differentiated cells
    - little cytoplasm
    - numerous mitoses
    - necrosis
    - extrathyroidal invasion
ANAPLASTIC THYROID CANCER
Primary Thyroid Lymphoma

- A rare type of thyroid cancer
  - Affects fewer than 1 in 2 million people
- Constitutes 5% of thyroid malignancies

Large Cell Lymphoma of the Thyroid
Primary Thyroid Lymphoma
Characteristics and Diagnosis

- Develops in the setting of pre-existing lymphocytic thyroiditis
- Often diagnosed because of airway obstruction symptoms
- Tumors are firm, fleshy, and usually pale
THYROID CANCER STAGING
THE TNM STAGES OF THYROID CANCER

There are 4 main T stages for thyroid cancer
- T1 – Tumor entirely in thyroid and <1cm across in any direction
- T2 – Tumor entirely in thyroid and >1cm but <4cm in any direction
- T3 – Tumor entirely in thyroid and >4cm across in any direction
- T4 – Cancer has grown outside the covering of the thyroid gland.

There are 2 possible stages of lymph Node involvement.
- NO - No lymph nodes containing cancer cells
- N1 - Lymph nodes containing cancer cells
  - N1a – LN w/ cancer cells on one side of the neck (same side as cancer)
  - N1b – LN w/ cancer cells anywhere else (other side of the neck or in chest)

There are 2 possible stages of cancer spread Metastasis.
- M0 - Cancer has not spread
- M1 – Cancer has spread
Staging system for papillary and follicular thyroid carcinoma
(American Joint committee on Cancer, TNM system)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Age &lt;45 yr</th>
<th>Age &gt;/=45 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>M0</td>
<td>T1</td>
</tr>
<tr>
<td>II</td>
<td>M1</td>
<td>T2-3</td>
</tr>
<tr>
<td>III</td>
<td>....</td>
<td>T4 or N1</td>
</tr>
<tr>
<td>IV</td>
<td>....</td>
<td>M1</td>
</tr>
</tbody>
</table>

- **T**: size (T1 <1cm, T2 1cm - <4cm, T3 >4cm, T4 direct extension or invasion through the thyroid capsule)
- **N**: lymph node
- **M**: distant metastases
<table>
<thead>
<tr>
<th>Stage</th>
<th>&lt;45 yo</th>
<th>&gt;45 yo</th>
<th>Local Recur</th>
<th>Distant Recur</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Any T</td>
<td>T1</td>
<td>5.5%</td>
<td>2.8%</td>
<td>1.8%</td>
</tr>
<tr>
<td></td>
<td>Any N</td>
<td>N0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>M0</td>
<td>M0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Any T</td>
<td>T2,3</td>
<td>7%</td>
<td>7%</td>
<td>11.6%</td>
</tr>
<tr>
<td></td>
<td>Any N</td>
<td>N0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>M1</td>
<td>M0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>T4, N0, M0</td>
<td>27%</td>
<td>13.5%</td>
<td>37.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any T, N, M</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Any T, N, M1</td>
<td>10%</td>
<td>100%</td>
<td>90%</td>
<td></td>
</tr>
</tbody>
</table>
ANAPLASTIC STAGING

• There is no number staging system used

• All is stage IV: Any T, Any N, Any M

• This is because there is a high risk of the cancer spreading.

• Treatment dependent on whether the cancer is only in neck and may be able to be completely removed

• Level of fitness for treatments such as surgery or radiotherapy
MEDULLARY STAGING

• Stage 1 – Cancer < 1 cm across
  T1, N0, M0

• Stage 2 – Cancer 1 – 4 cm across
  T2, 3, 4; N0, M0

• Stage 3 – There is spread to lymph node
  Any T, N1, M0

• Stage 4 – There is spread to distant part of body
  Any T, Any N, M1
Staging system for medullary and anaplastic thyroid carcinoma

(American Joint Committee on Cancer, TNM system)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Medullary</th>
<th>Anaplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>....</td>
</tr>
<tr>
<td>II</td>
<td>T2-4</td>
<td>....</td>
</tr>
<tr>
<td>III</td>
<td>N1</td>
<td>....</td>
</tr>
<tr>
<td>IV</td>
<td>M1</td>
<td>Any</td>
</tr>
</tbody>
</table>

- **T**: size (T1 <1cm, T2 1cm - <4cm, T3 >4cm, T4 direct extension or invasion through the thyroid capsule)
- **N**: lymph node
- **M**: distant metastases
General management scheme for papillary and follicular thyroid cancer

- Thyroidectomy
- (Selective lymph node dissection)
- Post-op radioactive iodine ablation therapy
- TSH suppression therapy
- Periodic surveillance for recurrence and metastasis:
  - Blood test: thyroglobulin level
  - Imaging studies: Radioactive iodine whole body scan, neck ultrasound, CXR, CT, PET CT, bone scan.
Management

• Surgery is the definitive management of thyroid cancer, excluding most cases of ATC and lymphoma

• Types of operations:
  – lobectomy with isthmusectomy - minimal operation required for a potentially malignant thyroid nodule
  – total thyroidectomy - removal of all thyroid tissue
Subtotal vs. total thyroidectomy
Arguments for Total Thyroidectomy

- **Radioactive iodine** may be used to detect and treat residual normal thyroid tissue and local or distant metastases.
- **Serum thyroglobulin** level is a more sensitive marker for persistent or recurrent disease when all normal thyroid tissue is removed.
- In up to 85% of papillary cancer, **microscopic foci** are present in the contralateral lobe. Total thyroidectomy removes these possible sites of recurrence.
Arguments for Total Thyroidectomy

- **Recurrence** develops in 7% of contralateral lobes (1/3 die)
- Risk (though very low [1%]) of dedifferentiation into anaplastic thyroid cancer is reduced
- **Survival** is improved if papillary cancer greater than 1.5cm or follicular greater than 1cm
- Need for **reoperative** surgery associated with higher risk is lower
Arguments against total thyroidectomy

- Total thyroidectomy may be associated with higher complication rate than lobectomy
- 50% of recurrences can be controlled with surgery
- Fewer than 5% of recurrences occur in the thyroid bed
Arguments against total thyroidectomy

- Tumor **multicentricity** has little clinical significance
- **Prognosis** of low risk patients (age, grade, extent, size) is excellent regardless of extent of resection
Indications for total thyroidectomy

1) Patients older than 40 years with papillary or follicular carcinoma

2) Anyone with a thyroid nodule with a history of irradiation

3) Patients with bilateral disease
• Managing lymphatic involvement
  - Pericapsular and tracheoesophageal nodes should be dissected and removed in all patients undergoing thyroidectomy for malignancy.
  - Overt nodal involvement requires exploration of mediastinal and lateral neck.
  - If any cervical nodes are clinically palpable or identified by MR or CT imaging as being suspicious, a neck dissection should be done.

Prophylactic neck dissections are not done (Gluckman)
Radioactive iodine ablation

- Advantages:
  - It may destroy microscopic cancer cells.
  - Subsequent detection of persistent or recurrent disease by radioiodine scanning is facilitated.
  - The sensitivity of serum thyroglobulin measurements is improved.
PAPILLARY & FOLLICULAR FOLLOW UP

• Radioactive Iodine (Administration)

• Scan At 4-6 Weeks Postop

• Repeat Scan At 6-12 Months After Ablation

• Repeat Scan At 1 Year Then...

• Every 2 Years Thereafter
THS suppression therapy

• Patient after thyroidectomy is given thyroid hormone not only for physiological replacement, but also to suppress TSH as TSH can stimulate growth of thyroid cells.

• TSH level should not be “mid normal” range for patients with thyroid cancer.
THS suppression therapy

- TSH level needs to be subnormal or suppressed, depending on the aggressiveness of the disease.

- The degree of TSH suppression needs to be tailored to each patient.
## Target TSH Suppression in Patients With Thyroid Cancer

<table>
<thead>
<tr>
<th>TSH, mIU/L</th>
<th>Patients</th>
<th>Optimal TSH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low to Undetectable</td>
</tr>
<tr>
<td></td>
<td>&lt;0.1</td>
<td>Suppressed but Detectable</td>
</tr>
<tr>
<td></td>
<td>Persistent or recurrent disease</td>
<td>Most patients with no evidence of disease</td>
</tr>
<tr>
<td></td>
<td>High-risk patients</td>
<td>Low Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5 to 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.1 to 0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5 to 1</td>
</tr>
</tbody>
</table>
Management (WDTC) - Hurthle Cell Carcinoma

- Total thyroidectomy is recommended because:
  1) Lesions are often Multifocal
  2) They are more aggressive than WDTCs
  3) Most do not concentrate iodine
Management - Hurthle Cell Carcinoma

• Postoperative management
  - Thyroid suppression
  - Measure serum thyroglobulin every 6 months
  - Postoperative radioactive iodine is usually not effective (10% concentrate iodine) (Clark, 1994)
Management of Medullary Thyroid Carcinoma

• Recommended surgical management
  - total thyroidectomy
  - central lymph node dissection
  - lateral jugular sampling
    - if suspicious nodes - modified radical neck dissection

• If patient has MEN syndrome
  - remove pheochromocytoma before thyroid surgery
Management of Medullary Thyroid Carcinoma

• Postoperative management
  - Disease surveillance
    - Serial calcitonin and CEA
      - 2 weeks postop
      - 3/month for one year, then...
      - Biannually
Management of Medullary Thyroid Carcinoma

- If persistent elevated CEA or calcitonin, CT scan for residual disease (50% of pts)
- Aggressive neck dissection advocated by many if persistent disease
- Consider laparotomy for possible liver mets
- Prolonged survival with significant symptoms not uncommon with widely metastatic disease
Management of Medullary Thyroid Carcinoma

- Familial cases positive for RET proto-oncogene mutation
- If positive family history, then genetic testing
- If MEN IIA or FMTC then total thyroidectomy and central lymph node dissection between ages of 5-6 years
- If MEN IIB then total thyroidectomy and central node dissection ages 6mos - 3 years
- SURGERY IS ONLY EFFECTIVE THERAPY
Incidentaloma/Micrometastatic Disease

- Lesions detected by imaging or found after surgery for unrelated indication
- Thyroid nodules common in population (4-10% have palpable nodules any given time)
- Female/male incidence 6.4 / 1.6%
- 12% detected by palpation vs. 45% by imaging
- Lesions less than 1 cm—observe
- Lesions 1-2cm “gray zone”
- Lesions > 2cm are NOT INCIDENTAL
Incidentaloma/Micrometastatic Disease

- Consider suspicious features:
  - Increased vascularity
  - Irregular margin
  - Central microcalcification
  - Cervical adenopathy
Anaplastic Carcinoma
(Management)

- Most have extensive extrathyroidal involvement at the time of diagnosis
  - Surgery is limited to biopsy and tracheostomy
- Current standard of care is:
  - Maximum surgical debulking, possible
  - Adjuvant radiotherapy and chemotherapy

(Jereb and Sweeney, 1996)
Local Invasion of the Neck

Tracheal resection repaired primarily
Local Invasion of the Neck

Crycoid invasion with local muscle flap reconstruction
Local Invasion of the Neck

Vertical hemilaryngectomy
Local Invasion of the Neck

Circumferential tracheal resection with primary anastomosis
Thyroid Tumor

Postoperative Complications

• Postoperative hypocalcaemia (transient / permanent hypoparathyroidism)
• Recurrent laryngeal nerve dysfunction (vocal cords paralysis)
• Postoperative bleeding
• Postoperative infection
Thyroid Tumor

Monitoring of Differentiated Carcinoma

- Follow up at intervals of 6 -12 months throughout the patient’s life

- To evaluate effectiveness of TSH suppression
  - Serum TSH (< 0.1 mU/L)

- To evaluate presence of recurrence
  - Serum thyroglobulin (< 1ng/ml)

- To evaluate presence and location of recurrence
  - Chest X-ray (CT) and cervical ultrasound
  - $^{131}$I total-body scanning
$^{131}\text{I}$ Total Body Scan
**PROGNOSIS**

- Prognostic schemes:
  - **AMES** (Lahey Clinic, Burlington, MA)
  - **GAMES** (Memorial Sloan-Kettering Cancer Center, NY)
  - **AGES** (Mayo Clinic, Rochester, MN)

- AMES scoring (PAPILLARY & FOLLICULAR CANCER)
  - **A** Age of patient when tumor discovered
  - **M** Metastases of the tumor (other than Neck LN)
  - **E** Extent of primary tumor
  - **S** Size of tumor (>5 cm, or about 2 inches)
PROGNOSIS

The patients are categorized into:

- **Low risk group** - men younger than 40 years and women younger than 50 years regardless of histologic type (intrathyroid papillary & follicular) – No distant mets & size <5cm - recurrence rate -11%; death rate - 4%

- **Intermediate risk group** - Men older than 40 years and women older than 50 years who have papillary carcinoma - size <5cm - recurrence rate - 29%; death rate - 21%

- **High risk group** - Men older than 40 years and women older than 50 years who have follicular carcinoma - with distant mets, size >5cm - recurrence rate - 40%; death rate - 36%
PROGNOSIS

• MAICS Scoring (PAPILLARY THYROID CANCER)

A mathematical calculation developed by the Mayo Clinic for staging. It is known to be the most accurate predictor of a patient's outcome with papillary thyroid cancer

(M = Metastasis, A = Age, I = Invasion, C = Completeness of Resection, S = Size)

<table>
<thead>
<tr>
<th>MAICS Score</th>
<th>20 year Survival</th>
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</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>99%</td>
</tr>
<tr>
<td>6-7</td>
<td>89%</td>
</tr>
<tr>
<td>7-8</td>
<td>56%</td>
</tr>
<tr>
<td>&gt;8</td>
<td>24%</td>
</tr>
</tbody>
</table>
THANK YOU!!
Evaluation of a Thyroid Nodule
Thyroid Nodule

- **Prevalence:** 4% - 7%

- **Diagnosis of single thyroid nodule:**
  - Malignant thyroid disease: 5 - 7%
  - Benign follicular neoplasms: 13 - 15%
  - Benign colloid nodule: 32 - 36%
  - Benign cyst: 18 - 20%
  - Hashimoto thyroiditis: 20 - 24%
Thyroid Nodule

Diagnostic Work-Up

- Clinical history and physical examination
Clinical History & Physical Examination

*(suspicion of Benign disease)*

- Autoimmune thyroid disease
- Family history of benign thyroid nodule
- Pain or tenderness
- Soft, smooth, mobile nodule
Clinical History & Physical Examination

(suspicion of malignant disease)

- Age < 20 years; > 60 years
- Gender – male
- Exposure to irradiation
- Hoarseness and dysphagia
- Rapid growth
- Firm, irregular and fixed nodule
- Cervical lymphadenopathy
Diagnostic Work-Up

- Clinical history and physical examination
- Laboratory assessment
Laboratory Assessment

- **Thyroid function tests:** TSH, fT4, TT3
- **Serum thyroid antibodies**
- **Tumor markers:** calcitonin
  (in patients with family history of medullary thyroid carcinoma, or MEN type 2).
Diagnostic Work-Up

- Clinical history and physical examination
- Laboratory assessment
- Imaging –
  - Ultrasound
  - Radionuclide scanning
  - (CT, MRI)
Ultrasound

- Size
- Solitary or multiple
- Cystic, solid or mixed
- Hypoechoic or hyperechoic
- Calcifications
- Increased nodular flow
- Lymph nodes
- Trachea
- Detect non-palpable nodules
Solitary Thyroid Nodule
Radionuclide Scanning (Technetium)

- "Hot" nodule – 10%, nearly always benign
- "Warm" nodule
- "Cold" nodule – Has a 5% risk of being malignant
Thyroid Scan - Normal
Thyroid Scan - Cold Nodule
Thyroid Scan - “Hot” Nodule
Thyroid Scan – Multinodular Goiter

Nuclear Medicine Thyroid Scan

- Abnormally Decreased Uptake
- Enlarged Thyroid Gland
- Abnormally Increased Uptake
Diagnostic Work- Up

- Clinical history and physical examination
- Laboratory assessment
- Imaging –
  - Ultrasound
  - Radionuclide scanning
  - (CT, MRI)
- FNA biopsy
Fine Needle Aspiration (FNA)
FNA results

- Inadequate specimen
- Adequate specimen
  - Benign
  - Malignant
  - Suspicious
Benign thyroid nodules

- Differential diagnosis
  - Thyroid adenoma
  - Multinodular goiter
  - Hashimoto’s thyroiditis
  - Subacute thyroiditis
  - Thyroid cyst
Malignant thyroid nodules

- Differential diagnosis
  - Papillary thyroid CA (75-85%)
  - Follicular thyroid CA (10-20%)
  - Medullary thyroid CA (5%)
  - Anaplastic thyroid CA (rare)
  - Lymphoma (rare)
  - Squamous cell carcinoma (rare)
Historical Red Flags

- Male
- Extremes of age (<20 or >65)
- Rapid Growth
- Symptoms of local invasion (hoarseness, dysphagia, neck pain)
- History of radiation to the head or neck
- Family history of Thyroid Cancer or Polyposis
Thyroid Nodules

- FNA Results:
  - Suspicious--------Surgery
  - Negative---------6 month follow up
  - Indeterminant---repeat the FNA, if still indeterminant, surgery recommended
Suspicious nodules

- Not enough evidence to conclude that the lesion is benign or malignant.

- Follicular carcinoma may be indistinguishable from follicular adenoma on FNA.

→ If the FNA result is a follicular lesion, that nodule needs to be surgically removed for diagnostic purpose.
FNA – Papillary Thyroid Carcinoma
Thyroid Nodule

FNA Biopsy

- Benign - 70%
- Malignant - 5%
- Suspicious
- Insufficient
Thyroid Nodule

Diagnostic Work-Up

- Clinical history and physical examination
- Laboratory assessment
- Imaging -
  - Ultrasound
  - Radionuclide scanning
  - (CT, MRI)
- FNA biopsy
- TSH suppressive therapy (?)


Thyroid Nodules

- Non-toxic Solitary Nodules
  - Indications for treatment
    - Compressive Symptoms
    - Growth of Nodule
    - Recurrence of cystic nodule after aspiration
    - Other
  - Unilateral lobectomy-preferred therapy
- Aspiration
- Suppression (SOR=C, LOE=3)
  - 6-12 month trial
  - Premenstrual women, post-menopausal on HRT, men
  - Cochrane review pending
Thyroid Nodules

- Non-toxic Multinodular Goiter
  - Indications for treatment: Same

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Rapid Decompression and Pathological Interpretation</td>
<td>Hypoparathyroid or Hypothyroid, Recurrent Laryngeal Nerve Damage</td>
</tr>
<tr>
<td>Thyroxine</td>
<td>Easiest Option</td>
<td>Effectiveness unclear, bone mineral density decrease, Cardiac effects</td>
</tr>
<tr>
<td>I(^{131})</td>
<td>Very effective</td>
<td>Slower decompression, thyroiditis, thyroid dysfunction, ? Risk CA</td>
</tr>
</tbody>
</table>
Thyroid Nodules

- **Toxic Solitary or Multinodular Goiter**
  - Indications: Overtly Hyperthyroid or Young/Old at risk for cardiac disease or osteoporosis

<table>
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<tr>
<th>Therapy</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{131}$I</td>
<td>Highly effective for reversal of hyperthyroidism, 90%</td>
<td>Gradual effect, 10% hypothyroid, ? Increased risk for CA</td>
</tr>
<tr>
<td>Surgery</td>
<td>Rapid reversal of hyperthyroidism, Pathology</td>
<td>Surgical Morbidity and Mortality, 10-20% hypothyroidism</td>
</tr>
<tr>
<td>Anti-thyroid Drugs</td>
<td>Easiest Option</td>
<td>Lifelong treatment and Adverse effects</td>
</tr>
</tbody>
</table>
Special Populations

- Pregnant/Breastfeeding
  - Hyperthyroidism
    - Risks: Fetal Loss, severe pre-eclampsia, preterm delivery, heart failure, LBW neonate
    - Anti-thyroid drugs preferred treatment
    - No I\(^{131}\)
    - Neonates can get immune mediated hypothyroidism and hyperthyroidism in Mothers with Graves Disease
Special Populations

- **Pregnant/Breastfeeding**
  - Hypothyroidism:
    - Risks: pre-eclampsia, LBW neonates
    - Check TSH each trimester
    - May need to increase thyroxine dose
  - Nodules:
    - Manage same as non-pregnant, but up to 40% may be malignant
    - Surgery in 2nd trimester is preferred treatment
Special Populations

- Pregnant/Breastfeeding
  - Hyperemesis Gravidarum associated with biochemical hyperthyroidism but rarely with clinical symptoms
  - No treatment required
Special Populations

- **Children**
  - **Hyperthyroidism:**
    - I\(^{131}\) typically not used
  - **Hypothyroidism:**
    - Larger replacement dose often needed
    - Neonates screened to decrease risk of cretinism
- **Nodules:**
  - 14-40% malignant
Special Populations

- Elderly
  - General Comments:
    - Symptoms much more subtle, similar to normal aging
    - More sensitive to adverse and therapeutic effects of medicines
  - Hyperthyroidism:
    - Multinodular goiter more common in elderly
    - 10-15% with Apathetic Hyperthyroidism
Special Populations

- Elderly
  - Hypothyroidism:
    - Fewer classic symptoms
    - Treating sub-clinical disease likely more harm than good
  - Nodules:
    - Again...more common to have toxic multinodular goiter as cause of hyperthyroidism
Conclusions

Management

- Incidentally discovered small thyroid nodule
  - Clinical and ultrasonographic follow-up

- Benign thyroid nodule
  - Careful follow-up at periodic intervals
  - Repeated ultrasonography and FNA biopsy when the nodule enlarges or becomes suspicious
Conclusions

Management

- Cystic lesion
  - Complete cyst disappearance:
    - A benign lesion
  - Suspicious or insufficient FNAB findings:
    - Thyroid lobectomy
Conclusions

Management

- **Autonomously functioning “hot” nodule**
  Thyroid lobectomy, RAI therapy

- **Malignant thyroid nodule**
  Total or near total thyroidectomy

- **Suspicious thyroid nodule**
  Thyroid lobectomy
  (followed by total or near total thyroidectomy)
## TFT’s in Pregnancy and Disease

<table>
<thead>
<tr>
<th>Maternal</th>
<th>TSH</th>
<th>FT4</th>
<th>FTI</th>
<th>TT4</th>
<th>TT3</th>
<th>RT3 U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Hyperthyroid</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑ or no change</td>
<td>↑</td>
</tr>
<tr>
<td>Hypothyroid</td>
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<td>↓</td>
<td>↓</td>
<td>↓ or no change</td>
<td>↓</td>
</tr>
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Table 1, ACOG Practice Bulletin
Number 37, August 2002
Fetal Effects of Hyperthyroidism

- Treatment is key
- Less than adequate treatment may result in:
  - Increase in preterm deliveries
  - LBW
  - Possible fetal loss
Risks with Immune Mediated Thyroid Dysfunction

- Antibodies cross placenta
  - In Graves’
    - TBII
    - TSI
- In Graves’...1-5% of neonates have hyperthyroidism or neonatal Graves caused by maternal TSI
- Incidence low due to balance of antibodies with thioamide treatment
Neonatal Graves’

- Maternal abys cleared after thioamides
  - Results in delayed presentation
- Neonates of women Tx with $^{131}$I or surgery at higher risk for developing Neonatal Grave’s disease
Fetal Effects of Hypothyroidism

- Incidence of congenital hypothyroidism 1/4000
  - 5% of those identified clinically at birth
- High incidence of LBW
  - Preterm delivery
  - Preeclampsia
  - Placental abruption
- Unclear relationship between hypothyroidism and IUGR independent of other complications
Iodine Deficient Hypothyroidism

- Risk of congenital cretinism
- Treatment with iodine in 1\textsuperscript{st} and 2\textsuperscript{nd} trimesters significantly reduces abnormalities of cretinism
Cretinism

- Growth failure
- Mental Retardation
- Neuropsychologic deficits
Levothyroxine in Pregnancy

- Same for the nonpregnant pt
- Goal is to normalize TSH
- Adjust dose at 4 week intervals
- Should check TSH levels every trimester in pts with hypothyroidism
Other Obstetrical and Thyroid Conditions

- Hyperemesis Gravidarum
- Gestational Trophoblastic Disease
- Thyroid Storm
- Thyroid CA
- Postpartum Thyroiditis
Hyperemesis Gravidarum

- Associated with biochemical hyperthyroidism, but not clinical
- Routine screening and treatment not recommended
Clinical hyperthyroidism in ~7% of complete hydatidiform moles

Treat with $B$-blockers if hyperthyroidism is suspected

- If no Tx, surgery may precipitate thyroid storm