Thyroid disease for R2

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Thyroid

• Thyrotoxicosis/Thyroiditis
• Amiodarone and thyroid dysfunction
• Thyroid storm
• Hypothyroidism
• Thyroid nodule
Thyrotoxicosis

- Refers to the classic physiologic manifestations of excessive quantities of thyroid hormones.

Hyperthyroidism

- Reserved for disorders that result from sustained overproduction of hormone by thyroid itself.
Causes of Thyrotoxicosis

**Primary hyperthyroidism**
- Graves’ disease
- Toxic multinodular goiter
- Toxic adenoma

**Thyrotoxicosis without hyperthyroidism**
- Subacute thyroiditis
- Silent thyroiditis
- Amiodarone
- Thyrotoxicosis factitia

**Secondary hyperthyroidism**
- TSH-secreting pituitary adenoma
- Chorionic gonadotropin-induced
- Gestational hyperthyroidism
Graves’ disease

- Autoimmune thyroid disease
- Autoantibodies specific to Graves’ disease are directed against the TSHR (TSHR Abs) and behave as thyroid stimulating antibodies
Clinical manifestations

- Fatigue
- Heat intolerance
- Weight loss to an effective diet
- Dyspnea
- Palpitation
Eyes

- Lid retraction..“Stare”
- Lid lag
- Graves’ Orbitopathy
  - Soft tissue involvement
  - Proptosis
  - Extraocular muscle involvement
  - Corneal involvement

{Increased adrenergic tone}
Thyroid gland

- Diffuse goiter
- Soft to firm and rubbery
- Bruits: upper and lower pole
Cardiovascular System

- Tachycardia
- Widening of the pulse pressure
- Atrial fibrillation
- Heart failure

Neuromuscular System

- Anxiety / Psychosis
- Tremor
- Myopathy
- Hypokalemic periodic paralysis
Skin and Hair

- Warm and moist skin
- Palmar erythema
- Hair: fine and friable
- Plummer’s nails: Onycholysis typical involving the 4th and 5th fingers
- Vitiligo
- Graves’ disease
  - Thyroid acropachy
  - Pretibial myxedema
Onycholysis

Thyroid acropachy

Pretibial myxedema
Laboratory

- TSH ↓, T₃ & T₄ ↑
- Positive TSHRAbs
- Increased radioactive iodine uptake (RAIU)

![Imaging of thyroid gland showing normal and Graves' disease states](image.png)
Treatments

- Antithyroid Drugs: PTU, MMI
- B-Adrenergic antagonist drugs
- Glucocorticoids
- Inorganic Iodide
- Iodine-Containing Compounds
- Potassium Perchlorate
- Lithium Carbonate
- Rituximab
- Radioactive iodine
- Surgery
Antithyroid Drugs: Thionamides

Propylthiouracil (PTU), Methimazole (MMI)

- Inhibit thyroid hormone synthesis
- Immunosuppressive actions

- PTU: blocking of the conversion of thyroxine (T4) to triiodothyronine (T3)

- Dose adjustment is not necessary in persons who have impaired liver or kidney function.

Try medication 1.5-2 yrs.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MMI</th>
<th>PTU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative potency</td>
<td>10-50</td>
<td>1</td>
</tr>
<tr>
<td>Administration</td>
<td>oral</td>
<td>oral</td>
</tr>
<tr>
<td>Serum half-life (hours)</td>
<td>4-6</td>
<td>1-2</td>
</tr>
<tr>
<td>Duration of action (hours)</td>
<td>&gt;24</td>
<td>12-24</td>
</tr>
<tr>
<td>Metabolism during liver disease</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Metabolism during kidney disease</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Transplacental passage and level in breast milk</td>
<td>Low</td>
<td>Even lower</td>
</tr>
<tr>
<td>Inhibition of T4/T3 conversion</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Dosing</td>
<td>1-2 times daily</td>
<td>2-3 times daily</td>
</tr>
</tbody>
</table>
## Major toxic reactions with ATDs

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyarthritis</td>
<td>1-2%</td>
<td>-</td>
</tr>
<tr>
<td>ANCA+ vasculitis</td>
<td>Rare</td>
<td>Mostly PTU</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>0.1-0.5%</td>
<td>May be more common with PTU</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>0.1-0.2%</td>
<td>PTU</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>Rare</td>
<td>MMI</td>
</tr>
</tbody>
</table>
Mild side effects

- Skin reactions: rash, pruritus
- Arthralgias
- Gastrointestinal symptom
- Abnormal sense of taste
- Occasional sialadenitis
Agranulocytosis

- Defined as an absolute granulocyte count < 500/mL
- Often occurs within the first 3 months of therapy
- Most experts do not recommend routine monitoring of granulocyte count during treatment.
- Patients should be instructed to stop medication and to seek medical attention if they develop a fever or a sore throat.
- If the granulocyte count <1000/mL, the drug should be stopped.
Long-Term Follow-up

• Recurrence rate is 50 - 60%
• Most cases of relapse occur within 3 - 6 months of stopping the drug.
• Most women in remission who become pregnant have a postpartum relapse of GD or develop postpartum thyroiditis
• Life-long follow-up is recommended.
RADIOACTIVE IODINE

- RAI is considered effective, safe, and relatively inexpensive.
- Isotope of choice is $^{131}\text{I}$.

$\text{Dose (mCi)} = 80-200 \text{ microCi} \times \frac{^{131}\text{I} \text{g thyroid}}{\text{estimated thyroid gland weight (g)}} \times 24\text{-hour radioiodine uptake}$

- Increased risk of ophthalmopathy
- Following $^{131}\text{I}$ therapy, 50-70% of patients become euthyroid within 6-8 weeks

SURGERY

Indications

• Patient preference
• Children, adolescents, pregnant women
• Large goiters (whether causing pressure symptoms or for cosmetic reasons)
• Suspicion of thyroid malignancy
• +/-Pre-existing Graves’ ophthalmopathy

Total or nearly total thyroidectomy
Complications

• Permanent damage to the recurrent laryngeal nerve
• Hypoparathyroidism
• Transient hypocalcemia
• Postoperative bleeding
• Wound infections
• The formation of keloids
<table>
<thead>
<tr>
<th></th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thionamides</strong></td>
<td>- No radiation hazard</td>
<td>- Recurrent rate high (&gt;50%)</td>
</tr>
<tr>
<td></td>
<td>- No surgical and anesthesiologic risks</td>
<td>- Frequent testing required</td>
</tr>
<tr>
<td></td>
<td>- No permanent hypothyroidism</td>
<td>- Common mild side effect</td>
</tr>
<tr>
<td></td>
<td>- OPD</td>
<td>- Rare but potentially lethal side effects</td>
</tr>
<tr>
<td><strong>Radioactive iodine</strong></td>
<td>- Definitive treatment</td>
<td>- Potential radiation hazard</td>
</tr>
<tr>
<td></td>
<td>- No surgical and anesthesiologic risks</td>
<td>- Worsening of thyroid eye disease</td>
</tr>
<tr>
<td></td>
<td>- OPD, rapidly performed</td>
<td>- Decreasing efficacy with increasing goiter size</td>
</tr>
<tr>
<td></td>
<td>- Rapid control of hyperthyroidism in most</td>
<td>- May need to be repeated</td>
</tr>
<tr>
<td></td>
<td>- Low cost</td>
<td>- Hypothyroidism eventually develops in most cases</td>
</tr>
<tr>
<td></td>
<td>- Side effects mild, rare, transient</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Normalizes thyroid size within 1 yr</td>
<td></td>
</tr>
<tr>
<td><strong>Thyroidectomy</strong></td>
<td>- Definitive treatment</td>
<td>- Cost, IPD</td>
</tr>
<tr>
<td></td>
<td>- No radiation hazard</td>
<td>- Anesthesiologic risks</td>
</tr>
<tr>
<td></td>
<td>- Rapid normalization</td>
<td>- Hypoparathyroidism 1-2%</td>
</tr>
<tr>
<td></td>
<td>- Definitive histological</td>
<td>- Damage recurrent laryngeal nerve, bleeding, infection</td>
</tr>
<tr>
<td></td>
<td>- Most effective in cases with pressure symptoms</td>
<td>- Hypothyroidism</td>
</tr>
</tbody>
</table>
Toxic multinodular goiter

- Hyperthyroidism arises in MNG
- Autonomous function
- Usually occurs after the age of 50 in patients who have had nontoxic MNG
- Treatment: Radioactive iodine or surgery
Toxic adenoma

- Hyperfunctioning nodule
- Nodule diameter > 3 cm
- Typically in patients in their 30-40 years old
- Treatment: Radioactive iodine or surgery
Subacute granulomatous thyroiditis

- Subacute nonsuppurative thyroiditis, de Quervain's thyroiditis, viral thyroiditis, or subacute thyroiditis
- History of an upper respiratory infection, typically 2-8 weeks beforehand
- Mumps, coxsackie, influenza, adenoviruses and echoviruses
- Predominates in female, 30-50 years old
Subacute granulomatous thyroiditis

- Malaise, upper respiratory tract infection
- Gradual or sudden pain in thyroid gland, radiates to the ear, jaw by turning head or swallowing
- Neck pain, tender diffuse goiter
- Transient, usually subsiding in 2-8 weeks
Subacute granulomatous thyroiditis

Thyrotoxic phase
Day 10-20

Hypothyroidism phase
Day 30-63

Euthyroidism
Subacute granulomatous thyroiditis

**Laboratory**
- Elevated T4 and/or T3, RAIU that is low, High ESR/CRP

**FNA**
- Widespread infiltration with neutrophils, lymphocytes, histiocytes and giant cells
Radioiodine uptake และ thyroid scan พบว่ามี low uptake

THYROID SCINTIGRAPHY
Te99m Pertechnetate

Thyroid Uptake = 0.16 %
(Normal value 0.4~3.5%)
Subacute granulomatous thyroiditis

- High dose aspirin 600 mg oral q 4-6 hours
- NSAIDs COX2
- Severe pain: glucocorticoids (prednisolone 40-60 mg/day)

- Thyrotoxic phase: β-adrenagric blockers
- Hypothyroidism: Levothyroxine 50-100 µg/day
Painless thyroiditis

- Silent thyroiditis, subacute lymphocytic thyroiditis, and lymphocytic thyroiditis

- Variant form of chronic autoimmune thyroiditis, Amiodarone, Lithium

- Any woman (who is not postpartum) or man with symptoms < 2 months

- Small diffuse goiter or no thyroid enlargement
- Key: mild hyperthyroidism of short duration, little or no thyroid enlargement, and no signs of Graves'
Postpartum thyroiditis

- Variant form of chronic autoimmune thyroiditis (Hashimoto's thyroiditis)
- ~50% of patients have elevated antiTPO
- Hyperthyroidism: mild, anxiety, weakness, irritability, palpitations, tachycardia and tremor
  - **Beta blocker**
- Hypothyroidism: mild, lack of energy, sluggishness, dry skin and postpartum depression
  - **Eltroxin**
Postpartum thyroiditis

- **Hyperthyroidism**: 1-4 months
- **Hypothyroidism**: 2-8 weeks
- **Euthyroidism**: 2 weeks to several months
Amiodarone and thyroid dysfunction

- Risk ~ 2-30%
- Depending upon underlying thyroid status, dietary iodine intake, and subclinical thyroid disorders
- Intrinsic drug effects
- Extrinsic drug effects
Intrinsic drug effect
Extrinsic drug effect

• Wolff-Chaikoff effect
  • Iodine transport and thyroid hormone synthesis are transiently inhibited

• “Fail to escape" from the Wolff-Chaikoff effect
  • Autoimmune thyroid disease

• Jod-Basedow
  • Autonomous function
Normal, euthyroid individuals

<table>
<thead>
<tr>
<th>Acute phase</th>
<th>After 3-6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4</td>
<td>T4</td>
</tr>
<tr>
<td>20-24%</td>
<td>upper norm</td>
</tr>
<tr>
<td>T3</td>
<td>T3</td>
</tr>
<tr>
<td>30%</td>
<td>lower norm</td>
</tr>
<tr>
<td>rT3</td>
<td>rT3</td>
</tr>
<tr>
<td>20%</td>
<td>upper norm</td>
</tr>
<tr>
<td>TSH</td>
<td>TSH</td>
</tr>
<tr>
<td>upper norm</td>
<td>normal</td>
</tr>
</tbody>
</table>
Amiodarone-induced hypothyroidism

- Hashimoto's thyroiditis or positive antithyroid antibodies more likely to develop persistent hypothyroidism

- Amiodarone is usually not discontinued unless it fails to control the underlying arrhythmia.

- Replacement with T4 while amiodarone is continued.

- Hypothyroidism may persist after withdrawal of amiodarone in patients who have underlying chronic autoimmune thyroiditis
Amiodarone-induced thyrotoxicosis (AIT)

<table>
<thead>
<tr>
<th>TABLE 2. AIT-differential diagnosis and therapy</th>
</tr>
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<tbody>
<tr>
<td></td>
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<tr>
<td><strong>Baseline thyroid condition</strong></td>
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<tr>
<td>Baseline thyroid condition</td>
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<tr>
<td>Thyroid exam</td>
</tr>
<tr>
<td>Ultrasound</td>
</tr>
<tr>
<td>CFDS</td>
</tr>
<tr>
<td>Thyroid autoantibodies</td>
</tr>
<tr>
<td>IL-6</td>
</tr>
<tr>
<td>24-h radiiodine uptake</td>
</tr>
<tr>
<td>Therapy</td>
</tr>
<tr>
<td>Perchlorate may be necessary</td>
</tr>
<tr>
<td>?&lt;sup&gt;131&lt;/sup&gt;I</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
</tbody>
</table>

Prednisolone 40 to 60 mg/day
FOLLOWING PATIENTS RECEIVING AMIODARONE

**BASELINE**
- Thyroid exam
- TPO Ab*
- TSH
- T4
- FTI (or FT4)
- T3 (or FT3)

**EVERY 6 MONTHS**
- Thyroid exam
- TSH
- T4
- FTI (or FT4)
- T3 (or FT3)

Serum TSH ↓
- No change
  - T4, FTI (or FT4)
  - T3 (or FT3)
  - Frequent observations

Serum TSH ↑
- Increased
  - T4, (or FT4)
  - T3 (or FT3)
  - vs previous values
  - AIT

* If TPO Ab positive, increased risk of AIH

AIT: Autoimmune Thyroiditis
AIH: Autoimmune Hepatitis
Thyroid storm

• Thyroid storm is an extreme accentuation of the thyrotoxicosis.

• Uncommon but serious complication.

• Incidence of thyroid storm less than 10% of patients hospitalized for thyrotoxicosis

• Mortality rate due to thyroid storm 20 - 30%\textsuperscript{1,2}

Thyroid storm

- Underlying cause of thyrotoxicosis
  - Graves’ disease
  - Solitary toxic adenoma
  - Toxic multinodular goiter
Clinical features

- Abrupt onset
- Preexisting thyrotoxicosis has been treated incompletely or has not been treated at all

Precipitation

- Infection
- Trauma
- Surgical emergencies or operations
Clinical features

- Fever
- Marked tachycardia of sinus or ectopic origin and arrhythmias
- Pulmonary edema or congestive heart failure
- Tremulousness and restlessness
- Delirium
- Nausea, vomiting and abdominal pain
- Stupor and coma
Burch and Wartofsky score

- Thermoregulatory dysfunction
  - 99-99.9°F      5
  - 100-100.9       10
  - 101-101.9       15
  - 102-102.9       20
  - 103-103.9       25
  - >104            30

- CVS dysfunction:
  - Tachycardia
    - 99-109         5
    - 110-119        10
    - 120-129        15
    - 130-139        20
    - >140           25

- CNS effects
  - Agitation       10
  - Psychosis, delirium 20
  - Seizure, coma   30

- GI- hepatic dysfunction
  - diarrhea, nausea/vomit, abdominal pain 10
  - unexplained jaundice 20

- CHF
  - Pedal edema      5
  - Bibasilar rales 10
  - Pulmonary edema 15

- AF
  - Present          10

- Precipitate history
  - Positive        10
Diagnosis

- Elevated free T4 and free T3
- Depressed TSH (<0.05 μU/mL)
- Hyperglycemia, hypercalcemia, elevated alkaline phosphatase, leukocytosis and elevated liver enzymes.
- Chest radiograph: helpful to seek a possible infectious source as a precipitant.
ECG manifestations of thyrotoxicosis
• Sinus tachycardia \(\sim 40\%\) of cases
• Atrial fibrillation \(\sim 10\%\) of cases
Treatments

Aims

- Correct the severe thyrotoxicosis
- Correct the precipitating illness
- General support

- The patient thought to have thyroid storm should be monitored in a medical intensive care unit during the initial phases of therapy.
Thyroid storm

• PTU 1200 – 1600 mg / day
• Iodine: start after PTU at least 1-2 hr
  • SSKI 5 drops q 6 hr or
  • Lugol’s 10 drops oral q 6 hr
• Propanolol : 160 mg/day
• Dexamethasone : 8 mg/d
  = 2 mg iv q 6 hr for 3-4 days
• Precipitating cause
PTU via rectal route

- PTU can be effectively absorbed via the rectal route.
- The enema form appeared to provide better bioavailability than the suppository form.
- Water-suspension enema was prepared by grinding 50-mg tablets of PTU into small pieces with a mortar and pestle and suspend it in 90 mL of sterile water.
- The suspension was administered by a disposable urinary catheter via rectum.
- Significant decrease in serum FT3 levels was demonstrated at 30 minutes after PTU administration and throughout the study in both groups.
- No change of FT4 levels of both groups was demonstrated. *p < 0.05 when changes of serum FT3 levels were compared to baseline of each group.
Beta-adrenergic blockade

- May result in hypotension in some patients who have heart failure and are being treated for thyrotoxicosis
- Beneficial in the treatment of thyrotoxicosis, careful consideration is required
- If the cause of the heart failure were likely to be underlying tachycardia, beta-blockade would be particularly useful

Relative contraindications

- History of moderate to severe heart failure
- Presence of reactive airway disease
Anticoagulation in atrial fibrillation in the setting of thyrotoxicosis

- Thyrotoxic patients who have atrial fibrillation, antithrombotic therapies should be selected based on the presence of stroke risk factors.

- Thyrotoxic patients may require a lower maintenance dose of warfarin than euthyroid patients because of increased clearance of vitamin K–dependent clotting factors.
Definitive therapy

Radioactive iodine ablation
- May not be able to be used for several weeks or months following treatment with iodine for thyroid storm.

- Following the resolution of thyroid storm, the patient continues to require close follow-up with plans for definitive therapy to prevent a future recurrence of life-threatening thyrotoxicosis.

Surgery

Hypothyroidism

- Puffy appearance
- Enlargement of tongue
- Loss of temporal aspect of eyebrows
- Queen Ann’s sign
- Dryness and coarseness of the skin
Cardiovascular System

• Bradycardia
• Narrowing of pulse pressure
• Pericardial effusion

Respiratory System

• Pleural effusion (rare)
• Obstructive sleep apnea
• Depression of the both hypoxic and hypercapnic ventilatory drives
  ➡️ alveolar hypoventilation, CO$_2$ retention
Alimentary

• Weight gain, loss appetite
• Constipation
• Ascites: associated with pleural & pericardial effusion

CNS and PNS

○ Loss of intellectual function
○ Depression/dementia
○ Delayed muscle contraction and relaxation
○ Myoclonus
○ Carpal tunnel syndrome
Hashimoto’s Thyroiditis

- Autoimmune thyroid disease

- Chronic thyroiditis: intrathyroidal lymphocytic infiltration

- Autoantibodies to thyroid peroxidase (TPOAb) and thyroglobulin (TgAb)

- Goiter, Firm in consistency

- Thyroid lymphoma: should be suspected if there is rapid, usually painful, enlargement of the thyroid gland
Levothyroxine (LT$_4$)

- Half-life: 7 days
- About 80% of the hormone is absorbed relatively slowly.
- Typical dose: 1.6-1.8 µg/kg IBW per day
- Complete equilibration of free T$_4$ ~ 6 weeks
- Adverse effects: Bone loss, AF
- Monitoring
  - Primary hypothyroidism: TSH
  - Secondary hypothyroidism: free T$_4$
<table>
<thead>
<tr>
<th>Benign Nodules (95%)</th>
<th>Carcinomas (5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic nodules (85%)</td>
<td>Papillary (81%)</td>
</tr>
<tr>
<td>Adenomas (15%)</td>
<td>Follicular and Hurthle cell (14%)</td>
</tr>
<tr>
<td>Cysts (&lt;1%)</td>
<td>Medullary (3%)</td>
</tr>
<tr>
<td></td>
<td>Anaplastic (2%)</td>
</tr>
</tbody>
</table>
Clinical findings in favor of malignant thyroid nodules

Historical features

• Young (<20 years) or Old (>60 years)
• Male
• Neck irradiation during childhood or adolescent
• Rapid growth
• Recent changes in speaking, breathing or swallowing
• Family history of thyroid malignancy or MEN2
Clinical findings in favor of malignant thyroid nodules

Physical examination

- Firm and irregular consistency
- Fixation to overlying tissues

- Vocal cord paralysis
- Regional lymph adenopathy
Evaluation of Newly Discovered Thyroid Nodules

- Nodules >1 cm should be evaluated

- There may be nodules <1 cm that require evaluation because of...
  - Suspicious US findings
  - Associated lymphadenopathy
  - History of head and neck irradiation
  - History of thyroid cancer in one or more first-degree relatives
  - Rapid growth and hoarseness
  - Pertinent physical findings suggesting possible malignancy
Low TSH

123I or 99Tc scan

Hyperfunctioning

Evaluate and Tx for hyperthyroidism

Not functioning

Nodule on US

Do FNA

Result of FNA

Evaluate and tx for hypothyroidism

Normal or high TSH

Diagnostic US

No nodule on US

Elevated TSH

FNA not indicated

Normal TSH

Evaluate and Tx for hypothyroidism

History, physical, TSH
Result of FNA

Nondiagnostic
- Repeat US guided FNA
- Non-diagnostic
  - Close F/U or surgery

Malignant PTC
- Pre-op US
- Surgery
  - Not hyperfunctioning

Suspicious for PTC
- Hürthle cell neoplasm
  - Consider $^{123}$I scan if TSH low normal

Interminiate
- Follicular neoplasm

Benign
- Follow
- Hyperfunctioning
Management of Benign nodule

- Ultrasound monitoring, initially at 6 to 12 months, then at increasing intervals over time
- Cystic degeneration and hemorrhage are the most common causes of sudden enlargement
- Small changes in nodule size on serial ultrasonography do not require a repeat aspiration.

**Repeat aspiration when there is substantial growth**
- >50 % change in volume
- >20 % increase in nodule diameter with a minimum increase in two or more dimensions of at least 2 mm
- Change in the texture of a nodule, or
- New symptoms are attributed to a nodule
Nontoxic multinodular goiter (MNG)

- Prevalence 12%, Female predominate
- Mostly asymptomatic

- Large goiters, which may compress the trachea, esophagus and neck vessels
- Inspiratory stridor, dysphagia, choking sensation
Pemberton’s sign
Management of MNG

- FNA
- Small and asymptomatic goiter can be monitored by clinical examination and evaluated periodically with U/S
- No significant benefit of thyroxine therapy
- Surgery: obstructive symptoms, large goiters, substernal goiter