Management of Common Thyroid Issues
Disclosures

- I have no financial disclosures
Objectives

- Hypothyroidism
- Hyperthyroidism
- Thyroiditis
- Thyroid nodules

Regulation of thyroid hormone production

Thyrotropin-releasing hormone (TRH) increases the secretion of thyroid-stimulating hormone (TSH), which stimulates the synthesis and secretion of triiodothyronine (T3) and thyroxine (T4) by the thyroid gland. T3 and T4 inhibit the secretion of TSH, both directly and indirectly by suppressing the release of TRH. T4 is converted to T3 in the liver and many other tissues by the action of T4 monodeiodinase. Some T4 and T3 is conjugated with glucuronide and sulfate in the liver, excreted in the bile, and partially hydrolyzed in the intestine. Some T4 and T3 formed in the intestine may be reabsorbed. Drug interactions may occur at any of these sites.
16 yo F, no PMH, presents with 4-6 months of:
- Irregular periods
- 14 lb weight gain
- Puffy face
- Fatigue
- Tongue swelling
- Decreased concentration, falling asleep in class
- Unable to keep up with water polo practices
- Family history: mother and aunt with thyroid disease

Physical exam
- BMI 28
- Periorbital edema
- Delayed relaxation phase achilles tendon reflex

Labs
- TSH 288
- FT4 0.4
- TPO Ab >1000
- Tg Ab >20
Hypothyroidism

**Thyroid hormone biosynthesis**

1. Iodide (I) trapping by the thyroid follicular cells
2. Diffusion of iodide to the apex of the cells
3. Transport of iodide into the colloid
4. Oxidation of inorganic iodide to iodine and incorporation of iodine into tyrosine residues within thyroglobulin molecules in the colloid
5. Combination of two diiodotyrosine (DIT) molecules to form tetraiodothyronine (thyroxine, T4) or of monoiodothyronine (MIT) with DIT to form triiodothyronine (T3)
6. Uptake of thyroglobulin from the colloid into the follicular cell by endocytosis, fusion of the thyroglobulin with a lysosome, and proteolysis and release of T4, T3, DIT, and MIT
7. Release of T4 and T3 into the circulation
8. Deiodination of DIT and MIT to yield tyrosine

T3 is also formed from monodeiodination of T4 in the thyroid and in peripheral tissues.

**Structures of the thyroid hormones**

- **Thyroxine (T4)**
- **3,5,3'-Triiodothyronine (T3)**
- **3,3,5'-Triiodothyronine (rT3)**
Hypothyroidism

- Prevalence: 0.3% for TSH>5
  - Over age 60: 6-9% women, 1-2% men for TSH>10
- Positive TPO Ab prevalence: 11%
- 5-8X more common in women
- Etiology
  - Iodine deficiency (most common worldwide)
  - US: 95% primary, autoimmune (Hashimoto’s thyroiditis=chronic lymphocytic thyroiditis)
  - Drugs
    - Subacute thyroiditis recovery phase
  - Central: pituitary or hypothalamic dysfunction
  - Congenital
  - Consumptive (rare): paraneoplastic
Presentation of Hypothyroidism

- Hypercholesterolemia (especially LDL)
- Macrocytic anemia
- Hyponatremia
- Hyperuricemia
- Elevated CK
- Bleeding risk: acquired vWB syndrome
- Hypogonadism
- Carpal tunnel syndrome
- Peripheral neuropathy
- Hypothermia

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Symptoms</th>
<th>Signs</th>
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</thead>
<tbody>
<tr>
<td>Slowing of metabolic processes</td>
<td>Fatigue and weakness</td>
<td>Slow movement and slow speech</td>
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<tr>
<td></td>
<td>Cold intolerance</td>
<td>Delayed relaxation of tendon reflexes</td>
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<td></td>
<td>Dyspnea on exertion</td>
<td>Bradycardia</td>
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<tr>
<td></td>
<td>Weight gain</td>
<td>Carotenemia</td>
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<td></td>
<td>Cognitive dysfunction</td>
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<td></td>
<td>Mental retardation (infantile onset)</td>
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<tr>
<td></td>
<td>Constipation</td>
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<tr>
<td></td>
<td>Growth failure</td>
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<tr>
<td>Accumulation of matrix substances</td>
<td>Dry skin</td>
<td>Coarse skin</td>
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<tr>
<td></td>
<td>Hoarseness</td>
<td>Puffy facies and loss of eyebrows</td>
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<tr>
<td></td>
<td>Edema</td>
<td>Periorbital edema</td>
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<td></td>
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<td>Enlargement of the tongue</td>
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<tr>
<td>Other</td>
<td>Decreased hearing</td>
<td>Diastolic hypertension</td>
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<tr>
<td></td>
<td>Myalgia and paresthesia</td>
<td>Pleural and pericardial effusions</td>
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<tr>
<td></td>
<td>Depression</td>
<td>Ascites</td>
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<td></td>
<td>Menorrhagia</td>
<td>Galactorrhea</td>
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<td></td>
<td>Arthralgia</td>
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<td></td>
<td>Pubertal delay</td>
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</tbody>
</table>
Risk Factors for Hypothyroidism

- Goiter
- Iodine deficiency *or* excess
- History of postpartum or deQuervain’s thyroiditis
- History of thyroidectomy, radioactive iodine, head/neck radiation
- Family or personal history of autoimmune disease
- Radiation, surgery, trauma, or infiltrative diseases to pituitary or hypothalamus
- Drugs
- Increased TBG clearance: nephrotic syndrome, liver disease
### Screening for Hypothyroidism

#### Table 8
**Recommendations of Six Organizations Regarding Screening of Asymptomatic Adults for Thyroid Dysfunction**

<table>
<thead>
<tr>
<th>Organization</th>
<th>Screening recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Thyroid Association</td>
<td>Women and men $&gt;35$ years of age should be screened every 5 years.</td>
</tr>
<tr>
<td>American Association of Clinical Endocrinologists</td>
<td>Older patients, especially women, should be screened.</td>
</tr>
<tr>
<td>American Academy of Family Physicians</td>
<td>Patients $\geq 60$ years of age should be screened.</td>
</tr>
<tr>
<td>American College of Physicians</td>
<td>Women $\geq 50$ years of age with an incidental finding suggestive of symptomatic thyroid disease should be evaluated.</td>
</tr>
<tr>
<td>U.S. Preventive Services Task Force</td>
<td>Insufficient evidence for or against screening</td>
</tr>
<tr>
<td>Royal College of Physicians of London</td>
<td>Screening of the healthy adult population unjustified</td>
</tr>
</tbody>
</table>
TSH is the most sensitive screening test

What is the normal TSH range?

- 95% of young adults have TSH 0.4-2.5 mU/L
- Adults over 65:
  - higher TSH correlated with lower CV and all-cause mortality
  - No correlation between higher TSH (4-10) and symptoms, ADLs

- TSH>10 associated with increased CVD mortality and CHF
# Diagnosis of Hypothyroidism

## Table 7

**Thyrotropin Upper Normal**

<table>
<thead>
<tr>
<th>Group, study, society</th>
<th>TSH upper normal</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NACB</td>
<td>2.5</td>
<td>When there is no evidence of thyroid disease</td>
</tr>
</tbody>
</table>
| NHANES III, disease free | 4.5            | No self-reported thyroid disease  
                        |                  | Not on thyroid medications |
| NHANES III, reference population | 4.12           | No self-reported thyroid disease  
                        |                  | Not on thyroid medications  
                        |                  | Negative anti-thyroid antibodies  
                        |                  | Not pregnant  
                        |                  | Not on estrogens, androgens, lithium |
| Hanford Thyroid Disease Study | 4.10           | No evidence of thyroid disease  
                        |                  | Negative anti-thyroid antibodies  
                        |                  | Not on thyroid medications  
                        |                  | Normal ultrasound (no nodules or thyroiditis) |
| Pregnancy, first trimester | 2.0-2.5         | See sections *L-thyroxine treatment of hypothyroidism*  
                        |                  | and *Hypothyroidism during pregnancy* |
| Pregnancy, second trimester | 3.0            | See sections *L-thyroxine treatment of hypothyroidism*  
                        |                  | and *Hypothyroidism during pregnancy* |
| Pregnancy, third trimester | 3.5            | See sections *L-thyroxine treatment of hypothyroidism*  
                        |                  | and *Hypothyroidism during pregnancy* |

_Sources:_ Stagnaro-Green et al., 2011 (10); Hollowell et al., 2002 (11); Hamilton et al., 2008 (81); Baloch et al., 2003 (85).  
_NACB, National Academy of Clinical Biochemists; NHANES, National Health and Nutrition Examination Survey_
Diagnosis of Hypothyroidism

- TPO Ab 90% sensitive for autoimmune thyroiditis
- DDx of discordant thyroid function tests: thyroid hormone resistance, HAMA Ab, recovery from non-thyroidal illness, non-functioning pituitary adenoma, recovery from subacute thyroiditis, TSH-secreting adenoma
Subclinical Hypothyroidism

- Elevated TSH, normal FT4
- Prevalence: 4.3%
- Progression to overt hypothyroidism 5% per year
- TSH 2.5-4.5: treatment improves lipids, intima media thickness, endothelial dysfunction, but no data on outcomes
Treatment of Hypothyroidism

- Take on empty stomach 30 min before breakfast or 4 hours after dinner
- May be subtle differences in bioavailability between brands and generics, best to stick with the same formulation
- Full replacement dose: 1.6mcg/kg; more correlated to lean mass than total body weight
- Start with 25-50mcg in elderly or CVD patients
- 16% Hashimoto’s patients have type 2 deiodinase deficiency, may benefit from T4/T3 combination
- May need dose adjustments with OCP, pregnancy, menopause
# Drugs Affecting Thyroid Function

## Drugs that cause hypothyroidism, hyperthyroidism, or changes in thyroid function tests

<table>
<thead>
<tr>
<th>Drugs causing hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of thyroid hormone synthesis and/or release - thionamides, lithium, perchlorate,</td>
</tr>
<tr>
<td>aminogluthethimide, thalidomide, and iodine and iodine-containing drugs</td>
</tr>
<tr>
<td>including amiodarone, radiographic agents, expectorants (Organidin, Combid), kelp</td>
</tr>
<tr>
<td>tablets, potassium iodine solutions (SSKI), Betadine douches, topical antiseptics</td>
</tr>
<tr>
<td>Decreased absorption of T4 - cholestyramine, colestipol, colesvelam, aluminum</td>
</tr>
<tr>
<td>hydride, calcium carbonate, sucralfate, iron sulfate, ranolaxine, omeprazole,</td>
</tr>
<tr>
<td>lanoprazole, and possibly other medications that impair acid secretion, sevelamer,</td>
</tr>
<tr>
<td>lanthanum carbonate, and chromium; malabsorption syndromes can also diminish T4</td>
</tr>
<tr>
<td>absorption</td>
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<tr>
<td>Immune dysregulation - interferon-alfa, interleukin-2, alemtuzumab</td>
</tr>
<tr>
<td>Suppression of TSH - dopamine</td>
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<tr>
<td>Possible destructive thyroiditis - sunitinib</td>
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<tr>
<td>Increased type 3 deiodination - sorafenib</td>
</tr>
<tr>
<td>Increased T4 clearance and suppression of TSH - bexarotene</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs causing hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulation of thyroid hormone synthesis and/or release - iodine, amiodarone</td>
</tr>
<tr>
<td>Immune dysregulation - interferon-alfa, interleukin-2, ipilimumab, alemtuzumab</td>
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</tbody>
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<table>
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<tr>
<th>Drugs causing abnormal thyroid function tests without thyroid dysfunction</th>
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<tbody>
<tr>
<td>Low serum TBG - androgens, danazol, glucocorticoids, slow-release nacoc (nicotinic acid),</td>
</tr>
<tr>
<td>l-asparaginase</td>
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<tr>
<td>High serum TBG - estrogens, tamoxifen, ranolaxine, methadone, 5-fluorouracil, doflibrate,</td>
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<tr>
<td>heroin, mitotane</td>
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<tr>
<td>Decreased T4 binding to TBG - salicylates, aalsalate, furosemide, heparin (via free fatys</td>
</tr>
<tr>
<td>acids), certain NSAIDs</td>
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<tr>
<td>Increased T4 clearance - phenytoin, carbamazepine, ritapam, phenobarbital</td>
</tr>
<tr>
<td>Suppression of TSH secretion - dobutamine, glucocorticoids, octreotide</td>
</tr>
<tr>
<td>Impaired conversion of T4 to T3 - amiodarone, glucocorticoids, contrast agents for oral</td>
</tr>
<tr>
<td>cholecystography (eg, iopanoic acid), propylthiouracil, propanol, nadolol</td>
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</table>

T4: thyroid; TSH: thyroid-stimulating hormone; TBG: thyroid-binding globulin; NSAIDs: nonsteroidal anti-inflammatory drugs; T3: triiodothyronine.
Dessicated thyroid hormone: naturethroid, armour thyroid
- Porcine extracts cleaned of connective tissue
- Supraphysiologic ratio of T4/T3
  - Humans: 14:1
  - Pigs: 4:1

Crossover study of dessicated thyroid vs. LT4
- No difference in physiologic or psychologic parameters
- Significant difference in weight loss (mean 3 lbs)
Iodine Supplements

- RDA 150mcg/day, 250mcg/day pregnancy
- Kelp-containing supplements: up to 9x RDA
- Na/I symporter highly regulated based on dietary supply
- Wolff-Chiakoff effect
- Jod-Basedow effect
- AACE guidelines: “No data support the role of iodine in enhancing thyroid function”
Other Thyroid Supplements

- Phytoestrogens
  - Subclinical hypothyroidism-no difference at 8 wks
- Soy
  - No difference in TFTs at 2 years
- Selenium
  - May decrease anti-TPO Ab
  - No difference on thyroid hormone synthesis in normal population
  - Pregnant patients: decrease in postpartum thyroid dysfunction and incidence of hypothyroidism with selenium supplementation during and after pregnancy
Porcine or bovine thyroid extracts
- 9/10 supplements have T3 content
  - >10mcg=50% T3 produced/day
- 4/10 supplements have T4 content
  - 8.5-91.6mcg/day
- TRIAC(3,5,3’-triiodothyroacetic acid): metabolite of T4 with metabolic action
  - Binds to T3 receptor, decreases TSH
  - Increased hepatic and skeletal effects compared to T4
  - Banned by FDA but still available online
16 yo F, no PMH, presents with 4-6 months of:
- Irregular periods
- 14 lb weight gain
- Puffy face
- Fatigue
- Tongue swelling
- Decreased concentration, falling asleep in class
- Unable to keep up with water polo practices
- Family history: mother and aunt with thyroid disease

**Physical exam**
- BMI 28, 70 kg
- Periorbital edema
- Delayed relaxation phase achilles tendon reflex

**Labs**
- TSH 288
- FT4 0.4
- TPO Ab >1000
- Tg Ab >20

**Treatment**
- Levothyroxine 175mcg daily, recheck TSH, FT4 6 weeks
- Levothyroxine tapered down to 125mcg over the next 12 weeks
- Lost 12 lbs, menstruation normalized, symptoms improved
Thyrotoxicosis: TT3: TT4 >20

Thyroiditis or iodine excess
TT3: TT4 <20

The initial thyroid inflammation damages thyroid follicles and activates proteolysis of the thyroglobulin stored within the follicles. The result is unregulated release of large amounts of thyroxine (T4) and triiodothyronine (T3) into the circulation and therefore hyperthyroidism. This state lasts only until the stores of thyroglobulin are exhausted, because new hormone synthesis ceases. As the inflammation subsides, the thyroid follicles regenerate and thyroid hormone synthesis and secretion resume. There may be a transient period of hypothyroidism and increased TSH secretion before thyroid secretion becomes normal again. However, some patients have only a hyperthyroid or hypothyroid phase.
Case #2

- 42 yo F, no PMH, presents with:
  - Insomnia
  - Palpitations
  - Excessive sweating
  - Fatigue
  - Dry eyes
  - Mood swings
  - 8 months postpartum, lactating

- Physical exam
  - HR 108
  - Mild proptosis
  - Non-tender, symmetric, firm goiter
  - Fine tremor

- Labs
  - TSH <0.01
  - FT4 5.8
  - TT3  217
  - TPO Ab 270
  - Tg Ab neg
  - TSI 313
Hyperthyroidism can cause the thyroid gland to enlarge. This causes a swelling in the neck called a "goiter". Hyperthyroidism caused by Grave’s disease can also make the eyes bulge.

Reproduced with permission from: Anatomical Chart Company. Copyright © 2006 Lippincott Williams & Wilkins.
Hyperthyroidism

- Prevalence in US: 1.2%
- Etiology
  - Graves or Hashitoxicosis (autoimmune)
  - Toxic nodular goiter
  - Subacute or acute thyroiditis
  - Iodine excess
  - Exogenous thyroid hormone
  - Struma ovarii
  - Hyperemesis gravidarum or trophoblastic disease
  - Metastases from follicular thyroid Ca
Symptoms: anxiety, weakness, tremors, palpitations, heat intolerance, excessive sweating, menstrual problems, hyperdefecation, urinary frequency, insomnia, weight loss, increased appetite, dyspnea, depression, psychosis, apathy (older patients), hair loss.

Signs: atrial fibrillation, osteoporosis, CHF, hyperglycemia, lid lag, stare, proptosis, thyroid bruit, hyperthermia, systolic HTN, hyperreflexia, periorbital edema, pretibial myxedema, goiter, elevated AP, onycholysis, normochromic normocytic anemia, gynecomastia.
Diagnosis of Hyperthyroidism

- Suppressed TSH (usually undetectable), elevated FT4 and/or TT3
- Thyrotoxicosis: TT3: TT4 >20
- Thyroiditis or iodine excess TT3: TT4 <20
- Elevated TSI, elevated TPO or Tg Ab
- Increased radioactive iodine uptake
- DDx for discordant TFTs: thyroid hormone resistance, TSHoma, TBG abnormality, androgens or estrogens, antiepileptics, Ab to T3 or T4, paraneoplastic, non-thyroidal illness
123-I thyroid scan demonstrating an autonomous ("hot") nodule with suppression of isotope uptake elsewhere. The total 24-hour isotope uptake was normal (12 percent).

SSN: suprasternal notch.

Courtesy of Douglas Ross, MD.
Subclinical Hyperthyroidism

- Prevalence 0.7% (TSH<0.1)
- Most common cause toxic nodular disease
- Progression to overt hyperthyroidism: 6% year 1, 1-25% at 5 years
- Increased risk of cardiac events (HR 1.21), CVD (HR 1.39), CHF (2-3x)
- 20-30% increased RR CV and all-cause mortality
- Treat if TSH <0.1, consider if TSH 0.1-0.5

Increased incidence of atrial fibrillation in subclinical hyperthyroidism

Cumulative incidence of atrial fibrillation in subjects over age 60 according to the serum concentration of thyrotropin (TSH). The risk of atrial fibrillation was increased almost threefold in the subjects with marked suppression of TSH (left panel) as compared with those who had normal serum TSH concentrations and were presumably euthyroid (right panel); patients with slightly low serum TSH concentrations (middle panel) had a lesser increase in risk.

Treatment of Hyperthyroidism

- Beta-blockers
- Thionamides
  - Methimazole
  - Propylthiouracil
  - Remission in 30-50% after 18 months
- Radioactive iodine ablation
- Thyroidectomy
- Refractory disease: iodinated contrast, glucocorticoids, lithium, cholestyramine, rituximab
Case #2 Revisited

- 42 yo F, no PMH, presents with:
  - Insomnia
  - Palpitations
  - Excessive sweating
  - Fatigue
  - Dry eyes
  - Mood swings
  - 8 months postpartum, lactating

- Physical exam
  - HR 108
  - Mild proptosis
  - Non-tender, symmetric, firm goiter
  - Fine tremor

- Labs
  - TSH <0.01
  - FT4 5.8
  - TT3 217
  - TPO Ab 270
  - Tg Ab neg
  - TSI 313

- Treatment
  - Methimazole 10 BID→20 daily, propranolol 10-20mg TID PRN
  - Methimazole tapered down to 5 daily over the next 3 months, propranolol stopped
  - Goiter shrunk, lost 5 lbs, improvement in symptoms
Case #3

- 72 yo F, h/o HTN, osteoporosis, osteoarthritis, p/w 2-3 months right neck lump, discomfort with swallowing
  - 3cm right-sided thyroid nodule on exam
- Workup
  - TSH 2.46
  - Thyroid US: 3.6cm mixed solid/cystic nodule taking up most of the right thyroid lobe, no LN
  - US-guided FNA: benign
  - Right hemithyroidectomy-follicular thyroid cancer, 3.9cm tumor, no invasion, no LN
  - Left completion thyroidectomy-normal thyroid
Thyroid Nodules

This figure shows a thyroid nodule on the left side of the thyroid. Thyroid nodules feel round or oval-shaped, and differ from the surrounding normal thyroid tissue. A person may have one or more thyroid nodules.
Thyroid Nodules

- US: annual incidence 0.1%
- Risk increases 2-3x every half decade above age 25
- Risk of malignancy 5-10%
- Higher risk of nodules in women, but higher risk of malignancy in men
- Risk factors for thyroid cancer: 1\textsuperscript{st} degree FHx, head/neck radiation, compressive symptoms, high TSH, familial syndrome, rate of nodule growth
Indications for biopsy

- Suspicious US features: hypoechoic, increased vascularity, irregular margins, microacalcifications, absent/irregular halo, taller than deeper, cervical lymph nodes, invasion of muscle
- Mixed cystic/solid nodule
  - <1cm with risk factors, suspicious features
  - 1.5-2cm with suspicious features
  - >2cm
- Rapid growth, compressive symptoms
- Purely cystic-almost always benign, no need to biopsy
- Cold nodule on thyroid scan
Nonfunctioning thyroid nodule: Appearance on thyroid scintigraphy

123-I thyroid scan demonstrating typical appearance of a large, 3.5 cm hypofunctioning ("cold") nodule in the left upper lobe of the thyroid. The position of the nodule is outlined in white.

SSN: suprasternal notch.

Courtesy of Douglas Ross, MD.

Thyroid calcification

Sonogram of the right lobe of the thyroid gland in the longitudinal plane that shows a dense bright arc (arrow), which is a coarse calcification. Blockade of the ultrasound signal distally produces shadowing.

L: thyroid lobe.

Courtesy of Manfred Blum, MD.
Suppressive Therapy for Nodules

Thyroxine suppresses goiter growth

Relative changes in thyroid volume in patients with nontoxic goiter treated with placebo, thyroxine (T4) plus carbamazepine (CBZ), or thyroxine alone for nine months and then followed for an additional nine months. Thyroxine suppressed thyroid volume, an effect that persisted only during the phase of active treatment. Carbimazole was of no added benefit.

Functional thyroid disease is common
  - Screen with TSH
  - When to refer to endocrinology
    - Severe symptoms
    - Unable to achieve euthyroidism with standard treatment
    - Discordant thyroid function tests
    - Consideration for radioactive iodine treatment

Thyroid nodules risk increases with age
  - Most are benign
  - When to refer to endocrinology
    - Suspicious findings on ultrasound
    - Compressive symptoms
References