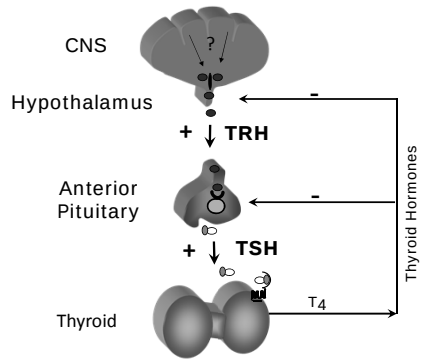
Update on Thyroid Disorders 2016

- **Objectives: Be able to diagnose and treat:**
- **Thyroid Dysfunction**
  - Hyperthyroidism
  - Hypothyroidism
  - Challenging Patients
- **Thyroid Nodules**
- **Thyroid Cancer**

Regulation of Thyroid Hormone Synthesis and Secretion



CASE I

- 23 year old white female medical student
- **CC:** 2 weeks of palpitations, 10 lbs weight loss, insomnia
- **HPI:** Usual state of excellent health until gradual onset of rapid heart beat, initially at HS
- Gradual dyspnea and palpitations after mild exertion during the day and at rest.
- Ferocious appetite, she has lost 10 pounds.
- **PMHx:** None **MEDS:** OCPs
- **ROS:** Irreg. Menses x 2 months
- **F&SH:** Mother/sister w/thyroid disease

CASE I: (continued)

- **PE:** Blood pressure: 140/90 mmHg
- Pulse 110/min
- Temperature 37°C
- Respirations: 10/min
- Weight 55 Kg; Height 5' 2" BMI 22.2 kg/m2

- + Stare, possible exophthalmos
- + Goiter 35-45 gm; diffusely enlarged, nontender
- -No obvious bruit
- + Hyperdynamic precordium
- + Velvety, moist, warm skin
- + Brisk reflexes with fine tremor

Thyroid Dysfunction - **Thyrotoxicosis**

- Which Tests do you order:
  - TSH? **Yes**
  - FT4? **Yes**
  - Total or Free T3? **Yes, if suspect T-Tox suspected**
  - Antithyroid antibodies? **Yes, if suspect Thyrotoxicosis**
  - Scan/Uptake? **For D/D of HYPER/Thyroiditis/Nodule**
  - Reverse T3? **NO, Almost NEVER**
  - Ultrasound? **NO, Almost NEVER unless you feel a nodule**

CASE I: (continued)

Initial Laboratory testing

TEST	PATIENT	NORMAL	
TSH	<0.01 mU/L	0.3-4.1	
FT4	5.84 ng/dl	0.9-1.7	3.4 X ulnl
TT3	350 ng/dl	90-110	3.2 X ulnl
Antibodies	Mc 1:2,420 Tg 1:64 TSI Pending TBII Pending	Positive negative <130% <10	

Differential DIAGNOSIS: **Autoimmune thyroid disease?**
Hyperthyroidism?
Graves' disease?
Toxic Nodular Goiter?
Painless subacute thyroiditis?
Iatrogenic thyrotoxicosis?

Thyrotoxicosis Treatment

- **General:**
  - Beta Blockers for symptomatic tachycardia
- **Specific for Hyperthyroidism:**
- Methimazole/Tapazole®
  - 15 mg po BID
  - Monitor LFTs and CBC at baseline
  - Monitor FT4 and T3 every 3-4 weeks
  - TSH may take months to normalize
  - Titrate down dose after TSH is detectable
  - Remain on therapy for 6-12 months and then decrease
    - 33% go into spontaneous remission
    - 33% become hypothyroid
    - 33% have a recurrence
- Propylthiouracil (PTU) is used in the first trimester of pregnancy only

Hyperthyroidism – AITD/TNG

- RADIOACTIVE IODINE (I-131)
  - When unable to tolerate antithyroid medications
  - In absence of ophthalmopathy
  - Can take up to 6 months to be affective
  - >50% of patients become hypothyroid
    - depending on dose, desirable outcome for CV health
- Surgical thyroidectomy
  - When failed medication, unable to wait for RAI to work
  - Suspicious FNA of cold nodule
  - Refusal of 131-I therapy

CASE I: (continued)

6 week follow up Laboratory testing (no Rx):

TEST	PATIENT	NORMAL	Previous	
TSH	<0.01 mU/L	0.3-4.1	<0.01	
FT4	0.7 ng/dl	0.9-1.7	5.84	(3.4Xnl)
TT3	56 ng/dl	90-110	350.00	(3.2Xnl)
Antibodies	Mc 1:2,200	positive	2,420.00	
	Tg negative	negative	1:64	
	TSI	<130%	65%	
	TBII	<10	6.0	

DIAGNOSIS: **RECOVERING THYROIDITIS**
AUTOIMMUNE THYROID DISEASE

RAIUptake would be close to 0%
No treatment would be indicated

CASE II

- 56 year old homemaker
- CC: hair loss, wgt gain, and fatigue 6 months
- HPI: Difficulty loosing weight and ultimately weight gain (+ 6 lbs.), listless, “brain fog”. Excess hair in shower drain.
- Has read on internet about “natural thyroid”.
- **PMHx:** Menopause **MEDS:** None
- **ROS:** Decreased libido **F&SH:** Mother thy Dz

CASE II: (continued)

- **PE:** Blood pressure: 140/90 mmHg
- Pulse 60/min
- Temperature 37°C
- Respirations: 12/min
- Weight 85 Kg; Height 5 ‘5”, BMI 31.8 kg/m2

- - no exophthalmos
- - no palpable thyroid gland
- - no visible alopecia
- - normal reflexes

Thyroid Dysfunction - **Hypothyroidism**

- Which Tests do you order:
  - TSH? **Yes**
  - FT4? **Defines degree of dysfunction**
  - Total or Free T3? **NO, Almost Never**
  - Antithyroid antibodies? **Yes, useful if TSH is borderline**
  - Scan/Uptake? **NO**
  - Reverse T3? **NO**
  - Ultrasound? **NO, unless you palpate a nodule**

CASE II: (continued)

Initial Laboratory evaluation:

TEST	PATIENT	NORMAL
TSH	6.0	0.3-4.1
FT4	0.95 ng/dl	0.9-1.7
Antibodies	Mc 1:120	negative
	Tg negative	negative

DIAGNOSIS: MILD HYPERTHYROTROPINEMIA?
?SUBCLINICAL HYPOTHYROIDISM
PROBABLY NORMAL?

"TREATMENT": REPEAT TSH IN 2 MONTHS OR SOONER, IF SYMPTOMS WORSEN

Thyroid Dysfunction
Hypothyroidism

FORMS OF THYROID HORMONE REPLACEMENT

LT4:
- **Levothyroxine (Generic)**
- **Synthroid®**
- **Levoxyl®**
- **Unithroid®**
- **Tirosint®**

LT3: Cytomel®, Liothyronine (Generic)

LT4 + LT3:
- **Armour Extract**
- **Thyroid - porcine**
- **NP Thyroid**
- **Nature-Thyroid**

Reasons not to give T3 or T3 and T4 in Combination

T3 has a short half life (hours)
- **-Inconvenient dosing**
- **-Non-physiologic PK**

T3 is not easily transported across the Blood Brain Barrier

Each tissue converts T4 to the exact amount of T3 needed
- **- Genetically determined**

No evidence that T3 alleviates the symptoms of hypothyroidism
- **- When compared to LT4 alone**

Variable amounts of T3 in the porcine preparations
- **-4:1 LT4/LT3 not physiologic (14:1 physiologic)**

Thyroid Dysfunction
Hypothyroidism

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LT4 + LT3:
- **Armour Extract** X
- **Thyroid - porcine** X
- **NP Thyroid** X
- **Nature-Thyroid** X

LT4 Dosing in Hypothyroid Patients

Per: Garber JR et al. Thyroid 2012 22(12):1200-1235.

1.6-1.7 mcg/kg/day

Per: Di Donna et al. Thyroid 2014: 25, 759

LT4 µg/kg/d	BMI ≤ 23	BMI 24-28	BMI > 28
Age ≤ 40 y	1.8	1.7	1.6
Age 41 – 55 y	1.7	1.6	1.5
Age > 55 y	1.6	1.5	1.4

Per: Ojoma et al. J Am Coll Surg 2013: 216, 454

LT4 (µg/kg/day) = -0.018 x BMI + 2.13

BOTTOM LINE: USE YOUR CLINICAL JUDGEMENT

SPECIAL CONSIDERATIONS IN TREATING PATIENTS WITH HYPOTHYROIDISM

GOAL = TSH wnl (except h/o high risk Thyroid Cancer ≤ 0.1 mU/L)

Adjustment of LT4 therapy in hypothyroid patients during pregnancy
- -Increase dose by 30% when pregnancy is confirmed
- -Monitor monthly, or at least every trimester
- -Readjust after delivery

Persistent symptoms of HYPOTHYROIDISM despite normal or suppressed TSH
- -Need to gain patient's confidence, symptoms often resolve in 6-9 months
- -Look for other causes of symptoms
- -Consider titration of TSH to 0.5-2.0 mIu/ml
- -Consider influence of high antithyroid antibody titers???

Unable to achieve a normal TSH despite supraphysiologic doses of LT4
- -Noncompliance
- -Nephrosis
- -Malabsorption (h/o gut surgery; celiac disease, lactose intol; gastritis
- -Concurrent ingestion of food, calcium, fibrates, iron, others

Ritratto di
Gentildonna
ca 1500

Jacopo de Barbari
1460-1516
Venezia

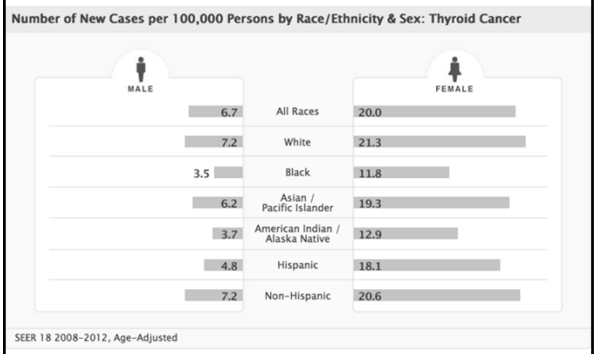
CASE III

- 56 year old welder
- CC: hair loss, wgt gain, and fatigue 6 months
- HPI: Difficulty loosing weight and ultimately weight gain (+ 6 lbs.), listless, “brain fog”.
- Has noticed “lump” in neck while shaving.
- **PMHx:** HBP, ↑ Chol **MEDS:** HCTZ, Statin
- **ROS:** Decreased libido **F&SH:** Mom Thy Ca

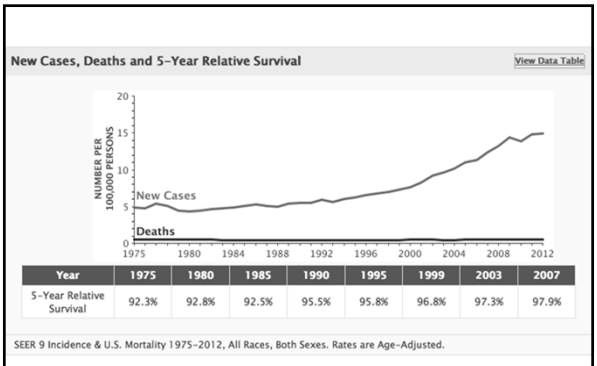
FACTS ABOUT THYROID NODULES AND CANCER

PREVALENCE of Nodules:
5% Woman; 1% Men on physical examination
High Resolution US: 19-68%!

CANCER prevalenced:
7-15% depending on age, gender, radiation exposure
Increasing as imaging increases



www.cancer.gov



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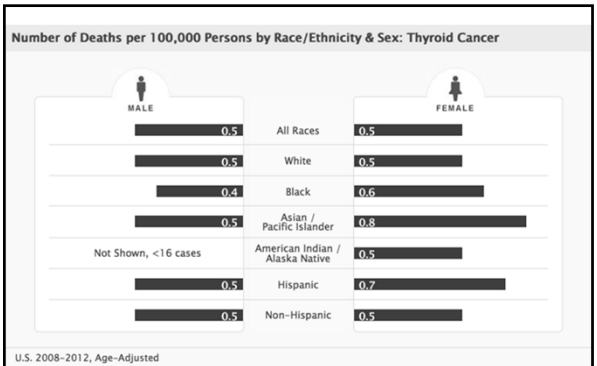

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- 5% Woman; 1% Men on physical examination
- High Resolution US: 19-68%!

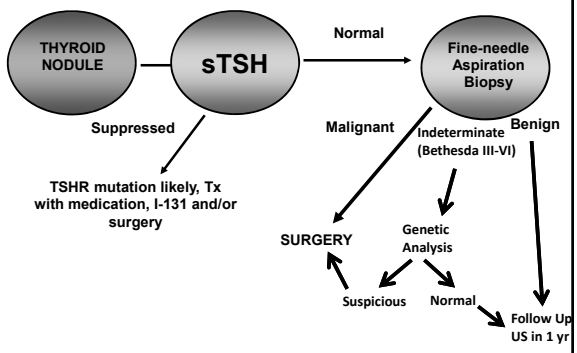
CANCER prevalenced:
- 7-15% depending on age, gender, radiation exposure
  - Increasing as imaging increases
- 2016: 5th most common cancer in women at cost of $19-21 Billion
  - 64,300 new cases estimated
  - 1,980 deaths from thyroid cancer (0.3% mortality)

Aggressive case finding Indications:
- High risk (exposure to radiation)
- Familial occurrence (3 or more?)
- Cowden's disease
- Familial adenomatous polyposis
- Carney Complex
- MEN 2
- Progeria

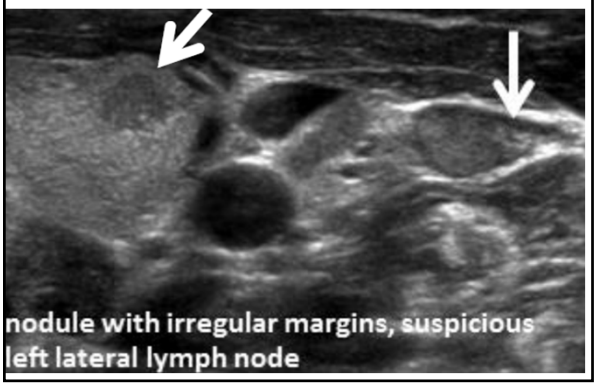
COMPARISON OF THYROID NODULES

BENIGN Characteristics	CANCER Risk Characteristics
Family history of benign goiter	Solitary Nodule
Diffuse or multinodular goiter	Higher /Nodule CA rate
-Decreased malignancy rate	Hard, fixed
-Cancer/nodule NOT/patient	Rapidly enlarging
Constant size over time	Hoarseness with vocal cord paralysis
US vs. Palpation	Age <14; >65 years
Benign FNA	Ultrasound: see next slide
Simple cyst by sonography	Abnormal FNA
Hyperfunctioning by ^{123}I scan	Abnormal genetic analysis

APPROACH TO EVALUATION OF THYROID NODULE



High Suspicion Images



Ultrasound Pattern = Risk

- **High Suspicion** = 70-90% Cancer Risk
  - Hypoechoic, microcalcs, irregular border
  - Hypoechoic, microlobulated margin
  - Hypoechoic, irreg margin, Taller than wide
  - Hypoechoic, irreg margin, X-thyroid Extension
  - Irregular margins, suspicious Lymph nodes
- **Intermediate suspicion** = 10-20% Risk
  - Hypoechoic with regular margins

Haugen BR et al. 2016 Thyroid 26(1):1-133

Ultrasound Pattern = Risk

- **Low Suspicion** = 5-10% Risk of cancer
  - Hy**per**echoic, solid, regular margins
  - **Iso**echoic, solid, regular margins
  - Partially Cystic, eccentric solid area

Haugen BR et al. 2016 Thyroid 26(1):1-133

Ultrasound Pattern = Risk

- **Low Suspicion** = 5-10% Risk of cancer
  - Hy**per**echoic, solid, regular margins
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  - Partially Cystic, eccentric solid area
- **Very Low suspicion** = <3% Risk of cancer
  - Spongiform, partially cystic no suspicions features

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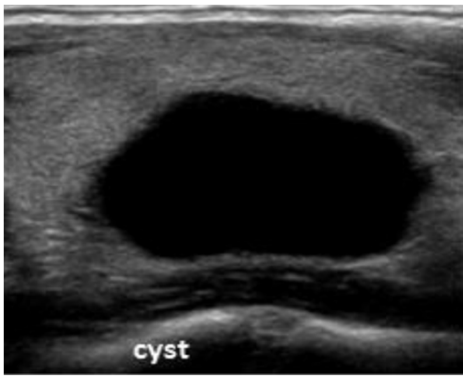
  - Partially Cystic, eccentric solid area
- **Very Low suspicion** = <3% Risk of cancer
  - Spongiform, partially cystic no suspicions features
- **Benign**
  - Purely cystic

Haugen BR et al. 2016 Thyroid 26(1):1-133

Benign



Who to Biopsy? R8

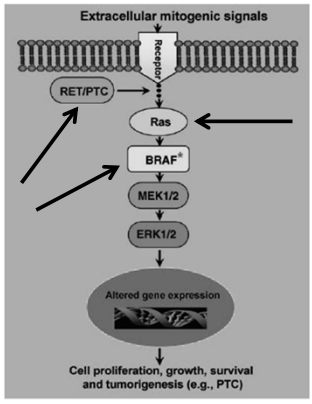
Sonographic Risk Pattern	Estimated Malignancy Risk	Consider Biopsy	Strength of Recommendation	Quality of Evidence
High Suspicion	>70-90%	≥ 1 cm	Strong	Moderate
Intermediate Suspicion	10-20%	≥ 1 cm	Strong	Low
Low Suspicion	5-10%	≥ 1.5 cm	Weak	Low
Very Low suspicion	< 3%	≥ 2 cm	Weak	Moderate
Benign	< 1%	No	Strong	Low
FNA NOT recommended for nodules not meeting above criteria, including ALL nodules < 1cm			Strong	Moderate

Haugen BR et al. 2016 Thyroid 26(1):1-133

Fine Needle Aspiration

- FNA is the procedure of choice in the evaluation of thyroid nodules when clinically indicated. **Rec. 7**
  - Strong Recommendation, High-quality evidence

Haugen BR et al. 2016 Thyroid 26(1):1-133



MAP kinase pathway

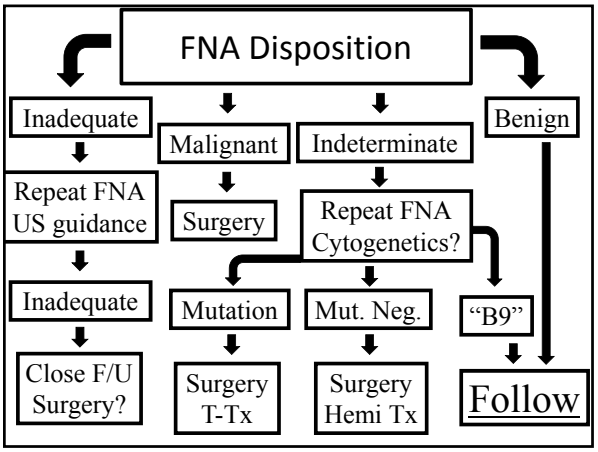
- B-type RAF kinase is abundant protein
- T1799A mutation results in BRAF(V600E) that is constitutively activated

Xing M, Endo Rev 2007 28(7):742-62

TABLE 11.1 Summary of genetic events involved in thyroid carcinogenesis

Gene	Tumor histology	Prevalence	References
RET (point mutations)	MTC (hereditary)	Germline: >95%	[1–3]
RET (point mutations)	MTC (sporadic)	Somatic: ~50%, up to 80% in some reports	[3–6]
RET rearrangements	PTC	Sporadic: ~20%	[3, 4, 7, 8]
		Radiation-associated: 50–80%	
BRAF mutation	PTC	29–69%	[8, 9]
	PDTC	0–15%	
	ATC	10–35%	
BRAF rearrangement	PTC	Sporadic: 1%	[3, 8, 10]
		Radiation-associated: 11%	
RAS mutation	PTC	~10%	[3, 8, 11]
	FTC	~45%	
	PDTC	20–35%	
	ATC	Up to 50–60%	
NTRK1 rearrangement	PTC	Sporadic: 5–13%	[3, 8, 12]
		Radiation-associated: 3%	
PIK3CA point mutation or amplification	FTC	10–30%	[3, 13]
	ATC	25–45%	
PTEN loss or point mutation	FTC	8–10%	[3, 14]
	ATC	~6%	
TP53 loss or point mutation	PTC	0–5%	[3, 8, 11, 15]
	FTC	0–9%	
	PDTC	20–25%	
	ATC	60–70%	
CTNNB1 point mutation	PDTC	0–25%	[3, 8, 16]
	ATC	Up to 65%	
PPARG rearrangement	FTC	~25–60%	[3, 8, 11, 17]

From Mitsiades and Fagin in Genetic Diagnosis of Endocrine Disease, 1st Edition: Weiss and Refetoff, eds 2009



TREATMENT OF THYROID CANCER: Surgery

Lobectomy vs. Total Thyroidectomy

Lateral vs. Central Neck dissection

Vocal cord evaluation prior to surgery

Lymph node Imaging prior to surgery

TREATMENT OF THYROID CANCER

- **^{131}I TREATMENT**

TNM Stage	Description	Evidence?	Recommendation
T1a;N0, Nx;M0,Mx	<1 cm (uni or multi)	No	No RAI
T1b,T2;N0,Nx;M0, Mx	>1-4 cm	Conflicting	? Histology
T3 N0, Nx, M0, Mx	Microscopic extra-Thyroidal extension	Conflicting	Yes
T1-3, N1a/b; M0, Mx	LN met	Conflicting	Yes
T4, Any N, Any M	Gross extrathyroid Distant mets	Yes	Yes

Which dose: 30 vs 100 vs 150 mCi?

2015 American Thyroid Association Guidelines

Advanced THYROID CANCER

- **Kinase Inhibitor (KI) Therapy**

Factors Favoring KI Therapy:
- **131-I refractory disease**
- Imminently threating disease **progression**
- Symptomatic disease
- Diffuse disease progression (eg. Multiple lung mets)

Factors Discouraging KI Therapy
- Active or recurrent intestinal disease
- Liver disease
- Recent bleeding
- Recent cardiovascular event
- Poorly controlled hypertension
- Recent tracheal radiation
- Recent suicidal ideation
- Prolonged QTc interval
- Cachexia/poor nutrition

2015 American Thyroid Association Guidelines

TREATMENT OF THYROID CANCER

- **Surgery**
- **^{131}I Ablation**
- **Tyrosine Kinase Inhibitors**
- **External Beam Radiation**

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