

Thyroid Disease Update

- Donald Eagerton M.D.

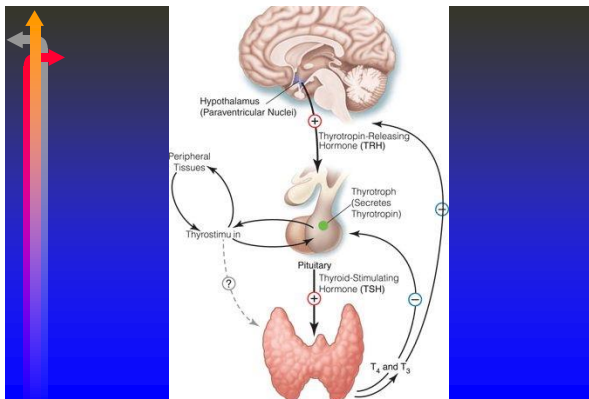
Disclosures

I have served as a clinical investigator and/or speakers bureau member for the following:

Abbott, Astra Zenica, BMS, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Novo Nordisk, Pfizer, and Sanofi Aventis

Thyroid Disease Update

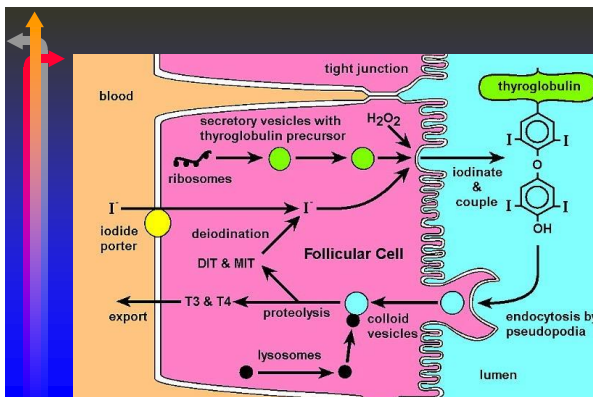
- Hypothyroidism
- Hyperthyroidism
- Thyroid Nodules
- Thyroid Cancer



Physiologic anatomy of the thyroid gland

- The thyroid gland is composed of closed follicles filled with colloid.
- Follicles are lined with cuboidal epithelial cells that secrete colloid.
- Colloid is mainly made from thyroglobulin (large glycoprotein).
- Thyroid hormones are found within thyroglobulin.

Follicle, Cuboidal epithelial cells, Red blood cells, Colloid



Case 1

- 50 year old white female is seen for follow up. Notices cold intolerance, dry skin, and some fatigue. Cholesterol is higher than prior visits.
- Family history; Mother had history of hypothyroidism. Sister has hypothyroidism.
- TSH = 14 (0.30- 3.3) Free T4 = 1.0 (0.95- 1.45)
- Weight 70 kg

Case 1

- Next step should be
- A. Check Free T3
- B. Check AntiMicrosomal Antibodies
- C. Start Levothyroxine 112 mcg daily
- D. Start Armour Thyroid 30 mg q day
- E. Check Thyroid Ultrasound

Case 1

Next step should be

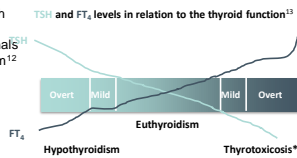
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Hypothyroidism

- Incidence 0.1- 2.0 % of the population
- Subclinical hypothyroidism in 4-10% of the adult population
- 5-8 times higher in women

An FT₄ test can confirm hypothyroidism

- In the presence of high TSH, low FT₄ (free thyroxine) usually signals primary hypothyroidism¹²



Thyrotoxicosis vs. hyperthyroidism*

While these terms are often used interchangeably, thyrotoxicosis (toxic thyroid), describes presence of too much thyroid hormone, whether caused by thyroid overproduction (hyperthyroidism); by leakage of thyroid hormone into the bloodstream (thyrotoxicosis); or by taking too much thyroid hormone medication. Hyperthyroidism, one cause of thyrotoxicosis, refers specifically to overproduction of thyroid hormone by the thyroid gland.

A wide range of signs and symptoms^{7,8}



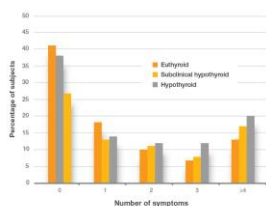
- | | |
|------------------------------|------------------------------------|
| • Bradycardia | • Hoarseness |
| • Brittle nails | • Infertility or miscarriage |
| • Coarseness or loss of hair | • Irregular or heavy menses |
| • Cold intolerance | • Mental impairment |
| • Constipation | • Myalgias |
| • Decreased concentration | • Puffy face |
| • Depression | • Reflex delay, relaxation phase |
| • Dry or yellow skin | • Weight gain from fluid retention |
| • Fatigue | |
| • Goiter | |

Hypothyroidism Clinical Features

- Highly Variable depending on age, duration of illness and severity of illness
- Fatigue, cold intolerance, weight gain, constipation, dry skin, myalgia, menstrual irregularities
- Exam : goiter, bradycardia, hypertension, delayed relaxation phase of reflexes
- Labs: increased cholesterol, CPK, macrocytic anemia, hyponatremia

Symptoms (or lack of symptoms) can make diagnosis difficult

- Patients may be asymptomatic and could go undiagnosed¹¹
- Symptoms can be mild, vague, or easily confused with those of other conditions (eg, depression) or assumed to be part of natural processes such as aging³



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Causes of Hypothyroidism

- Primary:
 - Principal Cause and Largely Autoimmune
- Central
 - Secondary + Tertiary
- More recently recognized etiologies
 - Chemotherapeutic Agents
 - Ipilimumab, Bexarotene, Sunitinib (tyrosine kinase inhibitors)

Principal Lab Tests to Diagnose and Monitor Hypothyroidism

- Free Hormone Hypothesis
 - Only free hormone metabolically active and determines thyroid status (not total which is largely bound to binding proteins)
 - Gold standard: Equilibrium Dialysis

Estimates

Free Thyroxine Assays - Use anti T4 Antibodies

- Free Thyroxine Index = Total T4 x T3 UPTAKE
 - T3 uptake ESTIMATES % free hormone

Total and Free T3 should not be used in hypothyroid diagnosis or management

Total T3

- Principal use is diagnosing and following Thyrotoxic patients, **NOT** Hypothyroid patients

Free T3

- Not as reliable as Total T3
- Can estimate with Total T3 X T3 UPTAKE

FTI is best

Free thyroxine by kit suboptimal and even worse in pregnancy
T3 and FT3 not useful for the Hypothyroid patient

Serum T3 Level Should not be Used to Diagnose Hypothyroidism

- R10. Serum total T3 or assessment of serum free T3 should not be done to diagnose hypothyroidism Grade A, BEL 2; **Upgraded** because of many independent lines of evidence and expert opinion.

TSH an excellent test except some pitfalls

- Central disease
- Abnormal isoforms, TSH receptor polymorphisms
- Drugs (glucocorticoids, dopaminergic drugs [metoclopramide], ?metformin)
- Diurnal Variation
- Heterophilic antibodies--particularly low titer
- Requires steady state: pitfalls in an inpatient population and early phases of pregnancy
- Adrenal Insufficiency (may raise TSH)

Case 2

- 50 year old female for routine exam
- No symptoms
- TSH = 6.2 Free T4 normal at 1.2
- Exam unremarkable
- What is next step?

Case 2

- A. Repeat labs in 6 weeks
- B. Check antimicrosomal antibodies
- C. Check ultrasound
- D. Check T3
- E. Start Levothyroxine

Case 2

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Hypothyroidism

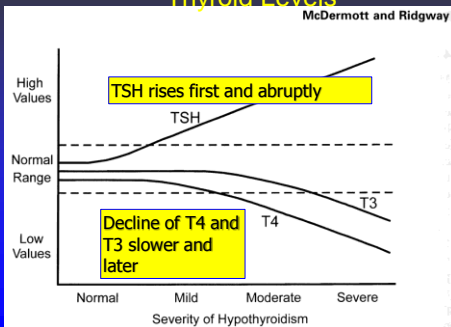
Subclinical

- Normal Free T4 Estimate
- TSH usually below 10
- 5% or more USA

Overt

- Low Free T4 Estimate
- TSH usually above 10
- Less than 1% USA

Severity of Primary Hypothyroidism by Thyroid Levels



Anti-Thyroid Antibodies

- Markers of Chronic Thyroiditis
- Anti- Thyroglobulin Antibodies
 - Does not Correlate with hypothyroidism
- Anti-Thyroid Peroxidase Antibodies (formerly known as Anti-microsomal Antibodies)
 - Correlate with the development of hypothyroidism

When Should Antithyroid Antibodies Be Measured?

- R1. Thyroid peroxidase antibody (TPOAb) measurement should be considered when evaluating patients with subclinical hypothyroidism. Grade B, BEL 1; **Downgraded**. If positive, hypothyroidism rate of 4.3% versus 2.6% per year. Therefore, **may or may not influence the decision to treat**.

CASE 3

- A 65 Year old female with a history of hypothyroidism returns for routine follow up. She notices more fatigue than usual. She is colder and has lost more hair than usual.
- TSH 6 months ago was normal.
- Now TSH is 11.

Causes of TSH change

- She missed several doses in the last month
- She started taking a multivitamin with iron along with her Levothyroxine
- She changed from a name brand to a generic
- Any of the above

Hypothyroidism

- AACE, TES, and ATA
- Joint Position Statement on the Use and Interchangeability of Thyroxine Products

Case 3

A 26 year old female with a history of hypothyroidism since age 13. She has been euthyroid on a stable dose of Synthroid 100 mcg for the last 3 years. She plans to become pregnant in the near future. She asks if there should be any changes in her Synthroid. You advise her

Case 3

- A) She should stop Synthroid immediately as it is teratogenic
 B) She should expect her thyroid hormone requirements to increase; you give her samples of 125 micrograms to begin as soon as she finds out that she is pregnant, and she will contact you at that time.
 C) She should expect her thyroid hormone requirements to decrease; you give her samples of 75 micrograms to begin as soon as she finds out that she is pregnant, and she will contact you at that time.
 D) She should expect no changes in her dose. See her back after delivery.
 E) She should add Triiodothyronine (Cytomel)

Hypothyroidism in pregnancy requires strict monitoring and frequent follow-up

- Follow TSH every 4 weeks in first half of pregnancy¹¹
- Remember that during pregnancy, appropriate management is required and should include careful monitoring and potential dose adjustment¹¹
- Adhere to the ATA's recommended *trimester-specific* TSH goals throughout pregnancy¹⁶

First trimester	Second trimester	Third Trimester
0.1–2.5 mIU/L	0.2–3.0 mIU/L	0.3–3.0 mIU/L

Potential consequences¹⁶

Maternal hypothyroidism is associated with adverse effects on the pregnancy and fetus that may include:

- Potential impaired fetal neurocognitive development
- Increased incidence of miscarriage
- Low birth weight
- Preterm delivery



Immediate factors to consider¹⁶

- Pregnancy can affect the thyroid, and hypothyroidism can profoundly affect the pregnancy
- During pregnancy, the thyroid gland increases in size by 10% and produces 50% more T_3 and T_4 along with a 50% increase in the daily iodine requirement¹¹
- Pregnant women should be verbally screened at initial prenatal visit for history of thyroid dysfunction and/or use of thyroid hormone or anti-thyroid medications
- Serum TSH should be obtained early in pregnancy in women at high risk for overt hypothyroidism (eg, history of thyroid dysfunction or prior thyroid surgery; age >30 years; type 1 diabetes; other)
- Because TFTs in healthy pregnant women differ from TFTs in healthy nonpregnant women, pregnancy-specific—and ideally trimester-specific—reference ranges for TSH and free T_4 (FT_4) are used



TPOAb and pregnancy¹⁶

- Euthyroid patients with TPOAb may be more likely to experience complications during pregnancy
- Evidence indicates an association between miscarriage and preterm delivery in euthyroid women positive for TPO and/or Tg antibodies
- However, there is insufficient evidence to recommend universal screening for anti-thyroid Ab during the first trimester

Abbreviations: TPOAb, thyroperoxidase antibodies;
Tg, thyroglobulin.



Remember that absorption can be affected by many factors

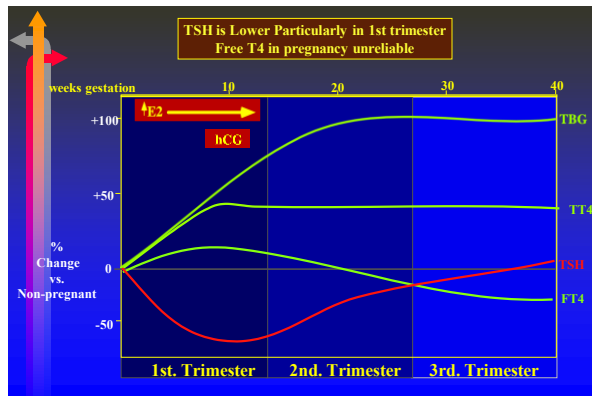
- **Supplements:** Patients must be instructed not to take hypothyroid medication within 4 hours of ingesting iron or calcium supplements¹⁰
- **Medication:** Rifampin, carbamazepine, phenytoin, phenobarbital, sertraline, lovastatin, and others can alter absorption²
- **Certain foods:** Fiber, bran, grapefruit juice¹⁹, and soy protein can reduce absorption¹
- **Administration:** Thyroid hormone replacement with levothyroxine should be taken on an empty stomach at least 30 minutes before breakfast every day¹

Normal range of TSH values?

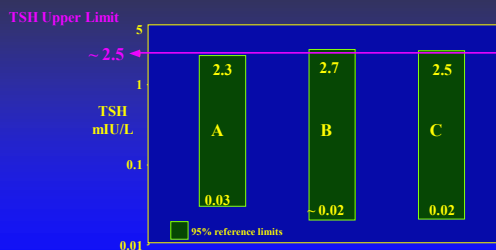
R14.1 The reference range of a given laboratory should determine the upper limit of normal for a third generation TSH assay. TSH levels **may rise with age**. If an age based upper limit of normal for a third generation TSH assay is not available in an **iodine sufficient area**, an upper limit of normal of 4.12 should be considered.

Grade A, BEL 1.

Hollowell RG et al. 2002 *NCMJ* 37:489-99 (R14.1), Hamilton TE et al. 2006 *NCMJ* 31:1224-30 (R14.1), Ronsav L et al. 2011 *Thyroid* 21:5-11 (R14.1)



1st TRIMESTER TSH NORMS DURING PREGNANCY



A: n=343 (Hong Kong) Panesar et al *Ann Clin Biochem* 38:329, 2001
B: n=17,296 (USA) Casey et al *Obstet Gynecol* 105:239, 2005
C: n=115 (Sweden) (USA) TTC, Buenos Aires, Argentina, 10/2005

Pregnancy Thyroid Testing

- Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in 1st trimester provides strong physiological evidence to support redefining TSH upper limit of normal in 1st trimester to 2.5 mIU/liter.
- R9. In pregnancy, the measurement of **total T4** or a free thyroxine index (FTI), in addition to **TSH**, should be done to assess thyroid status. Because of the wide variation in the results of free T4 assays, should only use when method-specific and trimester-specific reference ranges are available. Grade B, BEL 2

Negro, J Clin Endocrinol Metab, 2010 Sep;95(9)

Pregnancy normal-range TSH values

- R. 14.2 In pregnancy, the upper limit of the normal range should be based on trimester-specific ranges for that laboratory. If trimester-specific reference ranges for TSH are not available in the laboratory, the following upper normal reference ranges are recommended: **first trimester, 2.5 mIU /L**; second trimester, 3.0 mIU/L; third trimester, 3.5 mIU/L. Grade B, BEL 2.

Treatment prior to Pregnancy

- R19. Treatment with L-thyroxine should be considered in women of child bearing age with serum TSH levels **between 2.5 mIU/L and the upper limit of normal** for a given laboratory's reference range if they are in the first trimester of pregnancy or planning a pregnancy including assisted reproduction in the near future. Grade B, BEL 2

Controlled Antenatal Thyroid Study (CATS)

- Large, well done, long prospective randomized controlled trial of L-thyroxine treatment vs. no treatment in hypothyroid mothers starting in the 1st trimester.
- Primary Outcome: IQ of children tested between 3 years 2 months and 3 years 6 months
 - % IQ < 85 in children from treated vs non treated mothers

International Thyroid Congress, Paris 2010

Impact of treatment with LT4 on TPO Ab (+) Pregnancy

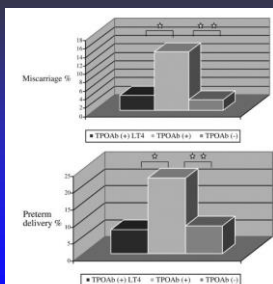


FIG. 4. Percentage of miscarriages (top) and premature deliveries (bottom) in group A (TPOAb⁺ treated with LT₄), group B (TPOAb⁺), and group C (TPOAb⁻). χ^2 , $P < 0.05$; χ^2 , $P < 0.01$.

Negro et al 2006

Role for TPOAb?

- R3. TPOAb measurement should be considered when evaluating patients with infertility, particularly recurrent miscarriage. Grade A, BEL 2; upgraded because of favorable risk-benefit potential.

Treatment of TPOAb+ Women?

- R20. Treatment with L-thyroxine should be considered in women of child-bearing age with normal thyroid hormone levels when they are pregnant or planning a pregnancy including assisted reproduction if they have or have had positive levels of serum TPOAb, particularly when there is a history of miscarriage or past history of hypothyroidism Grade B, BEL 2

Does treatment of hypothyroid patients result in weight loss?

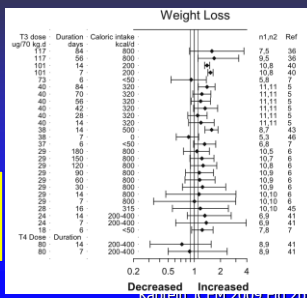
- Yes, if patients are overtly hypothyroid
- Edema improves; duration unknown but severely hypothyroid and underweight may tend to gravitate towards the mean

Plummer

Thyroid hormone impact on weight in euthyroid patients

Not effective weight loss drug

May increase metabolism but increases appetite



Thyroid hormone should not be used to treat obesity

- R30. Thyroid hormone should not be used to treat obesity in euthyroid patients. Grade A, BEL 2
- **Upgraded** to A because of potential harm— inconclusive benefit and induces subclinical hyperthyroidism

20 Year % Probability of Developing Hypothyroidism

Age (yr)	TSH (mIU/liter)									
	1		2		3		4		5	
	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.
20	1	6	1	6	3	13	4	21	7	29
30	1	8	2	8	3	17	6	26	8	35
40	2	10	2	11	4	21	7	32	11	42
50	2	13	3	13	5	25	9	38	14	48
60	3	17	3	17	7	31	12	44	17	55
70	4	21	4	21	9	37	15	51	21	62

TPOAb (+) patients with TSH of between 3-4 mIU/L have < 50% chance developing hypothyroidism over 20 years; if Negative, <20%!

Surks MI, et al. J Clin Endocrinol Metab. 2005;90:5489-96.

Value of Treating Patients with TSH Values Between 2.5 and 4.5

- No **prospective** study has shown TSH levels **lower** than 4.5 to 10 are associated with more cardiovascular disease
 - Pregnancy outcomes notable exception
- **Over half of individuals with TSH between 2.5 to 4.5 mIU/L may not have thyroid disease**
- Many who do are mild, at low risk for progression, and may even remit
- The risk of overtreatment is not trivial (approximately 20%)

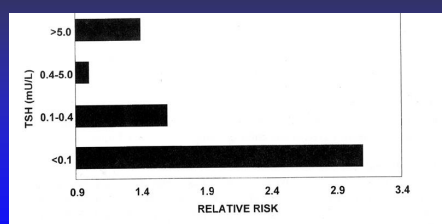
Surks MI, et al. J Clin Endocrinol Metab. 2005;90:5489-96.
Walsh JP, et al. J Clin Endocrinol Metab. 2006;91:2624-30.

Hazards of Overtreatment – Heart, Bone, Psychiatric

- High risk subclinical hyperthyroid in patients on thyroid medication
 - Colorado Prevalence Study, 2000
 - 20.7% (316) of patients on thyroid medication had subclinical hyperthyroidism
 - 0.9% (13) Overt hyperthyroidism
- More adverse effects with poor monitoring
 - Only 56% received standard monitoring
 - Atrial fibrillation, unstable angina with poor monitoring

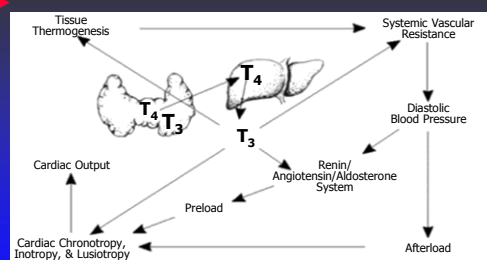
Canaris GJ, et al. *Arch Intern Med*. 2000;160:526-534.
Steffox HT, et al. *J Eval Clin Pract*. 2004;10:525-30.

Increased risk of developing atrial fibrillation in patients with subclinical hyperthyroidism



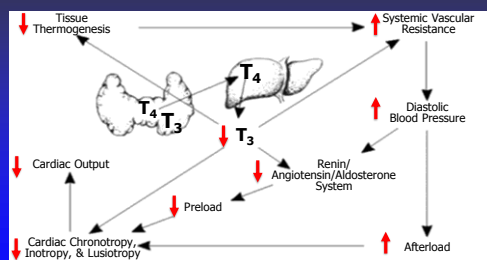
Modermott and Ridgeway

Sites of Cardiac Action of Thyroid Hormone



based on Klein and Danzi, In: *The Thyroid* 2004

Sites of Action of Thyroid Hormone on the Heart with Hypothyroidism



based on Klein and Danzi, In: *The Thyroid* 2004

Hypothyroidism and the Heart

- Hypertension (Diastolic)
- Diastolic Dysfunction
- Elevated Cholesterol*
- Long Q-T Syndrome
- Serum CK Elevation (*Statin Hazard?)
- Coagulopathy

Treatment of TSH between 5 and 10? Depends...

R16. Treatment should be considered particularly if they have symptoms suggestive of hypothyroidism, positive TPO antibodies or evidence of atherosclerotic cardiovascular disease, heart failure or have associated risk factors for these diseases.

Grade B, BEL 1; evidence not fully generalizable to stated recommendation and there are no prospective, interventional studies.

Vanderpump MP et al. 1995 Clin Endo 43:55-68 (EL2). Vanderpump MP & Tunbridge WM. 2002 Thyroid 12:839-47 (EL4). Hollowell JG et al. 2002 JCEM 87:489-99 (EL1). Huber G et al. 2002 JCEM 87:3221-26 (EL2). McQuade C et al. 2011 Thyroid 21:837-43 (EL3). Ochoa N et al. 2008 Ann IM 148:832-45 (EL1).

Subclinical Hypothyroidism

- 2017 study in elderly patients showed no significant benefit of treatment in patients over 70 in terms of quality of life and fatigue

SUBCLINICAL HYPOTHYROIDISM METANALYSES CHD and Mortality

- Ten studies evaluating Subclinical Hypothyroidism
 - CHD RR 1.2
 - Higher quality studies: LOWER: RR (1.02-1.08)
 - Older than 65 : LOWER: RR (0.98-1.26)
 - Younger than 65 : HIGHER: RR (1.09.-2.09)
- Conclusion: May increase risk of CHD, particularly in younger than 65

Ochs, AIM, 2008

Treatment of TSH levels > 10 is recommended

R15. Patients whose serum TSH levels exceed 10 mIU/L are at increased risk for heart failure and cardiovascular mortality, and should be considered for treatment with L-thyroxine.

Grade B, BEL 1; not generalizable and meta-analysis does not include prospective interventional studies.

- Hypothyroid patients treated with normalized TSH are still more likely to feel poorly (Saravani Clinical Endo 2002; Boewing Thyroid 2011)

Seike et al. 2004 JAMA 291:228-38 (EL4). Rodondi N et al. 2010 JAMA 304:1365-74 (EL2). Razzi S et al. 2010 JCEM 95:1734-40 (EL3). Gencer B et al. 2012 Circulation Epub before print (EL1).

Non-pregnant TSH target goals

- R17. In patients with hypothyroidism who are not pregnant, the target range should be the normal range of a third generation TSH assay. If an upper limit of normal for a third generation TSH assay is not available, an upper limit of normal of **4.12** should be considered and if a lower limit of normal is not available, **0.45** should be considered. Grade B, BEL 2

Has a Role in the Treatment of Hypothyroidism Been Demonstrated with T3?

- Endpoints have been mostly affective ones
- Trials have been relatively short
- Studies to date mixed...and meta-analyses negative, but not completely
- Combination therapy still not yet completely understood in the setting of patient preferences

Why Some Patients May Prefer T4/T3 therapy

The rarer CC genotype of rs225014 polymorphism in deiodinase 2 gene (DIO2) present in 16% of the study population (552) and associated with:

- Worse baseline GHQ scores in patients on LT4
- Enhanced response to combination T(4)/T(3) therapy, but did not affect serum thyroid hormone levels.

Panicker, 2009 JCEM

L-T4 is the Preferred Treatment

- **R22.1** Patients with hypothyroidism should be treated with L-thyroxine monotherapy Grade A, BEL1.
- **R22.2** Evidence does not support using L-T4 and L-T3 combinations to treat hypothyroidism. Grade B, BEL1.
- Not considered Grade A because unresolved issues raised by studies reporting some patients prefer and some patient subgroups may benefit from L-T4 and L-T3 combination.

Freeman-Morales HF et al. 2005 JCEM 90:3045-54 (EL4), Grossinsky-Glassberg S et al. 2006 JCEM 91:2572-99 (EL1), Panicker V et al. 2009 JCEM 94:3821-29 (EL3), Appleford BC et al. 2005 JCEM 90:6296-99 (EL3), Clarke N et al. 2008 Trans Endo 3:217-21 (EL4).

Question 3.12 How should hypothyroidism be treated and monitored?

R22.3 L-thyroxine and L-triiodothyronine combinations should not be administered to pregnant women or those planning pregnancy
Grade B, BEL 3; upgraded because of potential for harm of hypothyroxinemia during pregnancy

Pap VI et al. 1999 Clin Endo 50:149-55 (EL3), Pap VI et al. 2003 Clin Endo 59:282-88 (EL3), Koontra L. 2006 Pediatrics 117:161-67 (EL3), Henrichs J et al. 2010 JCEM 95:4227-34 (EL3).

Initiating therapy in overt hypothyroidism

- **Recommendation 22.7.1:** When initiating therapy in **young healthy adults with overt** hypothyroidism, beginning treatment with **full** replacement doses should be considered. **Grade B, BEL 2**
- **Recommendation 22.7.2:** When initiating therapy in **patients older than 50-60 years old with overt hypothyroidism, without evidence of coronary heart disease**, an L-thyroxine dose of **50 mcg** daily should be considered. **Grade D, BEL 4**

Initiating treatment in subclinical hypothyroidism

- **Recommendation 22.8:** In patients with **subclinical hypothyroidism** initial L-thyroxine dosing is **generally lower than what is required in the treatment of overt hypothyroidism**.
- A daily dose of **25 to 75 mcg** should be considered, depending on degree of TSH elevation. Further adjustments should be guided by clinical response and follow up laboratory determinations including TSH values. **Grade B, BEL 2**

Question 3.12 How should hypothyroidism be treated and monitored?

R23. L-thyroxine should be taken with water consistently 30 to 60 minutes before breakfast or at bedtime 4 hours after the last meal. It should be stored properly per product insert and not taken with substances or medications that interfere with its absorption.
Grade B, BEL 2.

Bulk N et al. 2010 Arch IM 170:1996-2003 (EL2)
Bach-Huyob TG 2009 JCEM 94:3905-12 (EL2)

Counsel Patients Taking Alternative Therapies About Potential Side Effects and Hazards

- Supraphysiologic amounts of **iodine** may alter thyroid status, particularly in those with disease
- Many **thyroid-enhancing products** have **sympathomimetic amines** and **iodine**
- Many **thyroid support products** have significant amount of thyroid hormone
- R34 Patients... should be counseled about the potential side effects of ... preparations containing iodine...sympathomimetic amines..."thyroid support" since they could be adulterated with L-thyroxine or L-triiodothyronine. Grade D BEL 4

Kang et al. 2011, ATA

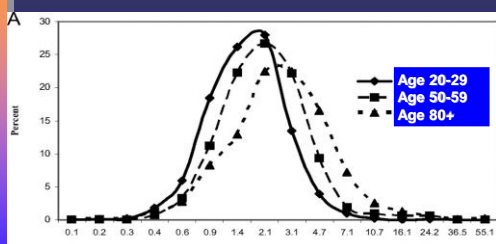
Case 4

- 85 year old man with history of hyperlipidemia, hypertension, and atrial fibrillation is found to have a TSH of 6.2. Free T4 is normal at 1.05. Other than some decreased stamina he has no symptoms.
- Weight 70 kg, Pulse 70 BP 128/70
- You should

Case 4

- A) Start Synthroid 112 mcg q day
- B) Start Methimazole 10 mg q day
- C) Order thyroid ultrasound
- D) Do nothing as this is normal for octogenarians
- E) Measure T3 and reverse T3

Disease-Free Thyroid Function Levels: May Narrow in Young But widens in Elderly



Surks MJ, Hollowell JG. J Clin Endocrinol Metab. 2007;92:4575-82. FROM LADENSON.

Case 5



- 40 y.o. female presents with palpitations, 15 lb weight loss, new anxiety, heat intolerance
- Pulse 115, regular BP 128/82
- TSH <0.001
- Free T4 elevated at 4.0 (0.9-1.5)

Case 5

- What is the next best option?
- A. Add beta blocker and discuss treatment options for Grave's disease
- B. Thyroid ultrasound
- C. Free T3
- D. Referral for surgery

Hyperthyroidism Signs:

- Tremor
- Hyperactivity
- Rapid speech
- Stare
- Lid lag
- Warm moist skin
- Fine thin hair
- Tachycardia
- A Fib
- proximal muscle weakness
- Systolic Hypertension

Hyperthyroidism

Graves' disease,
toxic adenoma,
toxic multinodular goiter (Plummer's disease),
thyroid-stimulating hormone (TSH)-producing adenoma,
human chorionic gonadotropin (hCG)-secreting tumors,
TSH receptor mutations resulting in increased sensitivity for hCG
(familial gestational hyperthyroidism)
functional metastatic thyroid carcinomas.
Ingestion of iodine and iodine-containing drugs
Amiodarone

Subclinical Hyperthyroidism

Subclinical hyperthyroidism refers to the combination of suppressed serum TSH concentrations and normal serum T3 and T4 levels, regardless of the presence of symptoms. This biochemical abnormality may occur in the setting of mild Graves' disease, toxic nodular goiter, thyroiditis, or ingestion of thyroid hormones.

Hyperthyroidism/ Graves

Features include the presence of a
Goiter,
Ophthalmopathy,
and/or pretibial dermopathy.
When Graves' disease is suspected but the diagnosis remains uncertain, measurement of thyrotropin receptor antibodies (TRAb) may be helpful.
Diffuse increased uptake on I 131 scan

Hyperthyroidism Other

- In patients with toxic adenoma, a palpable nodule is often found on clinical examination, whereas in patients with toxic multinodular goiter, a firm heterogeneous goiter of variable size is more common, although some patients may have retrosternal goiters.

THYROID ADENOMA

(also called Nodular toxic disease or Plummer's disease)

It is a localized adenoma or tumor that develops in the thyroid gland & secretes large quantities of thyroid hormone.

↓

↑ levels of TH

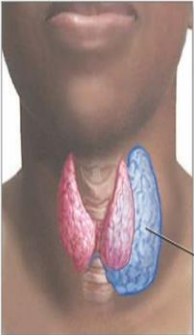
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Signs and symptoms of Hyperthyroidism

↓

Secretory function of the rest of the gland is almost totally inhibited as the thyroid hormone from the adenoma depresses the production of TSH from the anterior pituitary.

Hyperthyroidism caused by thyroid adenoma





Thyroid Storm

Life-threatening syndrome characterized by severe symptoms of hyperthyroidism, including fever, tachycardia, in some cases congestive heart failure, and altered mental status, usually with severe agitation, delirium, or psychosis, although stupor and coma can also occur. often precipitated by surgery, infection, an acute iodine load, or trauma and is considered a medical emergency.

Thyroid Storm Treatment

1. Supportive measures (such as I.V. fluids)
2. Antithyroid drugs to block production of new thyroid hormone (propylthiouracil [PTU] is preferred because of its ability to also block extrathyroidal conversion of T₄ to T₃),
3. Potassium iodide and ipodate to block the release of thyroid hormone, (AFTER loading dose of PTU or Methimazole)
4. Cortico-steroids, which decrease antibody production and also inhibit conversion of T₄ to T₃,
5. high-dose β -blockers to control adrenergic symptoms.
6. Treatment of underlying infection, if present, or other precipitating illness is also essential.

Hyperthyroidism Treatment Options

- Surgery
- Antithyroid meds
- I 131

β -Blockers are useful for symptomatic relief of adrenergic symptoms and should be considered, especially in elderly patients with symptomatic thyrotoxicosis and other thyrotoxic patients with resting tachycardia or coexisting cardiovascular disease; however, these agents do not affect thyroid hormone levels. Once euthyroidism is achieved, they can be stopped

AntiThyroid Meds

1. Inhibit the synthesis of thyroid hormones by interfering with iodination of tyrosine residues, oxidation, organification, and possibly, thyroglobulin synthesis, all important steps in the synthesis of thyroid hormones.
2. Generally, this effect is not clinically apparent until at least 1 to 2 weeks after initiation of the drug therapy.

Antithyroid Meds

- 3. Useful as primary therapy for patients with hyperthyroidism due to Graves' disease in whom remission is possible after discontinuation of treatment.
- 4. Also useful to lower thyroid hormone levels prior to radioiodine therapy or before surgery, especially in elderly patients or those at risk for cardiac complications.
- 5. Treatment of choice in children, adolescents, and pregnant women.

Antithyroid Meds

Not considered primary therapy for treatment of toxic multinodular goiters and autonomous solitary nodules because spontaneous remission is unlikely.
 PTU (but not methimazole) can inhibit conversion of T4 to T3 within the thyroid and in peripheral tissue
 May also have other clinically important immunosuppressive effects, usually resulting in decreasing concentrations of antithyrotropin receptor antibodies and other immunologically important molecules and cytokines over time.

Antithyroid Meds

Antithyroid drugs are the treatment of choice for Graves' disease in many countries, although in the United States, RAI is preferred by most endocrinologists. The most widely used antithyroid drugs are methimazole, at doses from 10 to 30 mg once daily and PTU in doses starting at 300 mg/day in 3 divided doses. Methimazole has the advantage of lower toxicity (particularly when used in lower doses) and a longer half-life, allowing single daily dosing, which usually results in increased adherence and more rapid decline in thyroid hormone levels. As a result, methimazole is now recommended as the first-line antithyroid drug in most patients. Because methimazole has been associated with certain rare congenital anomalies, such as choanal atresia and aplasia cutis, however, PTU is preferred during the first trimester of pregnancy as it is thought to be less likely to cross the placenta.

Propylthiouracil

- Propylthiouracil. 50-150 mg T.I.D.
- DOC for first and possibly second trimester. Less likely to cross placenta
- Converts T4-T3 as well
- Potential Hepatotoxicity

Methimazole

10 to 30 mg once daily
 Lower toxicity (particularly when used in lower doses)
 Longer half-life, allowing single daily dosing, which usually results in increased adherence and more rapid decline in thyroid hormone levels.
 Recommended as the first-line antithyroid drug in most patients. Has been associated with certain rare congenital anomalies, such as choanal atresia and aplasia cutis
 PTU is preferred during the first trimester of pregnancy as it is thought to be less likely to cross the placenta.

Antithyroid Meds Adverse Reactions : Minor

Occur in approximately 5% of patients taking either drug
 Include skin rash, urticaria, itching, and arthralgias.

Patients developing these reactions may be switched from one drug to the other, although cross-reactivity may still occur up to 50% of the time.

Discontinuation of drug therapy in favor of more definitive treatment with radioiodine or surgery is another option.

Anti-Thyroid Meds Adverse Reactions: Major

Severe reactions include agranulocytosis, hepato-toxicity, and vasculitis.

Agranulocytosis is the most serious side effect; it occurs in approximately 0.3% of patients, usually within the first 3 months of treatment, although it can occur more than a year after initiating therapy.

Discontinue use of their medication and contact their physician if they develop a sore throat and fever. A white blood cell count and differential should be obtained immediately. The drug should be discontinued if the granulocyte count is $< 1000/\text{cc}$. If sepsis is suspected, the patient should be hospitalized and treated with broad-spectrum antibiotics.

Anti-Thyroid Meds Adverse Reactions: Major

Hepatotoxicity. Estimated frequency of 0.1% to 0.2% (slightly higher in children).

Usually presents with markedly elevated transaminase levels associated with severe hepatic necrosis on biopsy.

Seen almost exclusively in patients taking PTU and can occur at any time during the course of therapy.

FDA recommended that PTU be considered second-line drug therapy

I 131

Used for treatment of hyperthyroidism for over 6 decades

Most commonly used treatment for this condition in the U.S.

It is effective and safe

Results in significant thyroid volume reduction.

10-15 mCi total, renders most patients hypothyroid within 3 months. This results in a lifelong need for levothyroxine replacement therapy for the patient and little risk of recurrent Graves' hyperthyroidism

I 131

Radiation Thyroiditis- occasionally, transient worsening of hyperthyroidism may occur within the first 2 weeks after radioiodine therapy due to radiation thyroiditis.

Radioiodine therapy is contraindicated during pregnancy and breastfeeding.

In patients with Graves' disease at high risk of complications due to worsening hyperthyroidism (i.e., the elderly, patients with very high FT4 levels, or patients who are very symptomatic), β -blockers should be used prior to radioactive iodine therapy, and pretreatment with methimazole may be considered as well.



Exophthalmos

Does I131 make it worse?
Steroid pretreatment?

Anti- TSH Receptor Antibodies TSHRAb

- Used in the diagnosis and monitoring of Graves'
 - TSI (Thyroid Stimulating Immunoglobulin)
 - TBII (TSH Binding Inhibitory Immunoglobulin)

Thyroidectomy

- For hyperthyroid patients with large goiters who have symptoms of compression,
- patients with a coexistent suspicious thyroid nodule,
- patients who have contraindications or refuse medical therapy and radioiodine,
- pregnant women whose symptoms cannot be controlled with or who experience allergic reactions to antithyroid drugs.
- Overall success rate of 92%. Use high-volume thyroid surgeon.

Evaluation of Hyperthyroidism

- When Grave's disease is obvious, no further evaluation is needed
- TSI (Thyroid Stimulating Immunoglobulin or TBII (TSH Binding Inhibitory Immunoglobulin) can clinch diagnosis
- If I131 is not wanted, uptake scan may be unnecessary
- Falsely low uptake after excess Iodine intake (CT with contrast, Amiodarone)

Other Hyperthyroidism

- Uptake scan increased diffusely in Graves
- Uptake scan increased in 1 area with suppression of the rest in Toxic Adenoma
- Uptake scan increased in patchy distribution in Toxic Multinodular Goiter
- Uptake scan decreased in Thyroiditis, thyroid hormone ingestion, strums ovarii,

Case 6

A 60 year old female was found to have an asymptomatic incidental right thyroid nodule on CT scan that was done for evaluation of radiculopathy. Thyroid ultrasound showed a 2.1 cm solid hypo echoic nodule with irregular borders. TSH was normal. The next step should be:

- A) Iodine uptake scan
- B) Fine needle aspiration
- C) Surgery
- D) Repeat ultrasound in 6 months
- E) PET scan

Thyroid Nodules

Thyroid nodules can be found in 2% to 20% of adults by palpation, 19% to 67% by ultrasound (US), and in 8% to 65% at autopsy

The prevalence of thyroid nodules increases with age, female gender, iodine deficiency, and a history of radiation exposure. Study comparing clinical examination with thyroid US demonstrated that 46% of nodules greater than 1 cm were not palpable

Occult thyroid nodules have the same risk of malignancy as palpable nodules

Thyroid Nodules History

Growth of the nodule(s) over weeks to months,

Presence of hoarseness or new dysphagia symptoms,

Family history of papillary or medullary thyroid carcinoma, or familial neoplastic syndromes [MEN2], Pendred syndrome, Werner syndrome, Carney complex type 1, PTEN-hamartoma tumor syndrome [Cowden disease], and familial adenomatous polyposis/Gardner syndrome)

Thyroid Nodules Exam

- Invasion with fixation of the thyroid nodule to surrounding structures,
- Cervical lymphadenopathy
- Hoarseness suggestive of vocal cord paralysis.
- Sudden pain and enlargement of a thyroid mass over hours is commonly caused by cystic or hemorrhagic degeneration of a pre-existing thyroid nodule, but malignancy should always be considered because thyroid nodules and nodes containing papillary thyroid carcinoma frequently undergo hemorrhagic necrosis.
- Anaplastic thyroid carcinoma, thyroid lymphoma, or metastatic disease to the thyroid should be considered when rapid growth of a solid thyroid mass occurs over weeks or a few months

What is the appropriate laboratory and imaging evaluation for patients with clinically or incidentally discovered thyroid nodules?

(A) Serum thyrotropin (TSH) should be measured during the initial evaluation of a patient with a thyroid nodule.

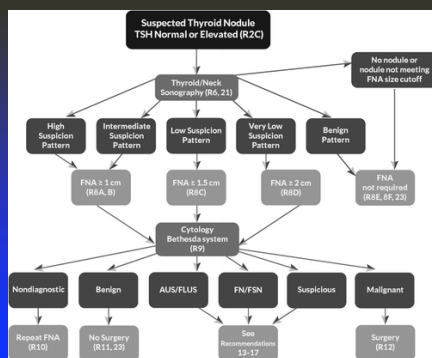
(B) If the serum TSH is subnormal, a radionuclide (preferably ^{123}I) thyroid scan should be performed.

(C) If the serum TSH is normal or elevated, a radionuclide scan should not be performed as the initial imaging evaluation.

(D) **Routine measurement of serum thyroglobulin (Tg) for initial evaluation of thyroid nodules is not recommended.**

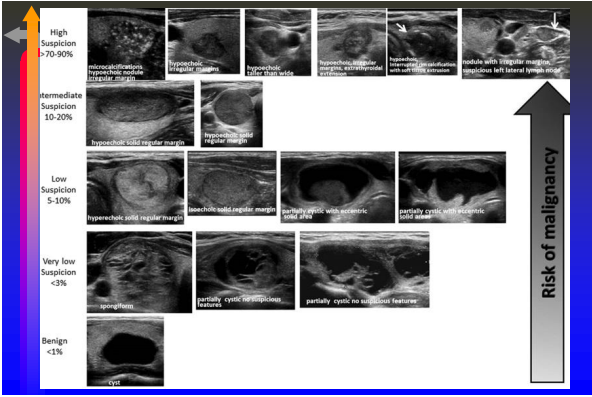
(E) The panel cannot recommend either for or against routine measurement of serum calcitonin in patients with thyroid nodules.

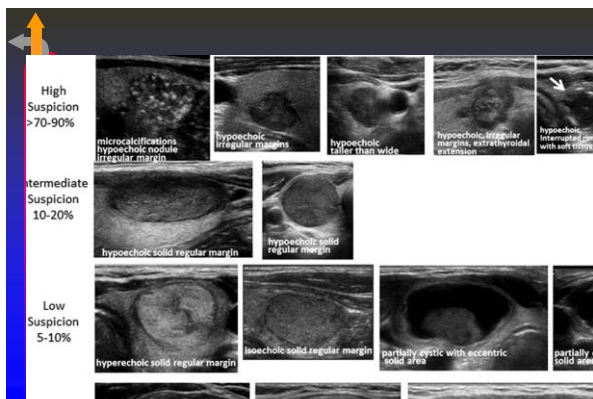
(Strong recommendation, Moderate-quality evidence)



Recommendations for FNAB 2009 ATA	2010 AACE/AME/ETA	
High-risk history*		
Any nodule	> 5 mm	Any size
Abnormal nodes	Any size	Any size
Suspicious US†	≥ 1 cm	Any size but especially if 2 US features
Solid hypoechoic nodule	> 1 cm	Any size
Solid iso- or hyperechoic	≥ 1-1.5 cm	> 1 cm
Mixed cystic-solid nodule		
With suspicious US†	≥ 1-1.5 cm	Any Size but especially if 2 US features
No suspicious US	≥ 2 cm	> 1 cm
Spongiform nodule;	≥ 2 cm	> 1 cm
Purely cystic nodule	FNAB not indicated	> 1 cm

Sonographic pattern	US features	Estimated risk of malignancy, %	FNA size cutoff (largest dimension)
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of ETE	>70-90s	Recommend FNA at ≥1 cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins without microcalcifications, ETE, or taller than wide shape	10-20	Recommend FNA at ≥1 cm
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, without microcalcification, irregular margin or ETE, or taller than wide shape.	5-10	Recommend FNA at ≥1.5 cm
Very low suspicion	Spongiform or partially cystic nodules without any of the sonographic features described in low, intermediate, or high suspicion patterns	<3	Consider FNA at ≥2 cm Observation without FNA is also a reasonable option
Benign	Purely cystic nodules (no solid component)	<1	No biopsy





Traditional Cytology Category	NCI Bethesda Cytology Category	Risk of Malignancy	Recommended Management
Benign	Benign	0%-3%	Clinical follow up with periodic US exam
Atypia of undetermined significance (AUS)/Follicular lesion of undetermined significance (FLUS)	5%-15%	Repeat FNA	
Indeterminate	Follicular neoplasm or Suspicious for follicular neoplasm	15%-30%	Lobectomy or total thyroidectomy if contralateral nodules or increased risk for thyroid cancer
Malignant	Suspicious of malignancy	> 60%-75%	Total thyroidectomy but consider lobectomy
Malignant	97%-99%	Total thyroidectomy	
Nondiagnostic	Nondiagnostic	< 3%	Repeat FNA with US

ATA Low Risk

- Papillary thyroid cancer (with all of the following):
 - No local or distant metastases;
 - All macroscopic tumor has been resected
 - No tumor invasion of loco-regional tissues or structures
 - The tumor does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma)
- If 131I is given, there are no RAI-avid metastatic foci outside the thyroid bed on the first posttreatment whole-body RAI scan
- No vascular invasion
- Clinical N0 or E5 pathologic N1 micrometastases (<0.2 cm in largest dimension)a
- Intrathyroidal, encapsulated follicular variant of papillary thyroid cancera Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasiona
- Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including BRAFV600E mutated (if known)a

Thyroid Cancer

Most common endocrine malignancy.
Estimated 56,460 new cases diagnosed in the United States in 2012.
The incidence of differentiated thyroid cancer is rising more rapidly than any other cancer type.
The overwhelming majority—and almost exclusively the cause of the increased incidence—are cases of papillary thyroid carcinoma (PTC), which have increased approximately 3-fold within this time frame and now represent more than 85% of all thyroid cancers.

In contrast, the less common follicular thyroid cancer (FTC), medullary thyroid cancer (MTC), and anaplastic thyroid cancer (ATC) have shown no significant change in incidence.

Thyroid Cancer

Surgery for nodules reported to be “suspicious for follicular neoplasm” generally takes the form of a lobectomy, with completion thyroidectomy offered at a later date for those lesions (approximately 20%) that prove to be malignant.

An alternative approach in use in a few centers is to determine the extent of primary surgery based on frozen section pathologic analysis.

Thyroid Cancer

Classification systems helps to further characterize low-risk DTC patients with a high degree of accuracy, allowing selective use of adjuvant therapy and appropriate targeting of high-risk patients for more intensive follow-up.

None of them, however, removes the need to apply experience and clinical acumen in the management of patients with thyroid cancer.

<http://www.thyroid.org/thyroid-cancer-staging-calculator/>

Thyroid Cancer

the goal of initial postoperative evaluation, performed 3 to 6 months after surgery, should instead be: (a) to confirm the absence of surgical complications or to manage those complications appropriately; (b) to assess the degree of thyrotropin (TSH) suppression necessary and to optimize thyroxine therapy; (c) to confirm anatomic and biochemical remission; (d) to determine the role for additional adjuvant therapy (specifically, radioactive iodine or external-beam irradiation); and (e) to design an appropriately tailored surveillance schedule, based on the risk the patient faces of future recurrence.

Thyroid Cancer

The goal for low-risk PTC patients should be to achieve a TSH at or toward the low end of the normal range, rather than frank suppression.

Higher-risk patients may benefit from more aggressive TSH suppression, targeting the TSH to values less than 0.1 mU/L.

The risks of thyrotoxicosis should be avoided by ensuring that the patient remains clinically euthyroid and that the free-thyroxine lies at or only slightly above the upper limit of the normal range. More aggressive thyroxine replacement carries with it increased risks for cardiovascular and skeletal complications

Thyroid Cancer

- Lungs are by far the most common site of distant metastatic spread.
- Some authorities suggest that chest CT.
- Others prefer to use whole body iodine scanning,
- Most endocrinologists rely, at least to some extent, on the postoperative level of Tg to determine how aggressively to seek pulmonary metastases.

Thyroid Cancer

- In a patient with a low-risk, node-negative, completely resected intrathyroidal PTC, whose Tg level is low postoperatively (either stimulated or unstimulated), the probability of identifying pulmonary metastases is remote and additional chest imaging will not be helpful.
- On the other hand, a large, locally invasive malignancy in an older patient, with bulky lymph node metastases has a significant risk of metastatic spread, even if the Tg level is not particularly high, and warrants a much more aggressive metastatic survey. This survey should certainly include whole-body iodine scanning (following I-131 ablation),

Thyroid Cancer

- With relaxation of those rules over the last 15 years in the USA, it has become commonplace to use higher I-131 doses of between 50 and 100 mCi,
- Following thyroid hormone withdrawal, doses of 30 mCi, 50mCi, 75 mCi, and 100 mCi of I-131 achieve almost identical rates (85%-90%) of complete ablation.
- FDA approved Thyrogen for RRA using this 100 mCi dose. More recently, however, a Thyrogen-stimulated 30 mCi RRA dose proved sufficient to achieve elimination of the thyroid remnant in up to 85% of patients and was equally effective as levothyroxine withdrawal

Thyroid Cancer

- Recurrent well-differentiated thyroid cancer is a very common clinical problem, affecting between 20% and 30% of PTC patients.
- Predictors of recurrence include incomplete disease resection, positive surgical margins, lymph node involvement (especially in the lateral neck compartments, and possibly multifocal disease.
- The overwhelming majority of recurrences represent progression of microscopic lymph node metastases, which grow to become detectable. Often these nodal metastases are first identified by stimulated Thyroglobulin measurement

Thyroid Cancer

- In patients initially deemed node negative, recurrence rates after adequate surgery range from 3% to 10%.
- In node-positive PTC, recurrence rates are between 15% and 30%.
- In both cases, the recurrences are most likely to be identified through a combination of Tg and US, both of which should be undertaken at 6 to 12 months after initial therapy and then annually for at least 5 years.
- More than 90% of all recurrences will be detectable within that time frame. Thereafter, annual TSH and thyroglobulin measurements are probably adequate when combined with clinical examination

Thyroid Cancer

- In addition, however, these patients should be considered for screening for iodine-avid metastases, using Thyrogen-stimulated or withdrawal I-123 scans, particularly in the first year or two following their initial therapy.

many of these patients have disease that produces Tg only at low levels so that Tg, even following stimulation, may be an insensitive marker of residual or progressive thyroid cancer.

Medullary Carcinoma

- 1-2% of all Thyroid cancers
- Cancer of the C- cells, calcitonin producing cells
- *RET* (*RE*arranged during *Trans*fection) oncogene is found in virtually all patients with MEN2A, MEN2B, and FMTC and approximately 50% of sporadic MTCs
- Do not take up iodine, so I 131 is of no benefit
- Surgery

Medullary Carcinoma

- If RET +, test family and operate ASAP on those that are +
- Follow doubling time of calcitonin
- External beam radiation
- Tyrosine Kinase Inhibitor

References

American Thyroid Association
 2015 American Thyroid Association Management
 Guidelines for Adult Patients with Thyroid Nodules
 and Differentiated Thyroid Cancer
 Thyroid. December 2014, 24(12): 1670-1751.
 doi:10.1089/thy.2014.0028.
 Guidelines for the Treatment of Hypothyroidism: Prepared by the
 American Thyroid Association Task Force on Thyroid Hormone
 Replacement
 Jonklaas Jacqueline, Bianco Antonio C., Bauer Andrew J., Burman
 Kenneth D., Cappola Anne R., Celli Francesco S., Cooper David S.,
 Kim Brian W., Peeters Robin P., Rosenthal M. Sara, and Sawka
 Anna
Published in Volume: 24 Issue 12: December 12, 2014

References

- AACE Guidelines for Treatment of Hypothyroidism
- AACE Guidelines for Treatment of Hyperthyroidism
- AACE ASAP Thyroid Diseases
