Thyroid Tidbits and Tricks

Janet Leung, MD

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Virginia Mason Endocrinology

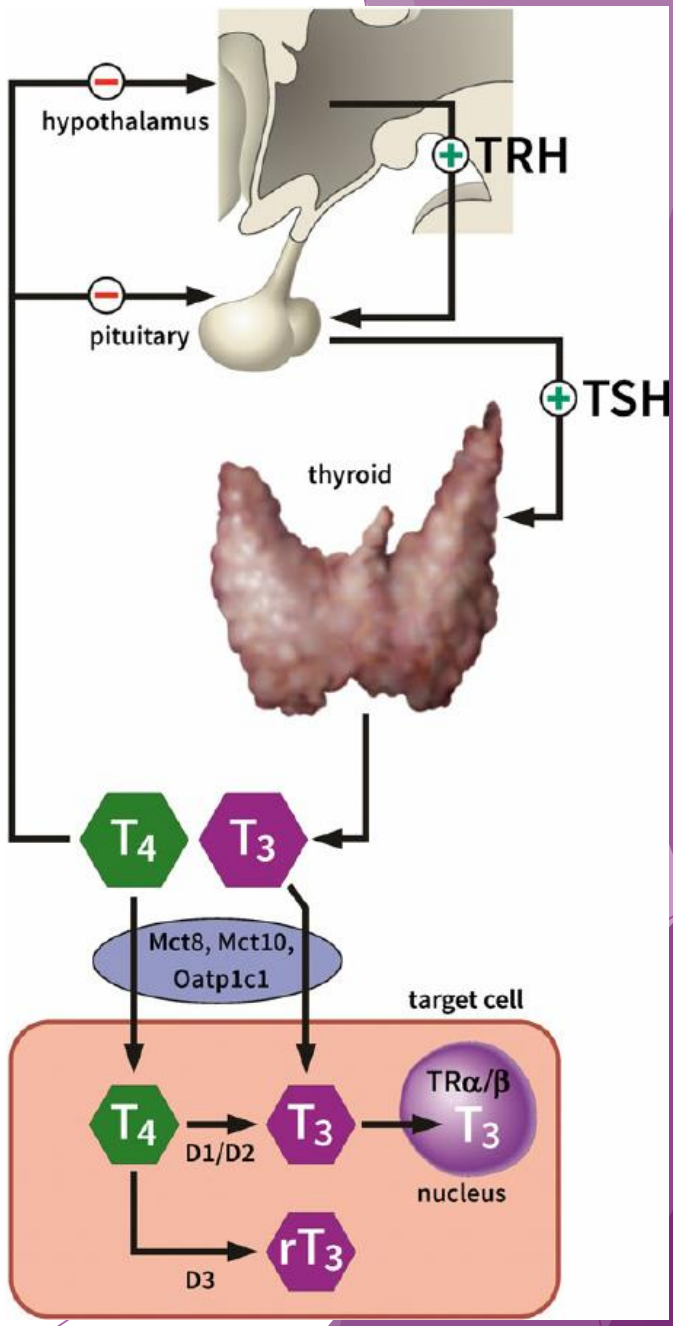
Disclosures

- Endocrine Section Editor for DynaMed

Thyroid Physiology

TSH, reflex FT4

- Check TT3 only if you have a suppressed TSH, normal FT4
- NEVER check RT3 unless you're doing research
- For hyperthyroid: TSH receptor antibodies (TRAb) or Thyroid Stimulating Immunoglobulins (TSI)
- For hypothyroid: could consider checking Thyroid Peroxidase Antibodies (TPO)
- For thyroid cancer: check thyroglobulin antibodies and thyroglobulin levels

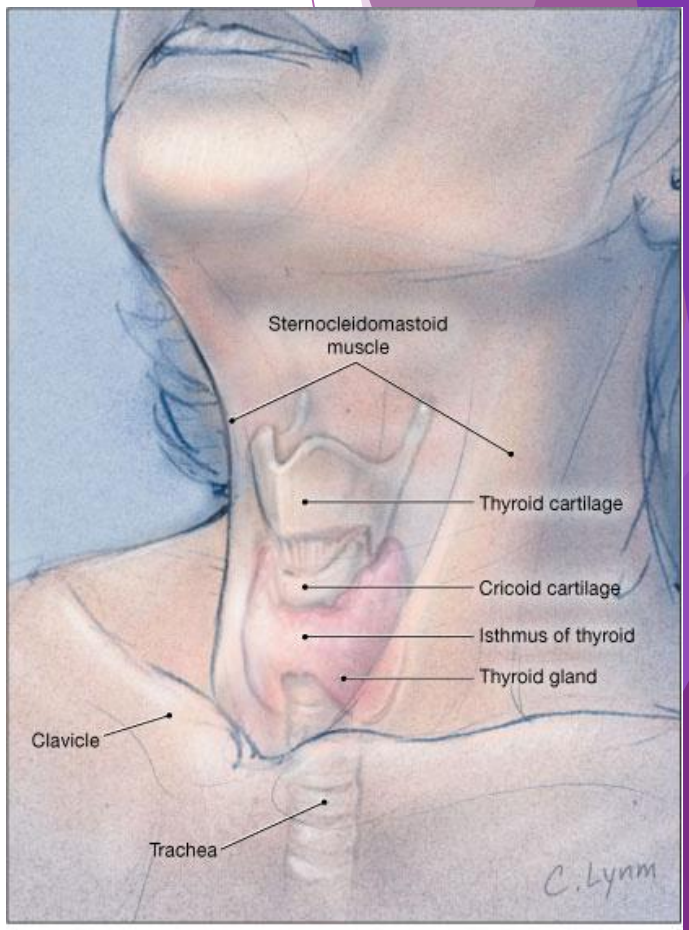


https://www.researchgate.net/figure/Thyroid-hormone-physiology-Circulating-thyroid-hormone-concentrations-are-regulated-via_fig1_271592550

Thyroid Exam:

https://stanfordmedicine25.stanford.edu/the25/thyroid.html
https://depts.washington.edu/physdx/thyroid/tech.html

- Start at tip of chin and walk down
- Past the thyroid cartilage, the cricoid, beginnings of trachea
- Flex patient neck forward and relax!
- Examine isthmus and then laterally to the lobes
- Then swallow to evaluate movement
- Feel for size, nodule, texture
- Understand thyroid exams are not very sensitive or specific: only 10% of radiographic nodules are palpable on exam



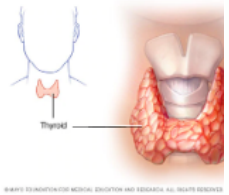
Source: Simel DL, Rennie D: *The Rational Clinical Examination: Evidence-Based Clinical Diagnosis:* http://www.jamaevidence.com

Hypothyroidism

Symptoms

The signs and symptoms of hypothyroidism vary, depending on the severity of the hormone deficiency. Problems tend to develop slowly, often over a number of years.

At first, you may barely notice the symptoms of hypothyroidism, such as fatigue and weight gain. Or you may simply attribute them to getting older. But as your metabolism continues to slow, you may develop more-obvious problems.



Thyroid gland

Hypothyroidism signs and symptoms may include:

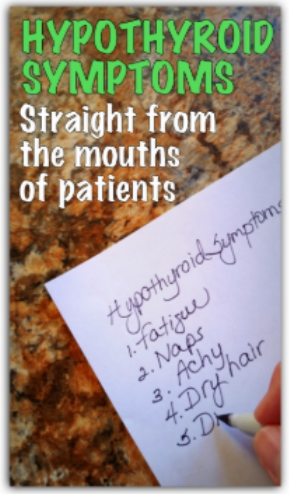
- Fatigue
- Increased sensitivity to cold
- Constipation
- Dry skin
- Weight gain
- Puffy face
- Hoarseness
- Muscle weakness
- Elevated blood cholesterol level
- Muscle aches, tenderness and stiffness
- Pain, stiffness or swelling in your joints
- Heavier than normal or irregular menstrual periods
- Thinning hair
- Slowed heart rate
- Depression
- Impaired memory
- Enlarged thyroid gland (goiter)

MAYO CLINIC

Long Pathetic List of Hypothyroid Symptoms

STTM

YOU KNOW WHY THIS IS THE BEST LIST of HYPOTHYROID SYMPTOMS ON THE INTERNET?? Because....



1) The majority of hypothyroid symptoms listed are totally based on *actual thyroid patient descriptions* of their symptoms while on a T4 medication (which leaves too many with continued hypothyroid) or from being undiagnosed or UNDERtreated . *i.e. it's not culled from all sorts of internet cold lists to build high numbers and empty volume...*

2) Like some lists do, it does not contain adrenal-specific symptoms to bulk up the list (unless noted in parenthesis as also related)

3) These are also symptoms which patients have reported greatly improved or totally went away once they moved over to Natural Desiccated Thyroid (or adding T3 to their T4) *and found their optimal dose, which is key along with having optimal iron and cortisol–the latter is important!*

4) Most of these have been reported by hypothyroid patients

ENERGY LEVELS

- Less stamina than others
- Less energy than others
- Easy fatigue
- Feeling weak
- The need to na
- Long recovery
- Arms feeling lik
- Legs getting tir

METABOLISM

- Often feeling cold
- Cold hands and feet
- Sweaty or clammy palms
- The need for extra clothing
- Feeling anxietal *(caused by excess adrenaline*
- High or rising cholesterol
- Feeling too hot *(Hashimoto's disease usually, t*
- Low body temperature
- Less perspiration than others
- Tendency to put on weight because of low met

THYROID

- Swollen *(especially Hashimoto's)*
- Goiter diagnosis
- Sore
- Painful
- Difficulty swallowing *(Hashimoto's)*

STOMACH, DIGESTION, FOODS

- Acid reflux
- Low stomach acid
- Diagnosis of 'too much acid' (it's reall
- The need for antiacids to quell sympt
- Food sitting in stomach a long time
- Bloating
- Craving sweets more than normal
- Burning stomach lining
- Inability to eat in the mornings
- Poor appetite
- No Appetite
- Reduced motility (slow movement of f
- Small Intestinal Bacterial Overgrowth

HAIR and SKIN

- No eyebrows
- Thinning outer eyebrows
- Dry Hair
- Hair feels like straw
- Excessive frizziness
- Hair Loss
- Broken hair

ISSUES in the HEAD AREA

- Dry Eye Syndrome
- Worsening vision
- Headaches and Migraines
- Slurred Speech
- Swollen Tongue
- Scalloped tongue (in spite of other
- Lowered voice
- Dry mouth
- Gum Problems
- Internal itching of ears

IMMUNE FUNCTION

- Seem to get more colds than others
- Bad colds
- Poor resistance to illnesses going around
- Taking longer to recover
- Recurring viral or bacterial illnesses
- Recurring sore throats
- Chronic sinus infections
- Persistant Candida
- Tightness in throat; sore throat
- Swollen lymph glands
- Inflammation

CERTAIN MEDICAL CONDITIONS (though not saying YOUR condition is caused by hypothyroid, but for some, it appears sol

- Asthma
- Dysautonomia symptoms *(overreaction of one's autonomic nervous system)*
- Hypoglycemia/Low Blood Sugar. And a study here.
- Lactose Intolerance *(due to low stomach acid from a poor treatment or undiagnosed)*
- Allergies *(which can also be a result of low cortisol–see link below)*
- Dysphagia *(nerve damage causing inability to swallow fluid, food, saliva; can also be caused by a goiter or anxiety)*
- Neurogenic bladder
- Chronic Fatigue Syndrome *(which for the vast majority of thyroid patients, is a catch-all diagnosis)*
- Fatty Liver

MISCELLANEOUS

- Bad motion sickness
- Clumsiness
- Worsening of other conditions

LEGS and FEET

- Bumps on legs
- Swollen legs that
- Shin splints
- Difficulty standing
- Sore feet aka pla
- painful soles of fe

BONES, MUSCLES

- Aching bones or
- Joint pain
- Clicking in joints
- Popping joints
- Stiffness
- Inflamed joints
- Diagnosis of Fibr
- Osteopenia
- Osteoporosis
- Muscular weakne
- Carpel Tunnel
- Back pain
- Shoulder pain
- Frozen shoulder
- Tender elbow
- pain in knees

BRAIN

- Inability to concentrate
- Inability to read long periods of time
- Inability to retain
- Forgetfulness

WEIGHT

- Inability to lose weight in spite of trying hard
- Losing only a little when trying hard
- Always gaining weight
- Obesity
- Weight loss *(a small minority experience this)*
- Fat tummy
- Water retention
- Edema

RELATIONSHIPS or WORK

- Inability to function well in a relationship
- No or poor sex drive
- Argumentative *(from not feeling well, but can also be due to low cortisol)*
- Avoidance
- Inability to work full time
- Constantly tired at work
- Lower quality work performance
- The need for sit-down jobs

SEX HORMONES or FEMALE ISSUES

- Failure to ovulate
- Constant bleeding *(see Rainbow's story)*
- Heavy bleeding
- Longer periods
- Irregular periods
- Moody periods
- Excruciating pain during period
- Worse PMS
- PCOS
- Inability to get pregnant
- Miscarriages
- Breast leakage
- Urinary Tract Infections

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ion
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f B12
f Vitamin D
f B-vitamins

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n to the point of Congestive Heart Failure
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ypotension *(low blood pressure upon standing)*

NTESTINAL and BLADDER

tools

s common than constipation)

ıl syndrome (IBS)

- Painful bladder; painful urination
- Bladder spasms
- Bladder urgency
- Not urinating much

associated with Hashimoto

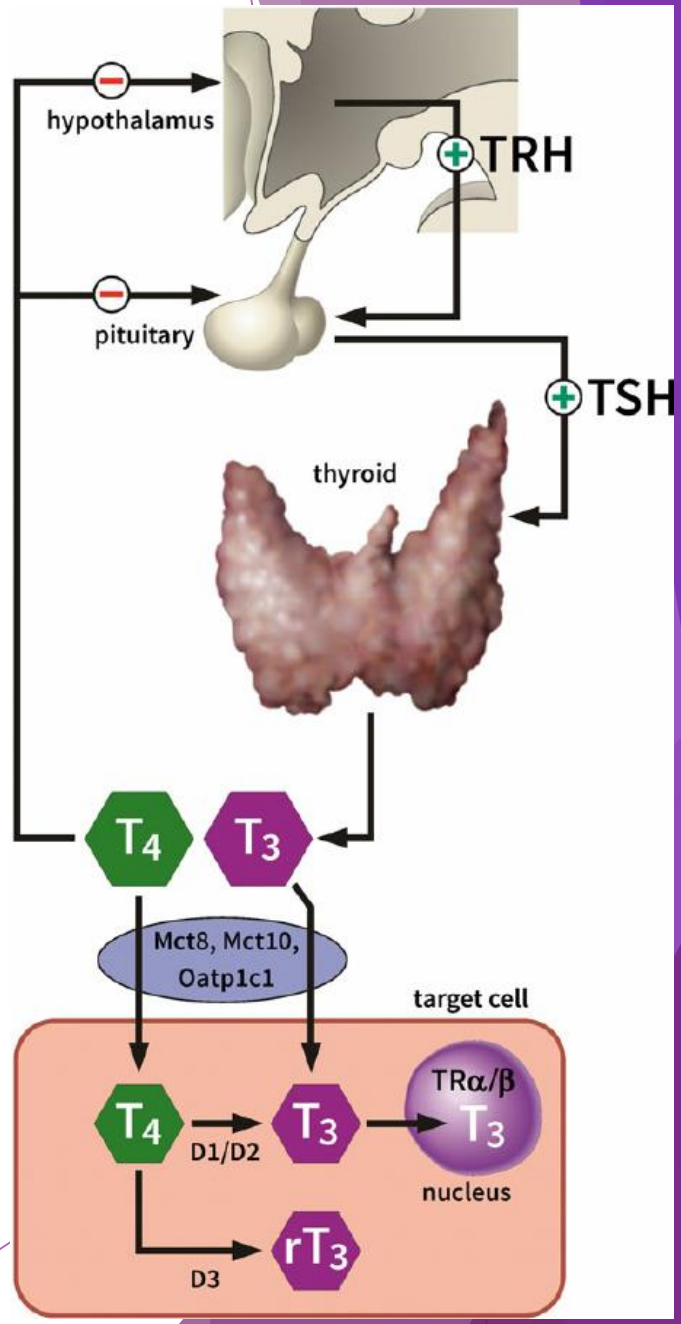
Hypothyroidism

- Diagnosed based on symptoms that make you order a TSH with reflex FT4
- >90% Hashimoto's: I don't check TPO antibodies (which are present in 20% of all women)

- If TSH elevated and FT4 is low – confirms clinical hypothyroidism, treat
  - 50 mcg daily to start, full replacement 1.6 mcg/kg/day, on empty stomach at least 30 min before food in AM
- If TSH elevated and FT4 is normal – subclinical hypothyroidism
  - Are you convinced about symptoms? Consider levothyroxine 25-50 mcg/day trial x 3 months

Hypothyroidism Tips: ?T3

- Spectacularly rare someone can't convert from T4 (prohormone) to T3 (most active hormone, 3-4x more active than T4)
  - Converts at cellular level, so serum level not necessarily reflective
  - Rarely patients s/p thyroidectomy may have a D2 isozyme that is a bit slow
- People like Armour/Nature-Throid/WP Thyroid because of supraphysiologic T4:T3 ratio.
  - Human 13:1 to 16:1
  - Pig 4:1 – big boost in AM
  - In metanalysis of randomized trials vs T4, not significantly different, and in studies that showed benefit in combo therapy, many patients got supraphysiologic T3
- If patients are on desiccated thyroid hormone, target TSH ONLY. FT4 will always be low, T3 will change depending timing of last dose



Hypothyroidism Tips: ?T3

- When I rarely prescribe T3: I trial x 3 months at physiologic dosing (cutting back the T4 at the same time) in patients who feel poorly despite stable optimal TSH, and dose BID
- I do NOT prescribe desiccated thyroid, nor this to women who may become pregnant or have thyroid cancer

Approach to conversion of T4 monotherapy to combined T4 and T3 therapy [1]

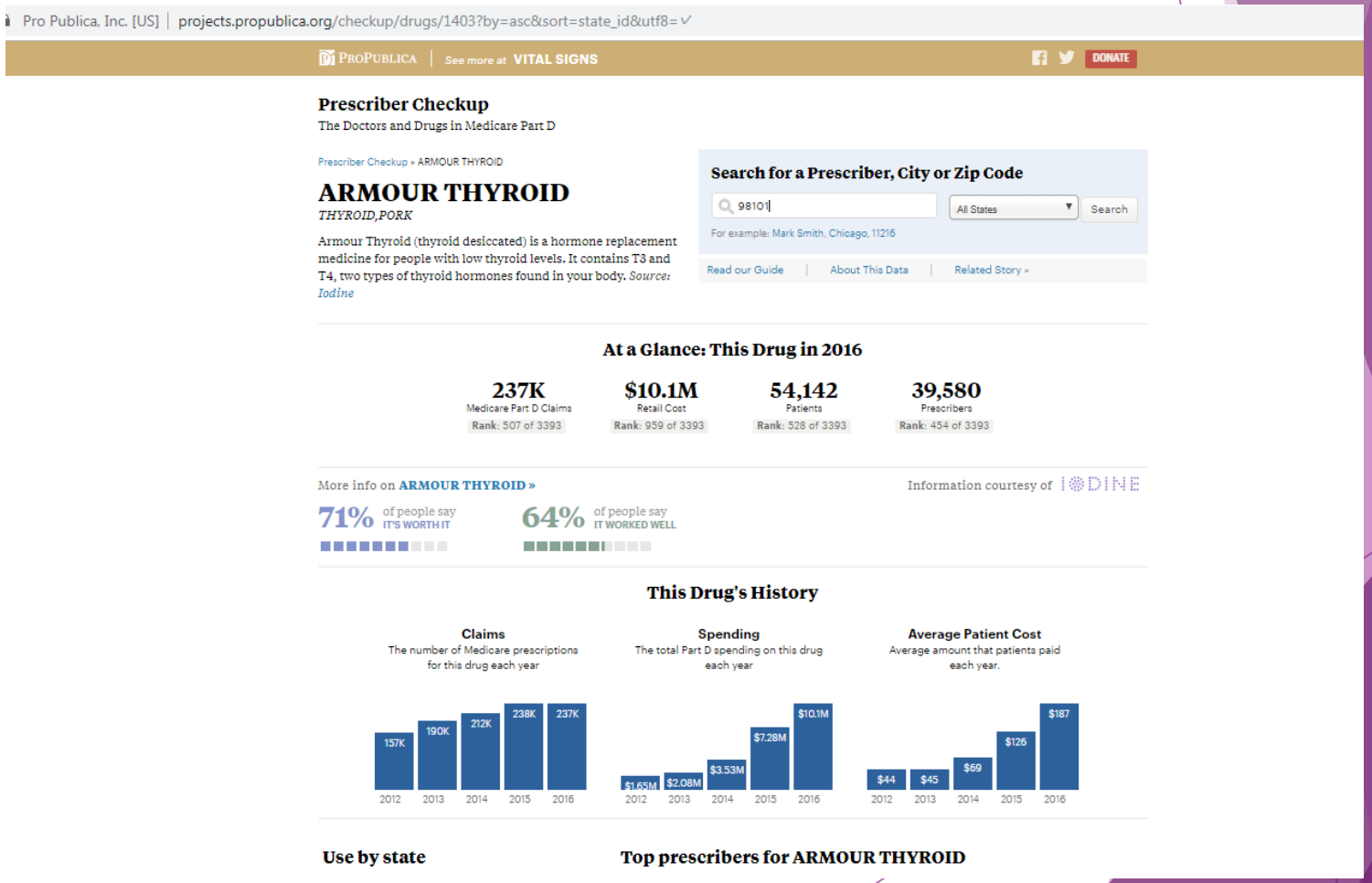
Current T4 therapy (mcg/day)	Combined T4 and T3 oral therapy reflecting a physiologic T4-to-T3 ratio of 13:1 to 16:1*	
	T4 oral dose (mcg/day)	T3 dose
75-100	50-75	2.5 mcg twice daily
112-137	88-112	2.5 mcg three times daily **or** 5 mcg AM and 2.5 mcg PM
150-175	112-137	5 mcg twice daily
200-250	150-200	7.5 mcg AM **and** 5 mcg PM

For patients in whom combined T4 and T3 therapy is pursued, the T4 and T3 components should be prescribed as separate levothyroxine and liothyronine pills according to the above conversions, which provide T4:T3 in a dose ratio that approximates normal physiology. Refer to UpToDate topic on treatment of primary hypothyroidism in adults for details, including patient selection considerations.

Most brilliant use of ProPublica Prescriber Checkup?

MEDICARE US DOCTORS:

Here is a list of those who accept Medicare and may prescribe Natural desiccated thyroid



Hypothyroidism Tips: dosing

- Start at 25-50 mcg if elderly, cardiac; 1.6 mcg/kg is full replacement for most
- Half life 7 days – can miss a few days if NPO, don't have to give IV
  - If extended NPO IV equivalent approx. 70-80%
- Labs in 4-6 weeks after starting/dose changes
- Poorly compliant – can give weekly in clinic orally (e.g. 700 mcg q7 days)
- Optimal is 30 minutes before breakfast, 4 hours from calcium/iron; 4 hours after dinner is next best
- Manufacturers are NOT bioidentical – up to 5% differences, so if changes, check TSH again. Dose changes 7-14% at a time (e.g. 1/2 -1 tab or next dose up or down)

Hypothyroidism in Pregnancy

- Fetus relies on maternal thyroid hormone through at least 8-10 weeks gestation
  - Only T4 passes through placenta (NO T3 in women who would want to keep a pregnancy!!)
  - Preemptive increase dose by 2 tablets per week as soon as miss a period (28%)
- Very mixed data on pregnancy risk and treatment of subclinical hypothyroidism
  - Consider treating if TSH >2.5, FT4 is normal, and:
    - If TSH is >4 to target TSH <2.5.
    - If TPO+ but TSH 2.5-4: consider treat with levothyroxine 50 mcg depending on TPO Ab+? (?decrease miscarriage?); if not treat, reassess labs q4 weeks in 1st trimester than once in 2nd and 3rd.
    - ATA wouldn't automatically treat until TSH >10 if FT4 wnl if TPO Ab negative
  - TSH <2.5: don't treat
  - Prospective data on screening of all women vs case finding and treating if TPO Ab and TSH >2.5: no difference in outcomes (Negro R, Schwartz A. JCEM 2010, PMID 20130074)
  - +TPO Antibody associated with higher fetal loss and premature delivery

Hyperthyroidism

- Clinical overt hyperthyroidism: tremor, heat intolerance, anxiety, emotional lability, weight loss despite normal/hyperphagia, anxiety, hyperdefecation, oligo/amenorrhea in women, ED and gynecomastia in men (increased SHBG so lower free testosterone, also more T->E conversion), palpitations, increased WOB
- Signs include weight loss, afib, pretibial myxedema, orbitopathy, worsening bone loss, warm skin, diaphoresis

- Some patients can gain weight due to disrupted metabolism from poor sleep or from hyperphagia. Older patients may not present with much in the way of symptoms
- Thyroid storm is life-threatening

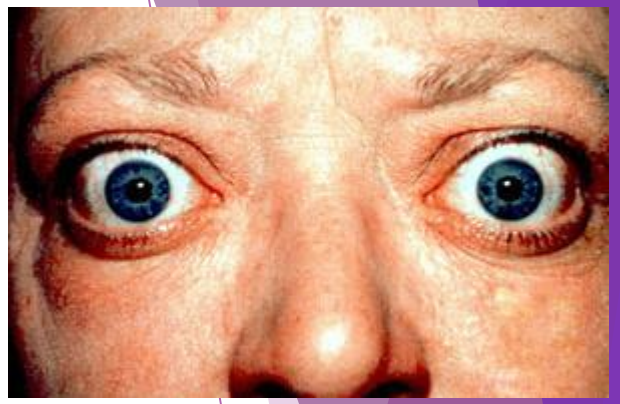
Hyperthyroidism

- Diagnose with suppressed TSH, elevated FT4 (or if normal, elevated TT3)
- DDx: hot nodule, Graves, thyroiditis
  - history and exam matters: gradual onset (autonomous nodule), <3 months sudden onset esp after sore throat (thyroiditis), eye symptoms (Graves)
  - TSH receptor antibody, uptake +/- scan
- Treat with beta blocker, radioactive iodine, surgery

Graves Disease Treatment

- Treat with methimazole in everyone but pregnant women (then propythiuracil)
  - Start most at 5-15 mg, adjust every 4-6 weeks initially, then titrate down dose as able. Higher doses, more likely side effects
  - Goal is 12-18 months of treatment, repeat TSH receptor antibody and if negative, likely can d/c (>50% chance of remission)
  - 50% of patients will go into remission… overall, 30% will have sustained remission
    - Monitor for recurrence: at 2-3 months, 6 months, 12 months, yearly, and if symptoms
- If recurs, consider definitive treatment:
  - radioactive iodine (stop MMI 3 days beforehand, +/- resume afterwards)
  - For surgery (render patient euthyroid on MMI first to avoid risk of thyroid storm, stop MMI day of surgery
  - Can consider long-term methimazole if low doses

Graves/Thyroid Eye Disease (TED)/Orbitopathy/Ophthalmopathy



- TSH receptor antibody attack thyroid, retroocular tissue
- More common in women (but more severe in men), smokers, prior radioactive iodine
- Symptoms: tearing, gritty eyes, eye/retroocular discomfort, diplopia, proptosis. Dry eyes in AM due to incomplete lid closure
- Treatment: natural tears and ocular lubricant at night (preservative free); selenium supplementation; pulse weekly high dose methylprednisolone; new monoclonal antibody up for FDA approval; radiation

Toxic nodule(s)

- Methimazole can work short term but recurs as soon as discontinued
- Radioactive iodine or surgery (with thionadmide pre-treatment)
  - Choose surgery for large goiters, compression, concern for thyroid cancer, need for rapid return to euthyroid
  - Radioactive iodine will decrease thyroid volume 38-45%, requires radiation precautions, ?small increased risk of secondary malignancy due to radiation exposure, but lower risk of complications

Thyroiditis

- Painful – subacute (supportive care x weeks), infectious (biopsy, drainage, antibiotics if abscess)
- Nonpainful –
  - painless (1-5% of hyperthyroidism cases – transient hyper +/- hypo, then recover, typically Hashimoto's),
  - post-partum (8-10% of pregnancies, higher risk of permanent hypothyroidism later),
  - Medication like IFN-alfa, IL-2, amiodarone (AIT1 with increase hormone from preexisting nodular goiter- treat with often high dose MMI; AIT2 destructive thyroiditis– treat with steroids pred 40-60mg daily x 1-3 months; no immediate benefit to stopping amio), TKI, checkpoint inhibitors
  - Reidel's thyroiditis (fibrosis and macrophage + eosinophilic infiltration – eval for other fibrosis)

Hyperthyroidism in Pregnancy

- Run mom hyperthyroid: TSH at low end of trimester range, target FT4 at ULN or TT4 at 1.5xULN

- Plan! Elective RAI 6-12 months beforehand or surgery, ensure euthyroid prior to pregnancy
- Switch to PTU before trying to conceive (and continue through 1st trimester!)
- If accidentally pregnant with MMI, try to stop (Graves often improves during pregnancy and flares post-partum)

- Don't treat mom if:
  - TSH low in 1st trimester but FT4 (or TT4) and FT3 wnl: physiologic
  - HCG-mediated over hyperthyroidism will resolve
  - Hyperemesis gravidarum-associated hyperthyroidism

- For Graves, check TRAb 1st trimester; if >3x ULN, again at 18-22 weeks, and at 30-34 weeks – if 3x ULN late in pregnancy, risk fetal/neonatal hyperthyroidism

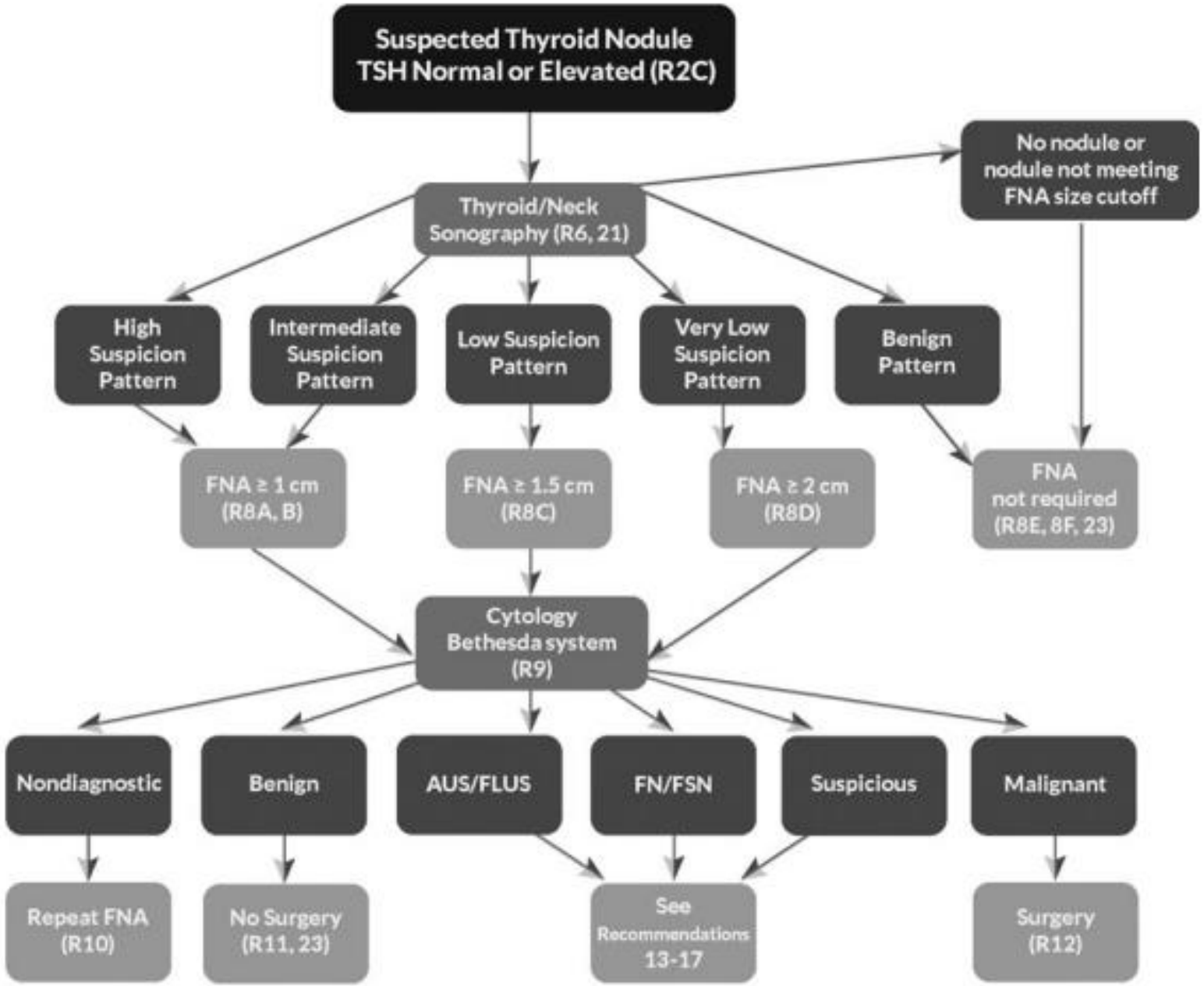
Thyroid Nodules

13-67% of us have them…

Don’t ultrasound yourself…

Thyroid nodules

- <8% of nodules are cancer
  - this decreases every year due to more incidentally found nodules
- Initial workup
  - Start off with H+P:
    - Higher risk: People <30 yo, hx of head and neck radiation, FHx thyroid cancer
  - Measure TSH,
    - If low, do uptake:
      - hot nodules <3% risk of malignancy
      - Graves – up to 35% will have nodules, of which 3.3% had malignancy (don't routinely ultrasound)
    - TSH >5.5, nodule up to 29.7% risk of malignancy
  - Thyroid US to evaluate sonographic features and LAD


Suspected Thyroid Nodule
TSH Normal or Elevated (R2C)
Thyroid/Neck Sonography (R6, 21)
No nodule or nodule not meeting FNA size cutoff
High Suspicion Pattern
Intermediate Suspicion Pattern
Low Suspicion Pattern
Very Low Suspicion Pattern
Benign Pattern
FNA ≥ 1 cm (R8A, B)
FNA ≥ 1.5 cm (R8C)
FNA ≥ 2 cm (R8D)
FNA not required (R8E, 8F, 23)
Cytology Bethesda system (R9)
Nondiagnostic
Benign
AUS/FLUS
FN/FSN
Suspicious
Malignant
Repeat FNA (R10)
No Surgery (R11, 23)
See Recommendations 13-17
Surgery (R12)

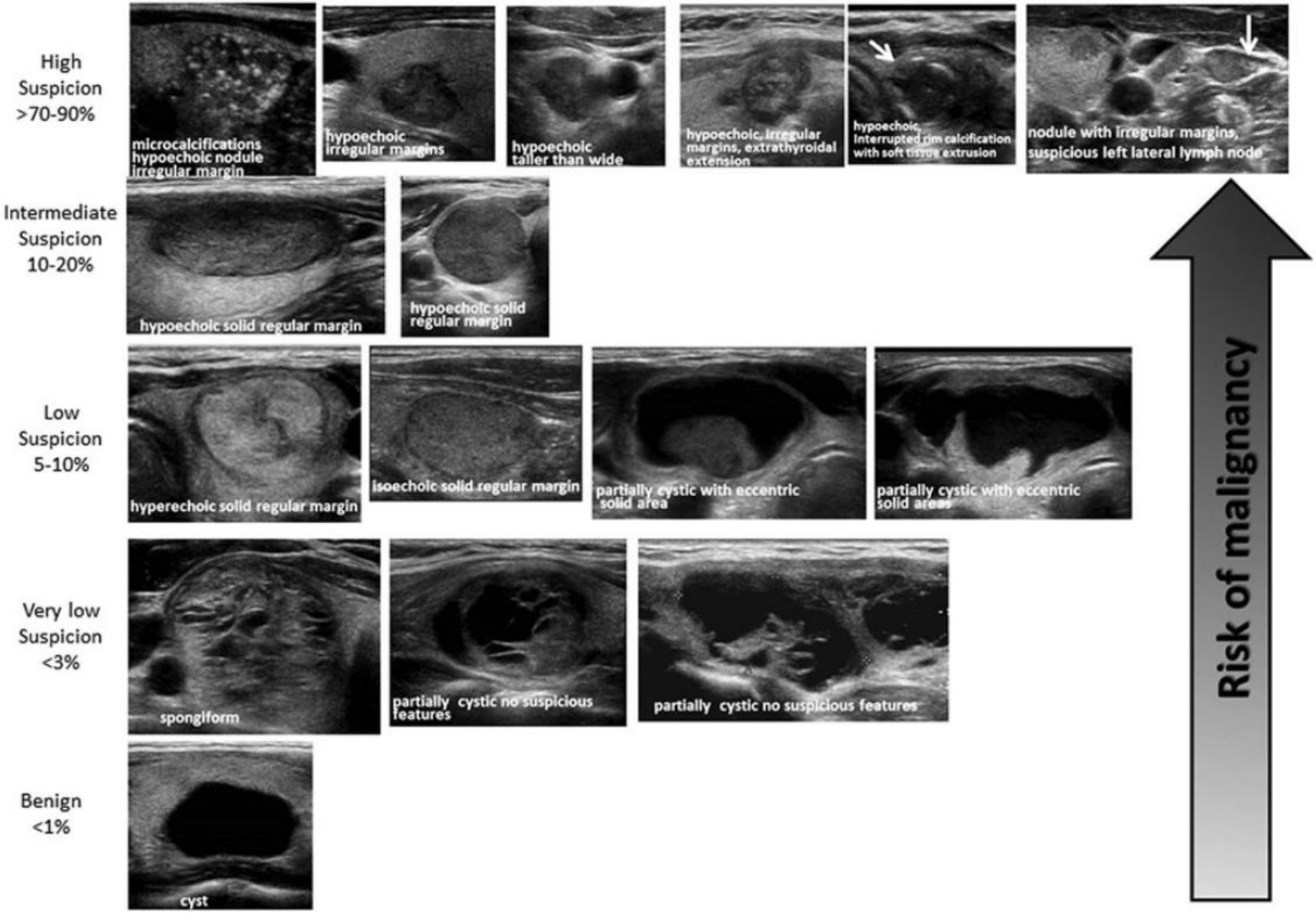


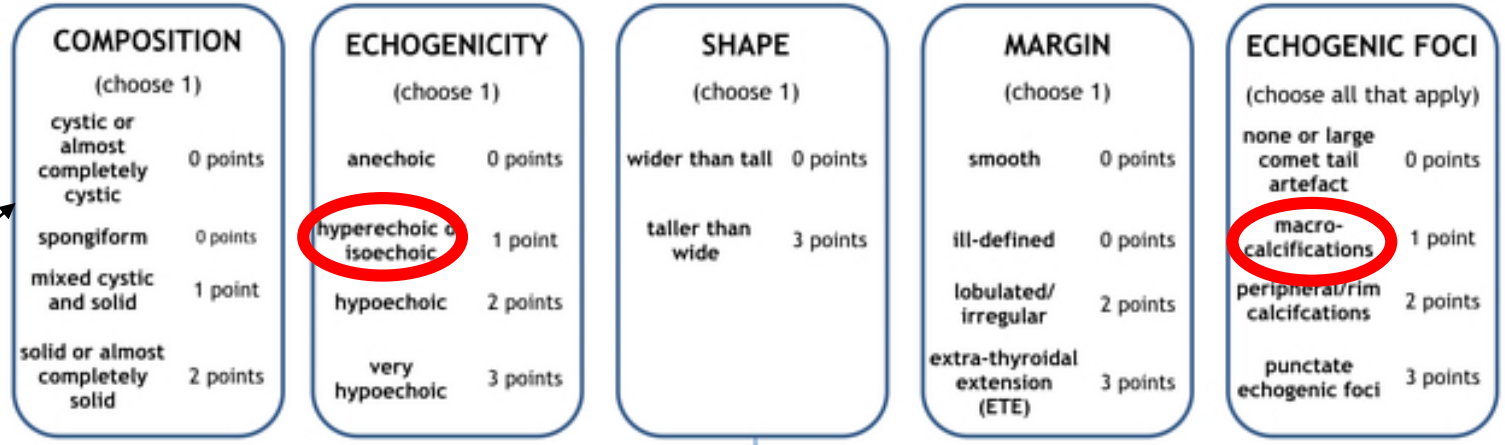
FIG. 2. ATA nodule sonographic patterns and risk of malignancy.

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	>70–90[a]	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[b]

US-guided FNA is recommended for cervical lymph nodes that are sonographically suspicious for thyroid cancer (see Table 7).
[a]The estimate is derived from high volume centers, the overall risk of malignancy may be lower given the interobserver variability in sonography.
[b]Aspiration of the cyst may be considered for symptomatic or cosmetic drainage.
ETE, extrathyroidal extension.

AND RISK OF MALIGNANCY

Diagnostic category	*Estimated/predicted risk of malignancy by the Bethesda system, %*[a]	*Actual risk of malignancy in nodules surgically excised, % median (range)*[b]
Nondiagnostic or unsatisfactory	1–4	20 (9–32)
Benign	0–3	2.5 (1–10)
Atypia of undetermined significance or follicular lesion of undetermined significance	5–15	14 (6–48)
Follicular neoplasm or suspicious for a follicular neoplasm	15–30	25 (14–34)
Suspicious for malignancy	60–75	70 (53–97)
Malignant	97–99	99 (94–100)



* Predominantly cystic or spongiform nodules are inherently benign. If these features are present no further points will be added (automatically TR1)

summation of points from each column to determine TI-RADS grade

0 points	2 points	3 points	4-6 points	≥7 points
TR1 benign	TR2 not suspicious	TR3 mildly suspicious	TR4 moderately suspicious	TR5 highly suspicious
no FNA	no FNA	≥ 1.5 cm follow up ≥ 2.5 cm FNA	≥ 1.0 cm follow up ≥ 1.5 cm FNA	≥ 0.5 cm follow up ≥ 1.0 cm FNA
	0% CA	3.4% CA	14% CA	86.5% CA

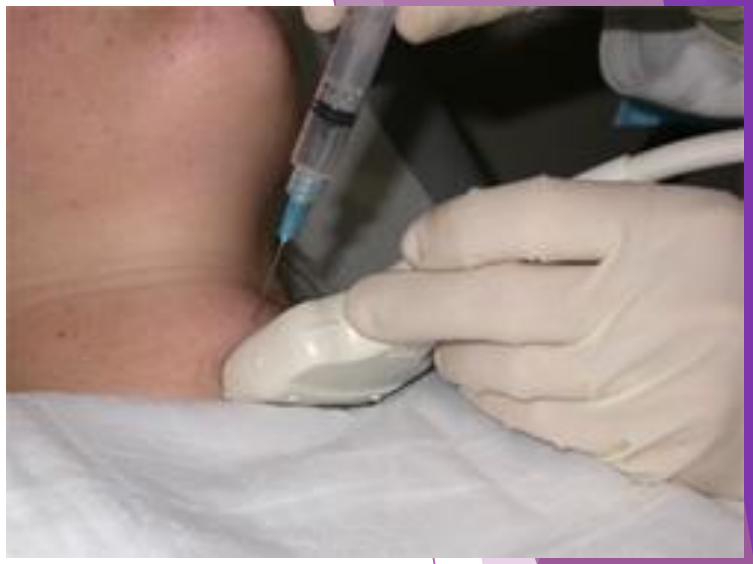
Source: ACR White Paper 2017

Considered benign in ATA

Generally, ATA more sensitive and less specific than TIRADS for predicting cancer on FNA.

One study found TIRADS had lowest false negative

Biopsy



- By endocrinologist or IR
- With or without local lidocaine
- Safe to biopsy on anticoagulation
- 1-5 passes (depending on institution and whether evaluating for sample adequacy immediately or saving sample for molecular testing)
- Typically under ultrasound
- Most will be papillary thyroid cancer, then follicular; then medullary, anaplastic, thyroid lymphoma

Image from: http://endocrinediseases.org/thyroid/nodule_fna.sh

Biopsy results: Bethesda Category (and risk of cancer)

- I Nondiagnostic (5-10%): repeat FNA in 4-6 weeks
- II Benign (<=3%): f/u US in 1-2 years, then less; repeat FNA if highly suspicious US characteristics or growing >50% volume
- III Follicular lesion/atypia of undetermined significance (FLUS, AUS)

  (10-30%): repeat bx or molecular markers
- IV Suspicious for follicular neoplasm (25-40%): repeat bx or molecular markers
- V Suspicious for malignancy (50-75% risk of CA or NIFTP): at least hemi
- VI Malignant (97-99%): at least hemithyroidectomy

If benign biopsy or no FNA

- If TIRADs, the TR will recommend f/u schedule

- Else, f/u US in 6-12 months if subcm and suspicious or high risk
- F/u US 12-24 months if low-intermediate risk
- F/u US in 24-36 months if very low risk

If cancer, send to a high volume surgeon!

Risk of Structural Disease Recurrence

(In patients without structurally identifiable disease after initial therapy)

High Risk
Gross extrathyroidal extension, incomplete tumor resection, distant metastases, or lymph node >3 cm

Intermediate Risk
Aggressive histology , minor extrathyroidal extension, vascular invasion, or > 5 involved lymph nodes (0.2-3 cm)

Low Risk
Intrathyroidal DTC
≤ 5 LN micrometastases (< 0.2 cm)

FTC, extensive vascular invasion (≈ 30-55%)
pT4a gross ETE (≈ 30-40%)
pN1 with extranodal extension, >3 LN involved (≈ 40%)
PTC, > 1 cm, TERT mutated ± BRAF mutated* (>40%)
pN1, any LN > 3 cm (≈ 30%)
PTC, extrathyroidal, BRAF mutated*(≈ 10-40%)
PTC, vascular invasion (≈ 15-30%)
Clinical N1 (≈20%)
pN1, > 5 LN involved (≈20%)
Intrathyroidal PTC, < 4 cm, BRAF mutated* (≈10%)
pT3 minor ETE (≈ 3-8%)
pN1, all LN < 0.2 cm (≈5%)
pN1, ≤ 5 LN involved (≈5%)
Intrathyroidal PTC, 2-4 cm (≈ 5%)
Multifocal PTMC (≈ 4-6%)
pN1 without extranodal extension, ≤ 3 LN involved (2%)
Minimally invasive FTC (≈ 2-3%)
Intrathyroidal, < 4 cm, BRAF wild type* (≈ 1-2%)
Intrathyroidal unifocal PTMC, BRAF mutated*, (≈ 1-2%)
Intrathyroidal, encapsulated, FV-PTC (≈ 1-2%)
Unifocal PTMC (≈ 1-2%)

D MODIFICATIONS

ctures
., tall cell, hobnail variant,

oci outside the thyroid bed on

(<0.2 cm in largest dimension)[a]
thyroid cancer[a]
with capsular invasion and

ifocal, including *BRAF*^{V600E}

tissues
ment whole-body RAI scan
nnar cell carcinoma)

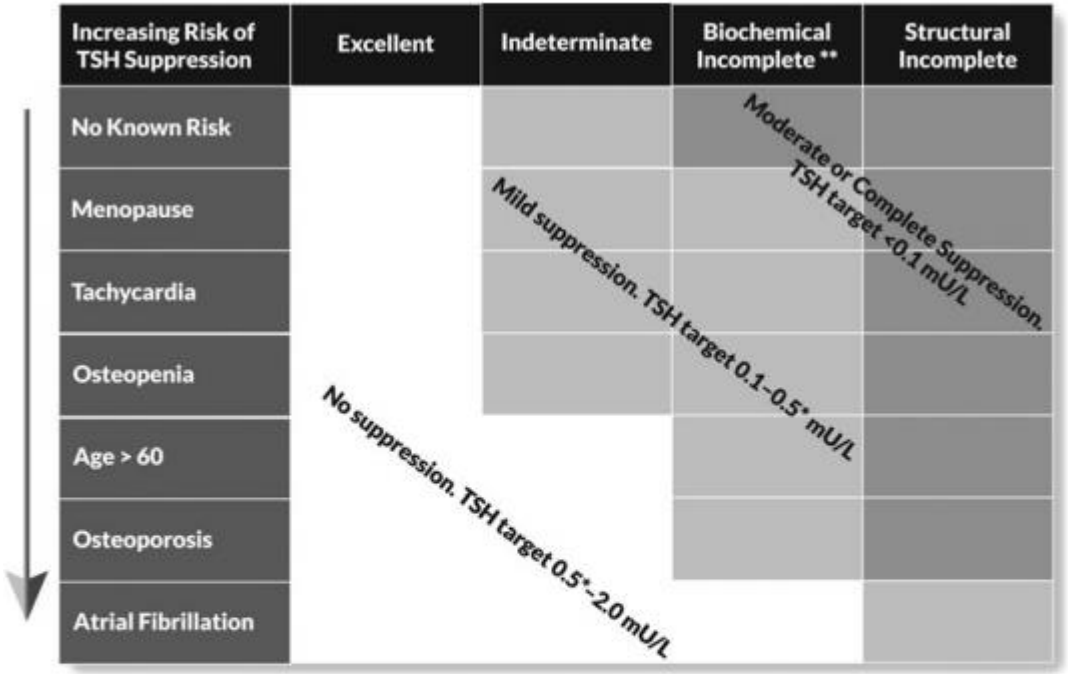
nodes <3 cm in largest dimension[a]
^{V600E} mutated (if known)[a]

ATA high risk
Macroscopic invasion of tumor into the perithyroidal soft tissues (gross ETE)
Incomplete tumor resection
Distant metastases
Postoperative serum thyroglobulin suggestive of distant metastases
Pathologic N1 with any metastatic lymph node ≥3 cm in largest dimension[a]
Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)[a]

[a]Proposed modifications, not present in the original 2009 initial risk stratification system. See sections [B19]–[B23] and Recommendation 48B.

	Stage	7th Edition Description	7th Edition 10 yr DSS	8th Edition Description	8th Edition Expected 10 yr DSS
Younger patients	**I**	< 45 years old All patients without distant metastases regardless of tumor size, lymph node status or extrathyroidal extension	97-100%	< 55 years old All patients without distant metastases regardless of tumor size, lymph node status or extrathyroidal extension	98-100%
	II	< 45 years old Distant metastases	95-99%	< 55 years old Distant metastases	85-95%
Older patients	**I**	≥ 45 years old ≤ 2 cm tumor Confined to the thyroid	97-100%	≥ 55 years old ≤ 4 cm tumor Confined to the thyroid	98-100%
	II	≥ 45 years old 2-4 cm tumor Confined to the thyroid	97-100%	≥ 55 years old Tumors > 4cm, Or tumors of any size with central or lateral neck lymph nodes, Or gross extrathyroidal extension into strap muscles	85-95%
	III	≥ 45 years old >4 cm tumor, Or minimal extrathyroidal extension, Or central neck lymph node metastasis	88-95%	≥ 55 years old Tumors of any size with gross extrathyroidal extension into subcutaneous tissue, larynx, trachea, esophagus, recurrent laryngeal nerve	60-70%
	IV	≥ 45 years old Gross extrathyroidal extension, Or lateral neck lymph node metastasis, Or distant metastasis	50-75%	≥ 55 years old Tumors of any size or lymph node status with gross extrathyroidal extension into prevertebral fascia, encasing major vessels Or distant metastasis	< 50%

TABLE 15. THYROTROPIN TARGETS FOR LONG-TERM THYROID HORMONE THERAPY



* 0.5 mU/L represents the lower limit of the reference range for the TSH assay which can be 0.3–0.5 mU/L depending on the specific assay

** TSH target for patients with a biochemical incomplete response can be quite different based on original ATA risk, Tg level, Tg trend over time and risk of TSH suppression

No suppression. TSH target 0.5*–2.0 mU/L

Mild suppression. TSH target 0.1–0.5* mU/L

Moderate or Complete suppression. TSH target <0.1 mU/L

Differentiated thyroid cancer: Monitoring during the first year after thyroid surgery

	Risk of recurrence		
	Low	**Intermediate**	**High**
Nonstimulated Tg*	4 to 6 weeks 3 to 6 months 9 to 12 months	4 to 6 weeks 3 to 6 months 9 to 12 months	4 to 6 weeks 3 to 6 months 9 to 12 months
Neck ultrasound	At 6 to 12 months	At 6 to 12 months	Every 6 to 12 months
Diagnostic WBS	Usually not indicated	Case specific	Case specific
MRI, CT	Not indicated	Not indicated	If Tg elevated or high clinical suspicion
FDG-PET	Not indicated	Not indicated	If Tg >10 ng/mL
Serum TSH goal	0.1 to 0.5 ng/mL if nonstimulated Tg detectable 0.5 to 2.0 ng/mL if nonstimulated Tg undetectable	0.1 to 0.5 ng/mL	<0.1 ng/mL

TABLE .TIFICATION SYSTEM: CLINICAL OUTCOMES FOLLOWING TOTAL EMNANT ABLATION OR ADJUVANT THERAPY

ATA risk	*NED, %*	*Biochemical incomplete, %*[b]	*Structural incomplete, %*
Low	86	11	3
	91	ND[a]	ND[a]
	88	10	2
	78	15	7
Intermed	57	22	21
	63	16	21
	52	14	34
High	14	14	72
	16	12	72
	31	13	56

TABLE 13. CLINICAL IMPLICATIONS OF RESPONSE TO THERAPY RECLASSIFICATION IN PATIENTS WITH DIFFERENTIATED THYROID CANCER TREATED WITH TOTAL THYROIDECTOMY AND RADIOIODINE REMNANT ABLATION

Category	*Definitions*[a]	*Clinical outcomes*	*Management implications*
Excellent response	Negative imaging ***and either*** Suppressed Tg <0.2 ng/mL[b] ***or*** TSH-stimulated Tg <1 ng/mL[b]	1%–4% recurrence[c] <1% disease specific death[c]	An excellent response to therapy should lead to an early decrease in the intensity and frequency of follow up and the degree of TSH suppression
Biochemical incomplete response	Negative imaging ***and*** Suppressed Tg ≥1 ng/mL[b] ***or*** Stimulated Tg ≥10 ng/mL[b] ***or*** Rising anti-Tg antibody levels	At least 30% spontaneously evolve to NED[d] 20% achieve NED after additional therapy[a] 20% develop structural disease[a] <1% disease specific death[a]	If associated with stable or declining serum Tg values, a biochemical incomplete response should lead to continued observation with ongoing TSH suppression in most patients. Rising Tg or anti-Tg antibody values should prompt additional investigations and potentially additional therapies.
Structural incomplete response	Structural or functional evidence of disease With any Tg level With or without anti-Tg antibodies	50%–85% continue to have persistent disease despite additional therapy[c] Disease specific death rates as high as 11% with loco-regional metastases and 50% with structural distant metastases[a]	A structural incomplete response may lead to additional treatments or ongoing observation depending on multiple clinico-pathologic factors including the size, location, rate of growth, RAI avidity, ^{18}FDG avidity, and specific pathology of the structural lesions.
Indeterminate response	Nonspecific findings on imaging studies Faint uptake in thyroid bed on RAI scanning Nonstimulated Tg detectable, but <1 ng/mL Stimulated Tg detectable, but <10 ng/mL ***or*** Anti-Tg antibodies stable or declining in the absence of structural or functional disease	15%–20% will have structural disease identified during follow-up[a] In the remainder, the nonspecific changes are either stable, or resolve[a] <1% disease specific death[a]	An indeterminate response should lead to continued observation with appropriate serial imaging of the nonspecific lesions and serum Tg monitoring. Nonspecific findings that become suspicious over time can be further evaluated with additional imaging or biopsy.

NED denotes a patient as having no evidence of disease at final follow-up.
[a]References (538,539).
[b]In the absence of anti-Tg antibodies.

ATA risk Staging (TNM)	*Description*	*Body of evidence suggests RAI improves disease-specific survival?*	*Body of evidence suggests RAI improves disease-free survival?*	*Postsurgical RAI indicated?*
ATA low risk T1a N0,Nx M0,Mx	Tumor size ≤1 cm (uni-or multi-focal)	No	No	No
ATA low risk T1b,T2 N0, Nx M0,Mx	Tumor size >1–4 cm	No	Conflicting observational data	Not routine[b]—May be considered for patients with aggressive histology or vascular invasion (ATA intermediate risk).
ATA low to intermediate risk T3 N0,Nx M0,Mx	Tumor size >4 cm	Conflicting data	Conflicting observational data	Consider[b]—Need to consider presence of other adverse features. Advancing age may favor RAI use in some cases, but specific age and tumor size cutoffs subject to some uncertainty.[a]
ATA low to intermediate risk T3 N0,Nx M0,Mx	Microscopic ETE, any tumor size	No	Conflicting observational data	Consider[b]—Generally favored based on risk of recurrent disease. Smaller tumors with microscopic ETE may not require RAI.
ATA low to intermediate risk T1-3 N1a M0,Mx	Central compartment neck lymph node metastases	No, except possibly in subgroup of patients ≥45 years of age (NTCTCSG Stage III)	Conflicting observational data	Consider[b]—Generally favored, due to somewhat higher risk of persistent or recurrent disease, especially with increasing number of large (>2–3 cm) or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use.[a] However, there is insufficient data to mandate RAI use in patients with few (<5) microscopic nodal metastases in central compartment in absence of other adverse features.
ATA low to intermediate risk T1-3 N1b M0,Mx	Lateral neck or mediastinal lymph node metastases	No, except possibly in subgroup of patients ≥45 years of age	Conflicting observational data	Consider[b]—Generally favored, due to higher risk of persistent or recurrent disease, especially with increasing number of macroscopic or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use.[a]
ATA high risk T4 Any N Any M	Any size, gross ETE	Yes, observational data	Yes, observational data	Yes
ATA high risk M1 Any T Any N	Distant metastases	Yes, observational data	Yes, observational data	Yes