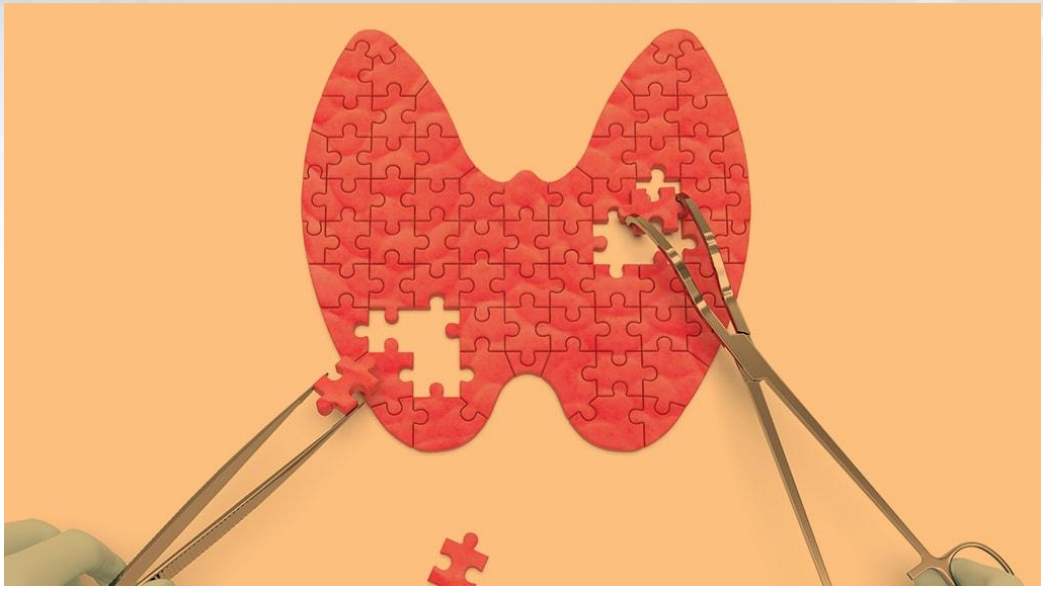
Evaluating the Thyroid Nodule: When to Observe, When to Operate and When to Ablate



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Professor and Chair

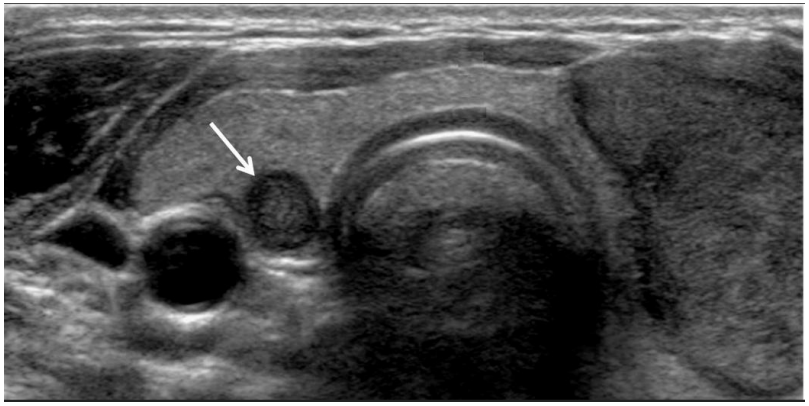
Department of Otolaryngology-Head and Neck Surgery
Penn State College of Medicine

- Thyroid nodules
- Diagnostic workup
- Imaging
- Biopsy
- Interpreting results
- Observation/Surgery/RFA

“Doc- What is a thyroid nodule”?

- Thyroid nodule is a discrete lesion within the thyroid gland that is radiologically distinct from the surrounding thyroid parenchyma.

- Nonpalpable nodules detected on US or other anatomic imaging studies are termed incidentally discovered nodules or ‘‘incidentalomas”



Thyroid nodules

- One in 12-15 young women has a thyroid nodule.
- One in 40 young men has a thyroid nodule.
- The incidence of thyroid nodules increases with age.

✓ 50% of 50 year olds will have at least one thyroid nodule.

✓ 60% of 60 year olds will have at least one thyroid nodule.

✓ 70% of 70 year olds will have at least one thyroid nodule.

- **5% of thyroid nodules are malignant**

Incidentalomas

- Thyroid nodules are incidentally discovered in approximately 9-70% of imaging studies performed for unrelated indications.
- 9.4-27.0% of carotid duplex studies
- 16-18% of CT and MRI scans of the neck
- 25% of contrast-enhanced chest CT scans
- Ultimately malignant 9-13%

- We found incidental nodules were discovered on CT scans (59.8%), with the most common indication being evaluation of an unrelated malignancy (26.9%). We overall malignancy rate of 13.3% in these incidental nodules.

Incidental Thyroid Nodules: Incidence, Evaluation, and Outcome. Chaikhoutdinov I, Mitzner R, Goldenberg D. Otolaryngol Head Neck Surg. 2014 Jun

We are asking 3 Questions about a patient Thyroid Nodules

1. Is it malignant?

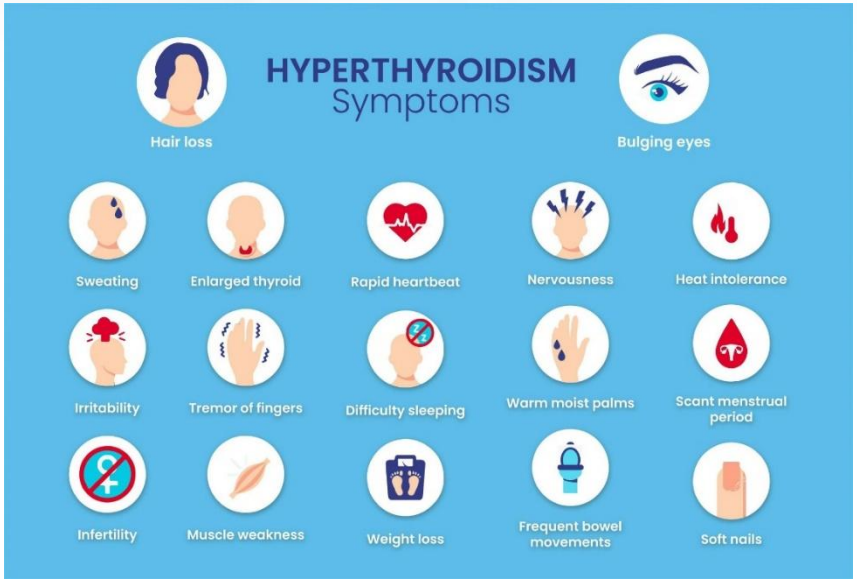
2. Is it causing compression?

3. Is it causing thyrotoxicosis?

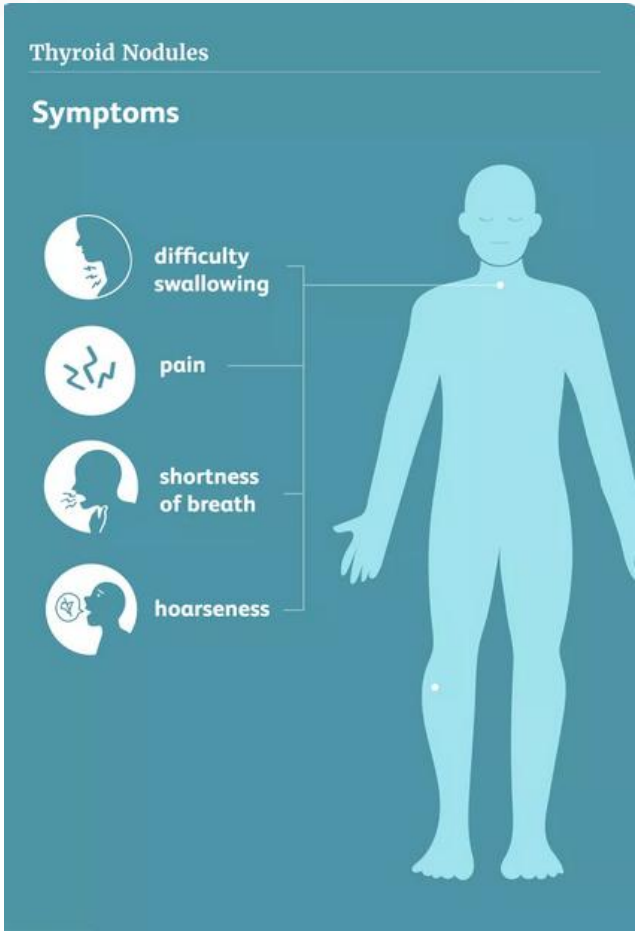
* After an appropriate work-up, most thyroid nodules will yield an answer of *NO* to all of the above

Symptomatic thyroid nodules (the minority)

Toxic nodule



Compressive Nodule



History

- Age (malignancy risk is higher in children/adolescents and slightly elevated in older adults and males)
- Previous head or neck irradiation
- Personal or family history of thyroid disease or cancer
- Symptoms of hyperthyroidism or hypothyroidism
- Use of iodine-containing drugs or supplements
- Prior Bariatric surgery

Thyroidectomy in patients who have undergone gastric bypass **surgery**. Goldenberg D, Ferris RL, Shindo ML, Shaha A, Stack B, Tufano RP. Head Neck. 2018 Jun;40(6):1237-1244. doi: 10.1002/hed.25098.

History

Factors suggesting a malignant diagnosis

- Age younger than 20 years or older than 70 years
- Male sex
- Associated symptoms of dysphagia or dysphonia
- History of neck irradiation
- Prior history of thyroid carcinoma
- Strong family history
- Firm, hard, or immobile nodule
- Presence of cervical lymphadenopathy

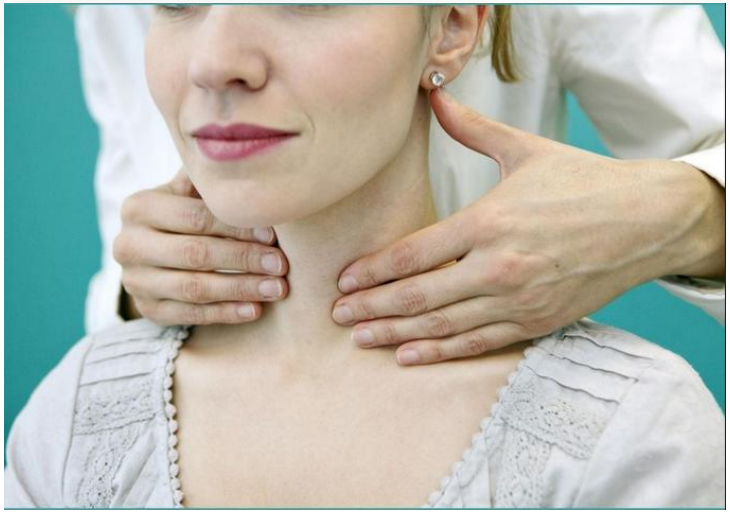
Factors suggesting a benign diagnosis

- Family history of autoimmune disease (e.g., Hashimoto thyroiditis)
- Family history of benign thyroid nodule or goiter
- Presence of thyroid hormonal dysfunction (e.g., hypothyroidism, hyperthyroidism)
- Pain or tenderness associated with nodule
- Soft, smooth, and mobile nodule

Exam

Inspection

- Examine with chin neutral, then with neck extended
- Observe during swallowing (thyroid moves with deglutition)
- Look for visible enlargement or asymmetry



Palpation of Thyroid

- Approach from anterior or posterior position
- Assess thyroid dimensions and consistency
- Document nodule location, size, number, consistency, and mobility

Cervical Lymph Node Examination

- Systematically palpate all cervical lymph node chains (levels IB-VII)
- Large, firm nodes ipsilateral to nodule suggest possible metastases

Physical exam findings that increase the concern for a malignant nodule include:

- Nodules larger than 4 cm in size (19.3% risk of malignancy.
- Firmness to palpation
- Fixation of the nodule to adjacent tissues
- Cervical lymphadenopathy
- Vocal fold immobility
- Older male

Diagnostic workup

- Labs: The most important laboratory test is a TSH assay, which is used to screen for hypothyroidism or hyperthyroidism. (Can do TFTs)

- Initial Imaging studies:

✓ *Thyroid scintigraphy*

✓ *Ultrasonography*

✓ CT scanning or MRI (* Not initial, but sometimes later)

- Ultrasound in King!
- Every thyroid ultrasound should include a neck ultrasound
- Radiology reports should say “No cervical adenopathy detected”

TI-RADS

- The ACR Thyroid Imaging Reporting and Data System (TI-RADS) is an ultrasound-based risk stratification system for thyroid nodules released in 2017 by the American College of Radiology.

- **Five Feature Categories (Points-Based Scoring)**
- Composition: Cystic, spongiform, mixed cystic/solid, solid
- Echogenicity: Anechoic, hyperechoic/isoechoic, hypoechoic, very hypoechoic
- Shape: Wider-than-tall, taller-than-wide
- Margin: Smooth, ill-defined, lobulated/irregular, extra-thyroidal extension
- Echogenic Foci: None, large comet-tail artifacts, macrocalcifications, peripheral calcifications, punctate echogenic foci (microcalcifications)

TIRADS Categories and Malignancy Risk

- **TR1** (0 points): Benign - No FNA
- **TR2** (2 points): Not suspicious - No FNA
- **TR3** (3 points): Mildly suspicious - ~5% malignancy risk
- **TR4** (4-6 points): Moderately suspicious - ~5-20% malignancy risk
- **TR5** (≥7 points): Highly suspicious - ~20-92% malignancy risk[4]

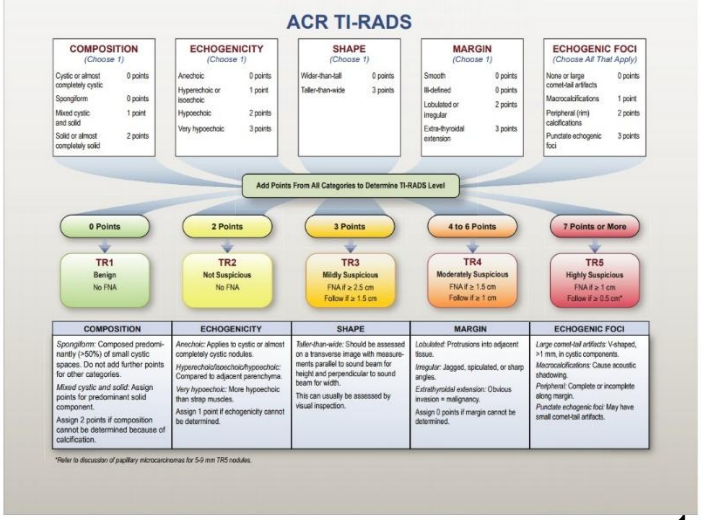
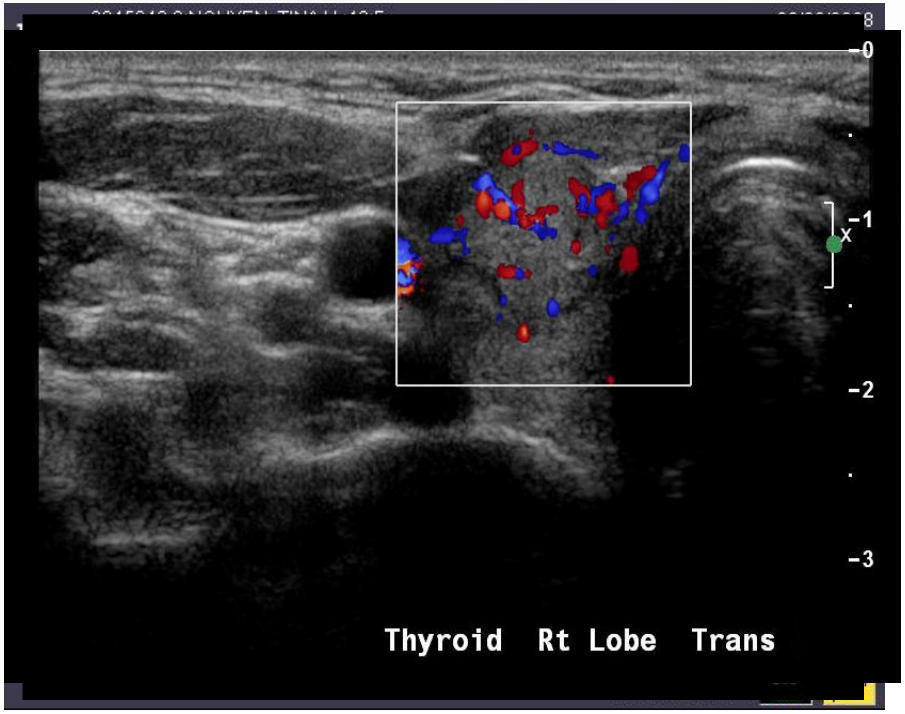


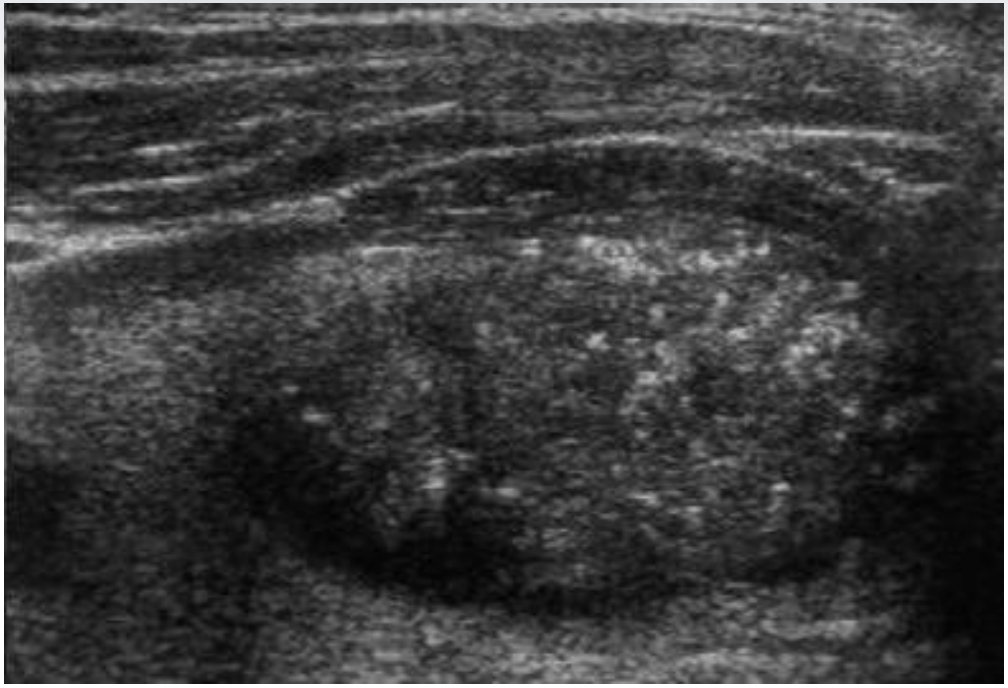
Fig 1. Chart showing five categories on the basis of the ACR Thyroid Imaging, Reporting and Data System (TI-RADS) lexicon, TI levels, and criteria for fine-needle aspiration or follow-up ultrasound. Explanatory notes appear at the bottom.

Ultrasound parameters of Malignancy



- Hypoechoic
- Microcalcifications
- Border irregularity
- Internal vascular flow
- Infiltrative margins
- Abnormal lymph nodes

*The Presence of abnormal lymph nodes in the neck supersedes the characteristic of the thyroid nodule



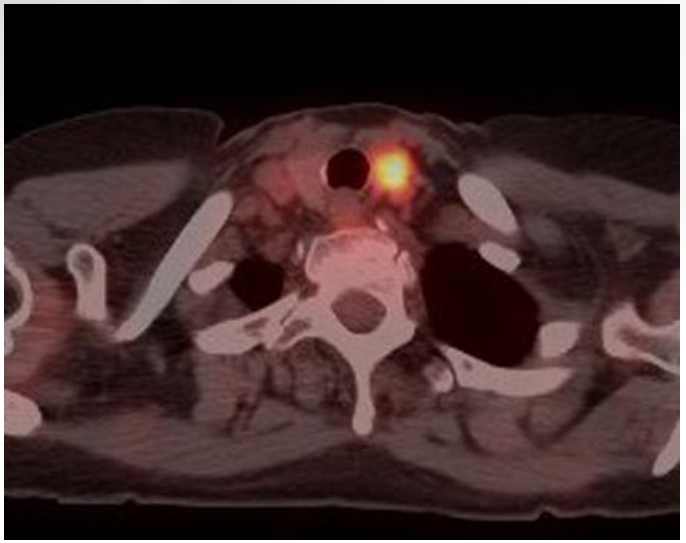
Thyroid sonography with survey of the cervical lymph nodes
may be performed in all patients with known or suspected thyroid nodules.

Which nodules to biopsy?

- Nodules of any size should be biopsied if ultrasonography suggests extracapsular invasion by the lesion or shows cervical lymphadenopathy.

- Nodules also should be biopsied if **Focal** 18FDG-PET uptake within a sonographically confirmed thyroid nodule is found (This conveys an increased risk of thyroid cancer.)

- Nodules should also be biopsied if the patient has a history of head and neck irradiation, thyroid cancer, or MEN type 2 in a first-degree relative.

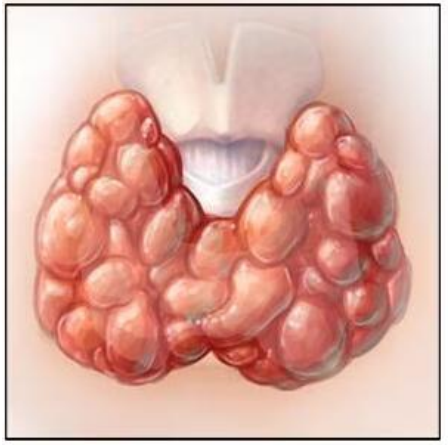


Which nodules not to biopsy?

- Nodules 1 cm or smaller may be followed with serial ultrasonography.

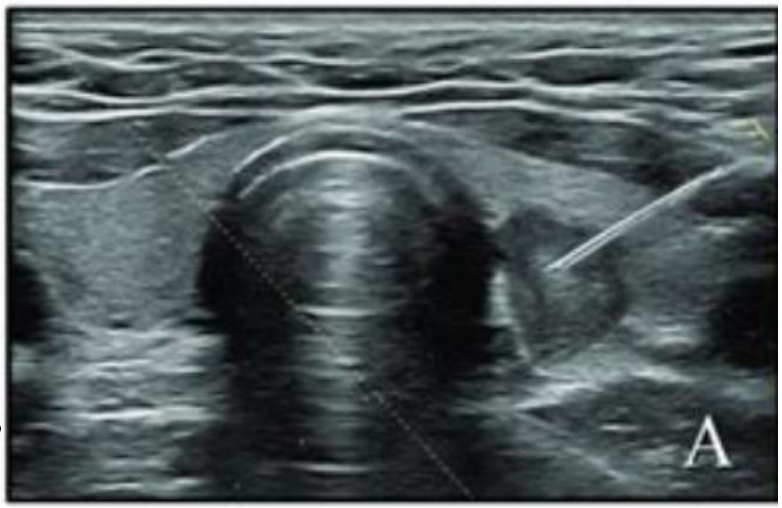
- Hyperfunctioning nodules do not need to be biopsied.

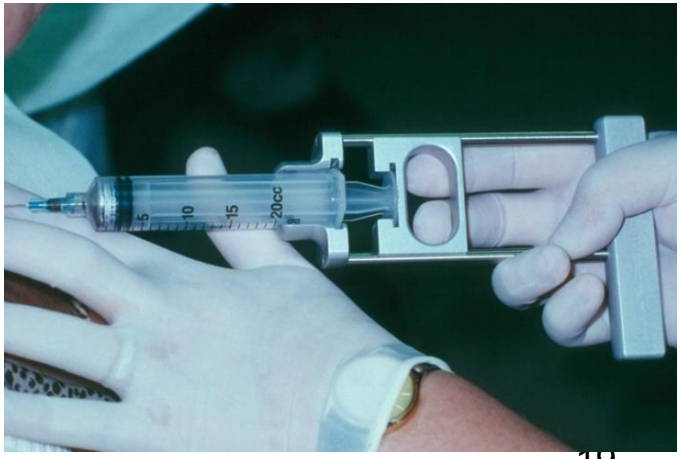
- Multinodular Goiter. In such cases, how many nodules should be biopsied??
  (Some authors suggest sampling no more than three, if they meet TIRADE criteria)



FNA Biopsy

- *Fine-needle aspiration biopsy:* FNAB is the most important step in the diagnostic evaluation of thyroid nodules.
- FNAB is highly accurate, with mean sensitivity >80% and mean specificity >90%.
- The accuracy highly depends on the cytopathologist's experience and the technical skill of the physician performing the biopsy.

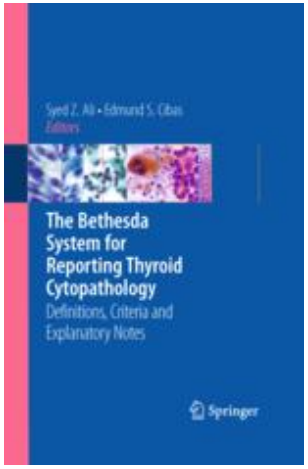




The Bethesda System for Reporting Thyroid Cytopathology: 6 Diagnostic Categories

- The National Cancer Institute sponsored a conference in 2008 to determine the use of FNA in the management of thyroid nodules and proposed a six-category scheme with the predicted probability of malignancy increasing from category II to VI:
- Bethesda I – nondiagnostic,
- Bethesda II – benign
- Bethesda III – follicular lesion of indeterminate significance, (cancer risk of 15%)
- Bethesda IV – follicular neoplasm or suspicious for follicular neoplasm, (cancer risk 30%)
- Bethesda V – suspicious for malignancy (75%)
- Bethesda VI – malignant

*The indeterminate categories comprise Bethesda III–V and have an approximate cancer risk of 5–10, 20–30 and 50–75%, respectively, allowing for variability between cytopathologists.



Thyroid cytology limitations (Benign)

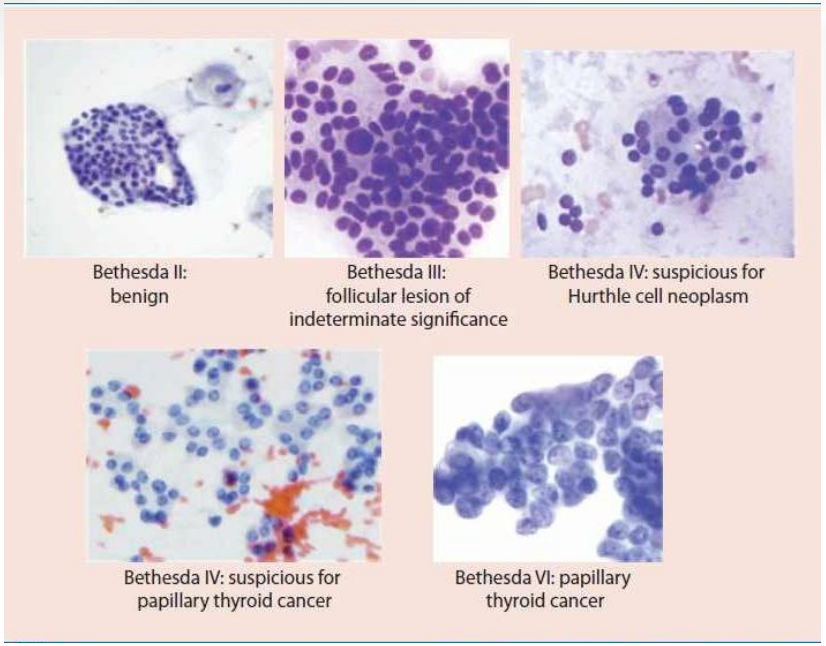
- Nondiagnostic and indeterminate results
- Indeterminate cytology categories (Bethesda III and IV)
- Discordance between cytology and imaging

Thyroid cytology limitations (Malignant)

- False-negative rates and nodule size
- Specific cancer subtypes cannot be diagnosed by FNA cytology. Follicular carcinoma and oncocytic (Hürthle cell)
- Medullary thyroid carcinoma

Nodules that are "Indeterminate"

- Follicular lesion/atypia of undetermined significance or follicular neoplasm = Indeterminate.
- The risk of malignancy with these cytologic classifications ranges from 5 to 32 %, and the majority of these patients undergo diagnostic thyroid surgery.
- However, most patients (75 to 95 %) undergo surgery for what is ultimately confirmed to be benign disease.
- Improvement in the assessment of indeterminate FNA results may allow better risk stratification.



Molecular testing

- FNA biopsy is the gold standard for evaluation
- Up to 30% of cases, results are indeterminate for malignancy
- Increased knowledge about the molecular underpinnings of thyroid neoplasia has transformed the approach to diagnosis, prognosis, and therapeutics.
- Molecular profiles have become an integral part of thyroid cancer management
- Molecular reporting focuses on the nodule tested, including related clinical information for that nodule (size of nodule, Bethesda category, etc.).
- This results in a comprehensive report to physicians that may also include patient-directed, clear language that facilitates conversations about nodule management

Afirma Genomic Sequencing Classifier (GSC)

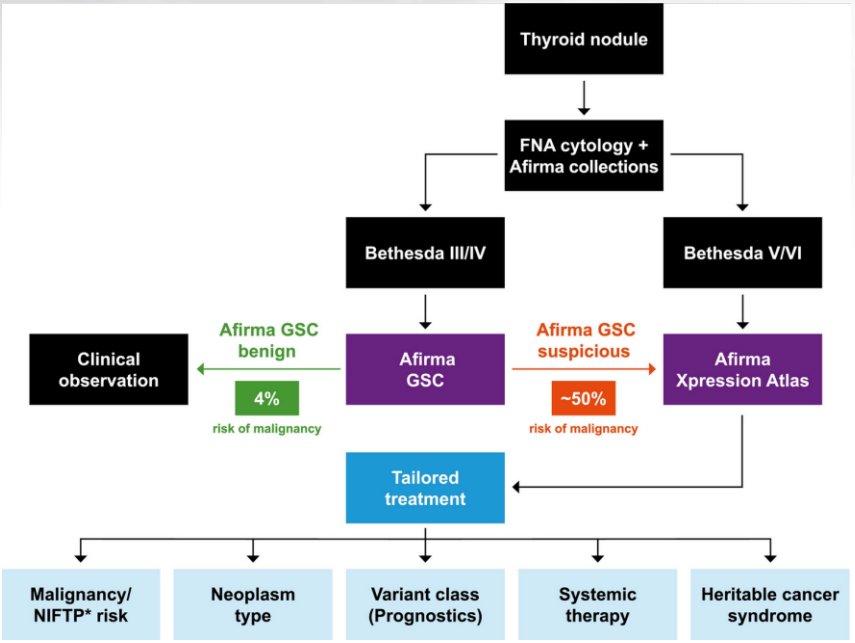
- RNA-based next-generation sequencing analyzing transcriptome, nuclear/mitochondrial RNAs, and genomic copy number
- Binary outcome: Benign or Suspicious
- **Clinical Performance**
- **Sensitivity:** 94-97%
- **Specificity:** 80-88%
- **NPV:** 98-99%
- **PPV:** 50-65%
- **Benign Call Rate:** 53-67%
- **False-Negative Rate:** 2%

- **Key Clinical Utility**
- Designed as "rule-out" test with excellent NPV
- Allows ~50% of patients with indeterminate nodules to avoid diagnostic surgery
- Superior performance in Hürthle cell nodules (benign call rate 63-88%)
- GSC-benign nodules can be observed similarly to cytologically benign nodules
- Only 22% of GSC-benign nodules grow during surveillance

ThyroSeq v3 Genomic Classifier

Platform Technology

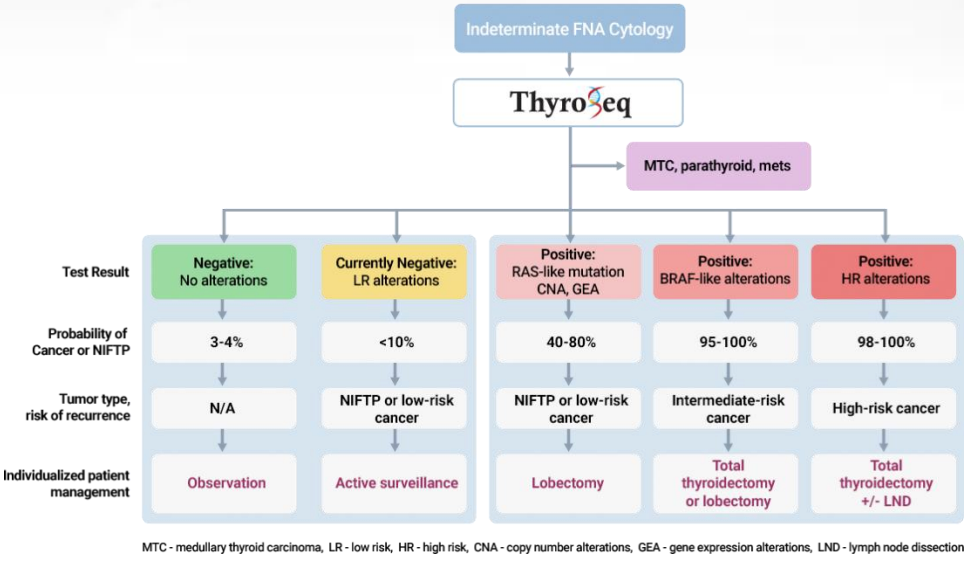
- DNA and RNA next-generation sequencing analyzing 112 thyroid cancer-related genes
- Detects 5 classes of alterations: point mutations, insertions/deletions, gene fusions, copy number alterations, gene expression changes
- Provides specific mutation identification and management recommendations[8]
- **Clinical Performance**
- **Sensitivity:** 89-98%
- **Specificity:** 82-85%
- **NPV:** 84-97%
- **PPV:** 63-66%
- **Benign Call Rate:** 61%
- **False-Negative Rate:** 0.6% over 3 years



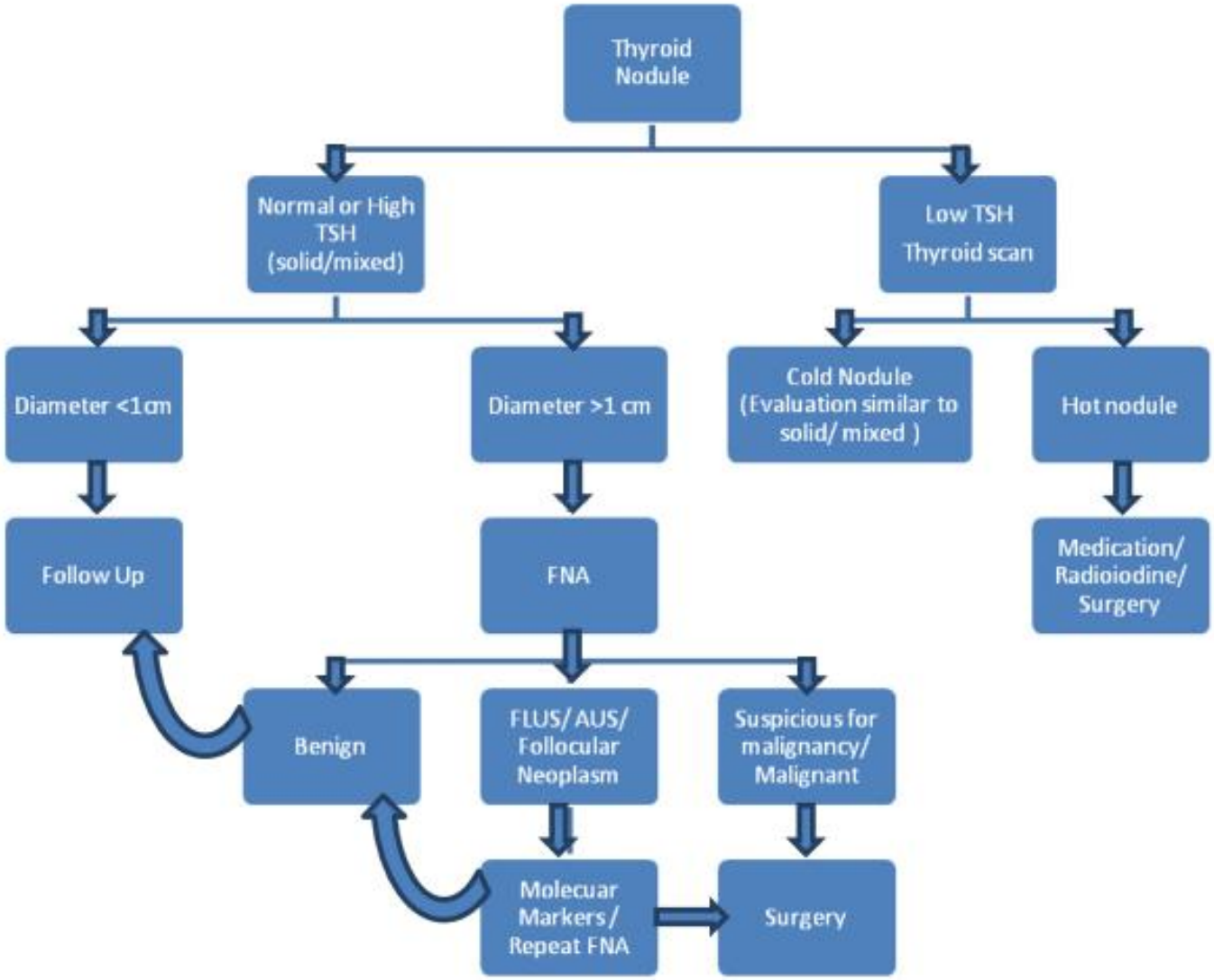
"Olden" days

Now

Diagnostic category	Risk of malignancy (%)	Usual management
Nondiagnostic or unsatisfactory	1-4	Repeat FNA with ultrasound guidance
Benign	0-3	Clinical follow-up
Atypia of undetermined significance or follicular lesion of undetermined significance	5-15	Repeat FNA
Follicular neoplasm or suspicious for a follicular neoplasm	15-30	Surgical lobectomy
Suspicious for malignancy	60-75	Near-total thyroidectomy or surgical lobectomy
Malignant	97-99	Near-total



Thyroid Nodule Workup Algorithm



Treatment Options

- Observation (**Active Surveillance)**
- Surgery
- Thyroid nodule ablation

Surgical Management

Thyroid lobectomy

- Smaller tumors (<4 cm) with suspicious or malignant cytology (Bethesda V-VI)
- Indeterminate nodules (Bethesda III-IV) requiring diagnostic surgery.

Total thyroidectomy is generally recommended for

- Nodules >4 cm,
- bilateral nodular disease requiring surgery,
- evidence of extrathyroidal extension, lymph node or distant metastases, high-risk molecular markers (e.g., BRAF mutation)
- History of head/neck radiation or family history of thyroid cancer.

* use judgment, not set in stone

Surgery

- When a benign diagnosis is confirmed, referral to a surgeon is reasonable for patients with symptoms, such as dysphagia or discomfort, or concerns about cosmesis.

- When findings from the aspirate are nondiagnostic, repeat the aspiration, follow or operate.

- When a nodules for which aspirates are repeatedly nondiagnostic, may ultimately require surgical management.

Autonomously functioning thyroid nodules

- Patients with solitary thyroid nodules associated with suppressed TSH levels, with overt or subclinical hyperthyroidism, do not require routine FNAB.

- In such cases, the patient may be referred to an endocrinologist to discuss iodine-131 treatment versus surgical intervention or Ablation.

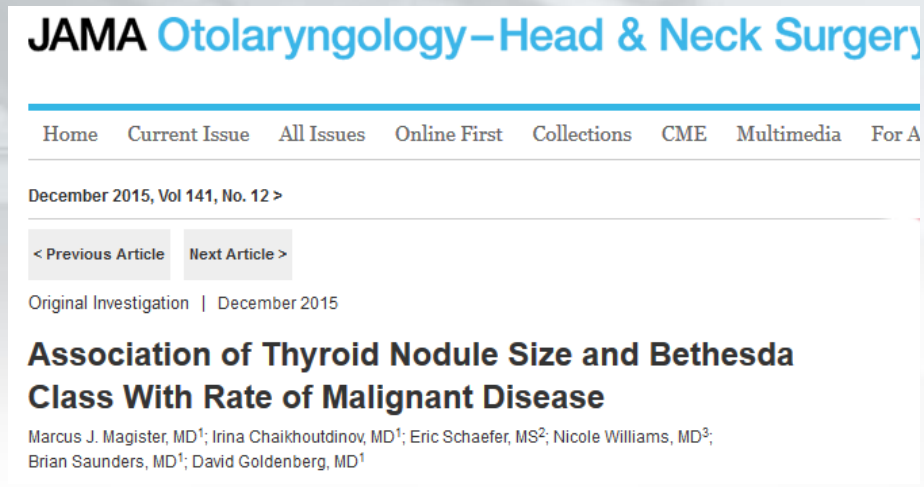
Nodule change as an Indications for Surgery

- If a thyroid nodule shows a significant increase in volume or a change in its US features, despite benign FNA biopsy results, surgical resection should be considered

- Extent of resection lobectomy plus isthmectomy

Nodule size

- Sampling error of a FNAB increases as the size of a thyroid nodule increases.
- A 17% false negative rate for solid thyroid nodules 3 cm or larger in size and a 30% false negative rate for cystic nodules 3 cm or larger led to a recommendation of diagnostic lobectomy for any nodule 3 cm or larger in size
- More recent research has reported that this measurement may be increased to 4 cm with the increased diagnostic yield of modern ultrasound guidance for FNAB.
- The rate of cancer for 4 cm nodules is 19% with a false negative rate for FNAB of 12.7% .



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Original Investigation | December 2015

Association of Thyroid Nodule Size and Bethesda Class With Rate of Malignant Disease

Marcus J. Magister, MD[1]; Irina Chaikhoutdinov, MD[1]; Eric Schaefer, MS[2]; Nicole Williams, MD[3]; Brian Saunders, MD[1]; David Goldenberg, MD[1]

- Smaller TNs (smaller than about 2.0 cm) are associated with increased probabilities of malignant disease irrespective of Bethesda class.
- Of the TNs smaller than 3.0 cm, 48.4% were malignant compared with 33.3% of TNs 3.0 cm or greater (P = .049)
- Routine diagnostic thyroid lobectomy solely owing to TN size of 3.0 cm or greater need not be performed.

Surgery and Nodule size

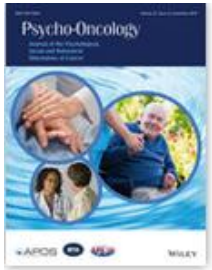
- Recommendations of surgery based on size alone are controversial, but the patient's risk factors and concerns often guide the management of nodules this large.

- The age and needs of the patient must also be considered, i.e. definitive lobectomy is often preferred to multiple FNABs required to follow a nodule in a younger patient.

- A single preoperative FNAB is still useful in nodules 3 to 4 cm in diameter that are destined for surgical excision, because a malignant biopsy allows planning for total thyroidectomy without the need for frozen section analysis.

What do our patients want?

- **Decision-Making After Indeterminate Thyroid FNA (Bethesda III–IV)**
- **Population:** English-speaking adults with indeterminate FNAB (Bethesda III–IV) undergoing molecular testing (ThyroSeq)
- **Counseling:** All patients evaluated by a single otolaryngologist and received standardized information on risks and benefits of **observation vs surgery**
- **Observation:** Serial clinical exams and ultrasounds every **3–6 months**; risk of growth or progression if malignant
- **Surgery:** Operative and follow-up visits; risks include **bleeding, pain, hypocalcemia, nerve injury (vocal cords), and rare mortality**
- **Key Driver: Risk tolerance** – willingness to accept vs eliminate a small cancer risk
  - Surgical patients: motivated by fear of cancer and desire for diagnostic certainty
  - Observation patients: more tolerant of residual cancer risk
- **Conclusion:** Treatment decisions are influenced by **risk perception, risk tolerance, trust in physician, support systems, and information sources**, beyond objective diagnostic risk alone.



CLINICAL CORRESPONDENCE

WILEY

Treatment preferences and decision-making in patients diagnosed with indeterminate thyroid nodules

Lauren E. Stahl[1] | Renee Stewart[2] | Michele M. Carr[3] | David Goldenberg[1] | Jane R. Schubart[4]

Intraoperative Frozen Section

- May be used during diagnostic lobectomy to avoid completion thyroidectomy
- Interpretation varies; results frequently deferred with uncertainty
- Clinical value remains debated
- **Limited utility in follicular neoplasms**

Frozen section analysis

- **Proponents:** May reduce completion thyroidectomies and be cost-effective in selected cases

- **Detractors:** Limited sensitivity for PTC (nuclear features poorly seen); high false-negative rate

- Added operative time and pathology cost without improved outcomes

- Utility varies by institution, surgeon, and pathologist

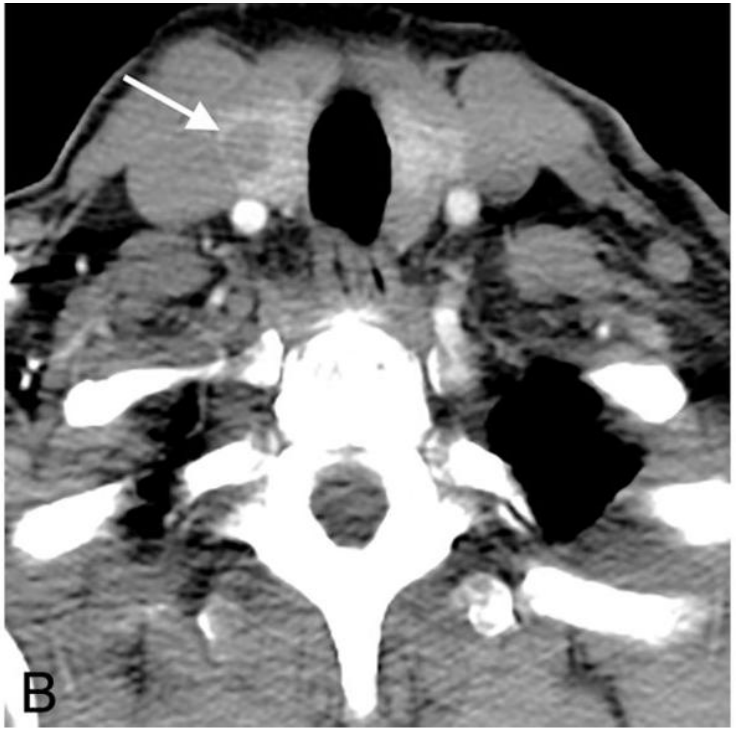
“In office” treatment of benign thyroid nodules Indications:

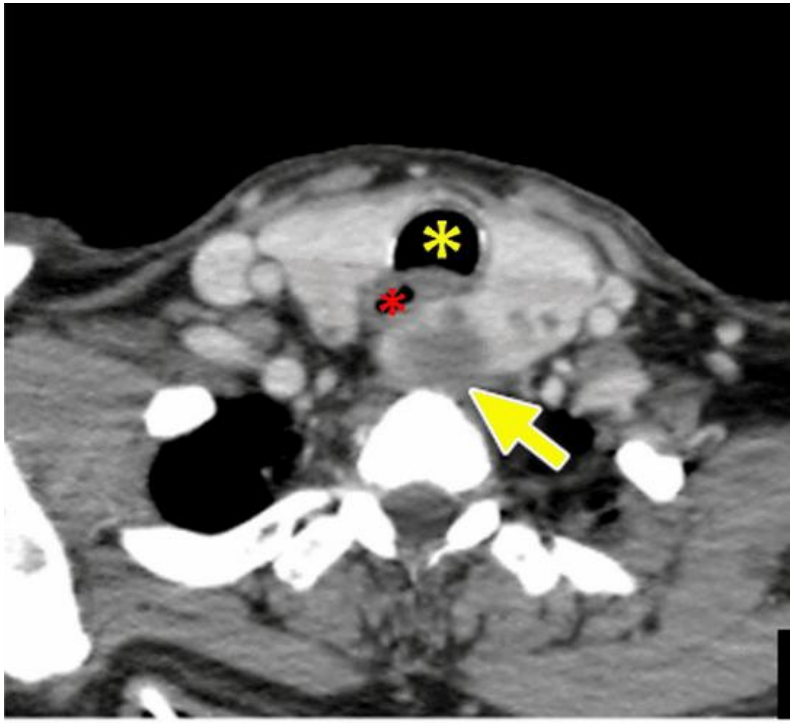
- Compression
- Cosmetic
- Hyper Functioning

In-Office Management of **Thyroid Nodules**. Heikel T, Goldenberg D. Otolaryngol Clin North Am. 2025 Aug;58(4):719-729. doi:

- **<u>You</u>** have to be convinced that the symptoms are attributable to the thyroid nodule.

- Remember… Reflux





Symptomatic Thyroid Nodules

- Benign thyroid nodules (cystic and non-cystic)
- Goiters (those confirmed to be benign)
- Compressive symptoms - experiencing neck fullness or discomfort, dysphagia, choking, or dyspnea.
- Toxic Thyroid Nodule
- Cosmetic concerns
- MicroPapillary thyroid Cancers

Thyroid RFA Indications

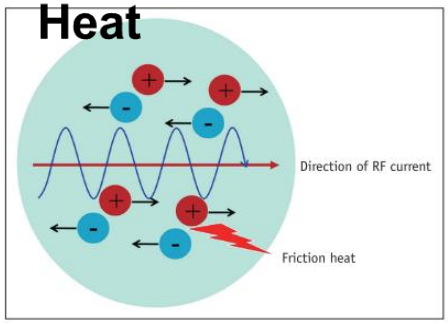
- **Indications**
  - Benign thyroid nodules (cystic and non-cystic)
  - Goiters (those confirmed to be benign)
  - Autonomously Functioning Thyroid Nodules (AFTN)
  - Nodules that increase in size and are bigger than 2cm
  - Malignant tumors (applicable cases ?)

Radiofrequency Ablation (RFA) – Theory

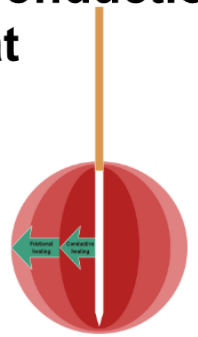
BASIC PRINCIPLES

- Radiofrequency ablation uses heat produced from radio waves to target “diseased” tissue.
- RF ablation uses energy from relatively high frequency alternating electric current oscillating between 200 and 1200 kHz (typically 350–500 kHz) to induce thermal tissue necrosis.
- RF waves passing through the electrode agitate adjacent tissue ions, and temperature within target tumor tissue increases (by frictional heat), resulting in the destruction of nodule tissue located very close (within a few mm) to the electrode.
- In addition to frictional heat, heat propagation also occurs via conduction, resulting in relatively slow damage to tissue remote from the electrode tip.

1. Frictional Heat



2. Conduction Heat

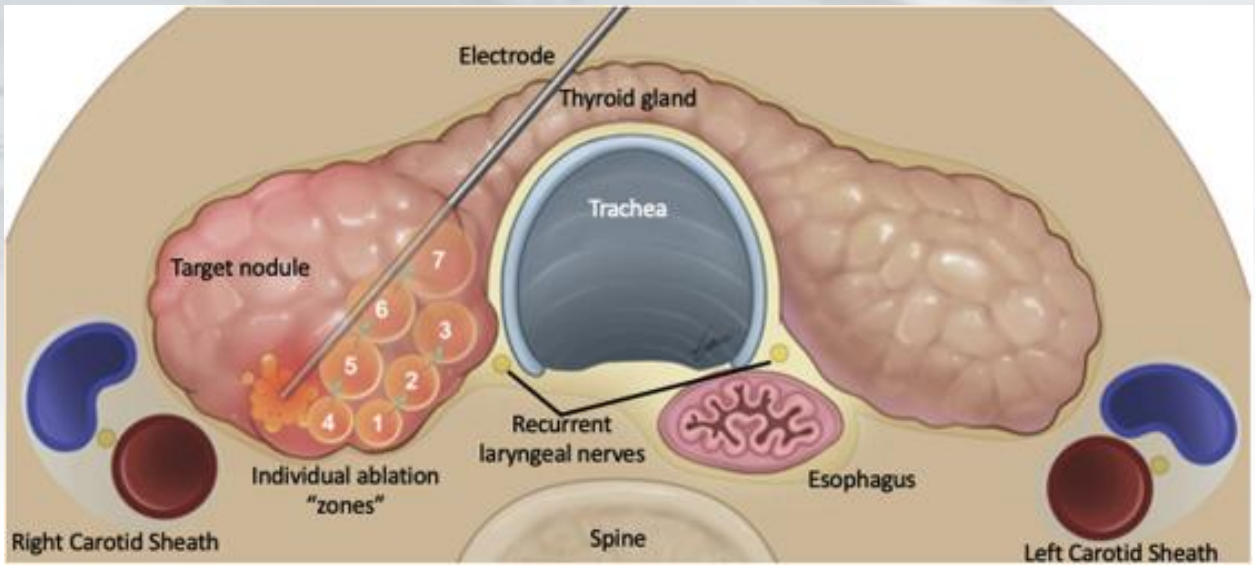


Treatments for Thyroid Nodules - RFA

- Advantages of Thyroid RFA

Easy to perform	less Invasive •No scar •Local anesthesia	Reduces healthcare expenses	High efficacy •93.5% VRR, at 4 years f/u*
Low complication rate (3-5%)	May be repeated, if necessary	Preservation of thyroid function	

*Lim HK, Lee JH, Ha EJ, et al. Radiofrequency ablation of benign non-functioning thyroid nodules: 4-year follow-up results for 111 patients. Eur Radiol 2013;23:1044-1049


Electrode
Thyroid gland
Trachea
Target nodule
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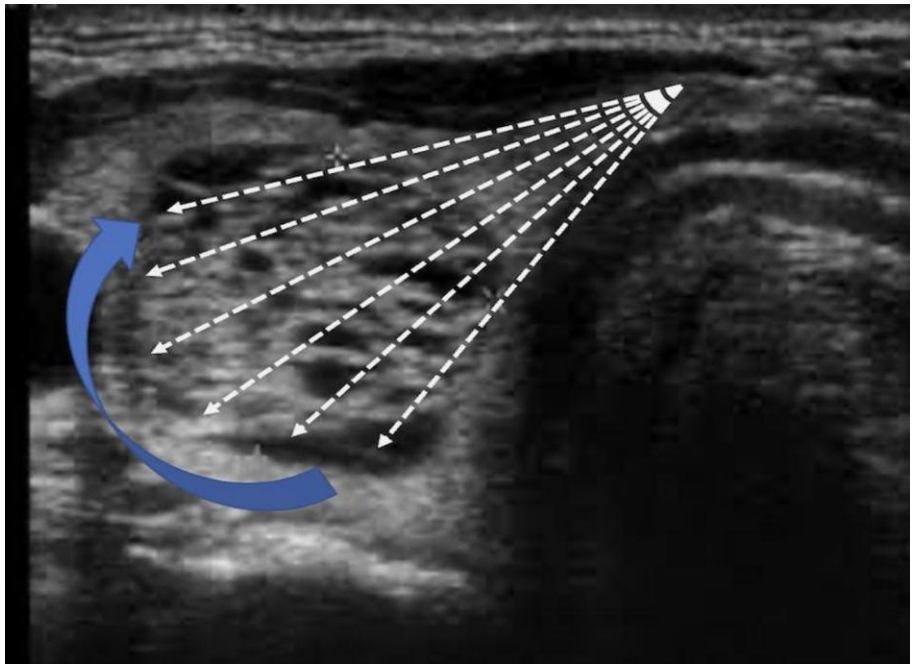
6
3
5
2
4
1
Recurrent
laryngeal nerves
Esophagus
Individual ablation
"zones"
Spine
Right Carotid Sheath
Left Carotid Sheath

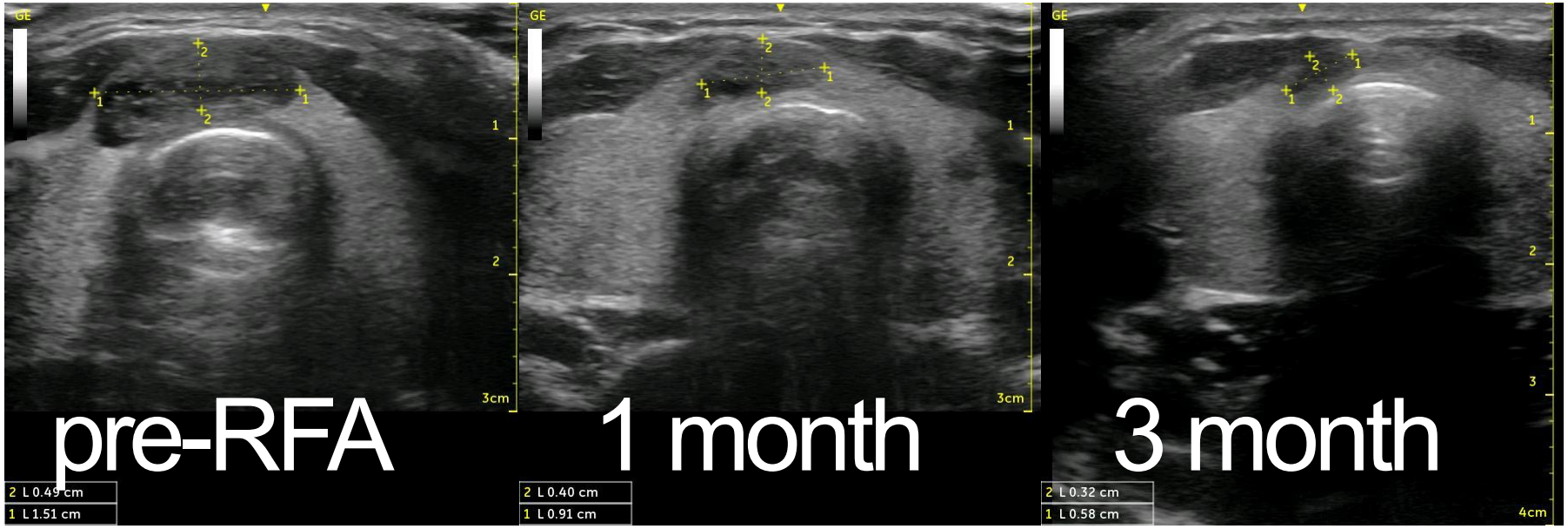



08/17/23 09:55:27AM ADM
L4-12t THYR_CONV MI 1.2 TIs 0.3
LOGIQ
1
2
3


07/06/23 08:53:25AM ADM
L4-12t THYR_CONV MI 1.2 TIs 0.3
LOGIQ
1
2
3

Results

VRR 81%



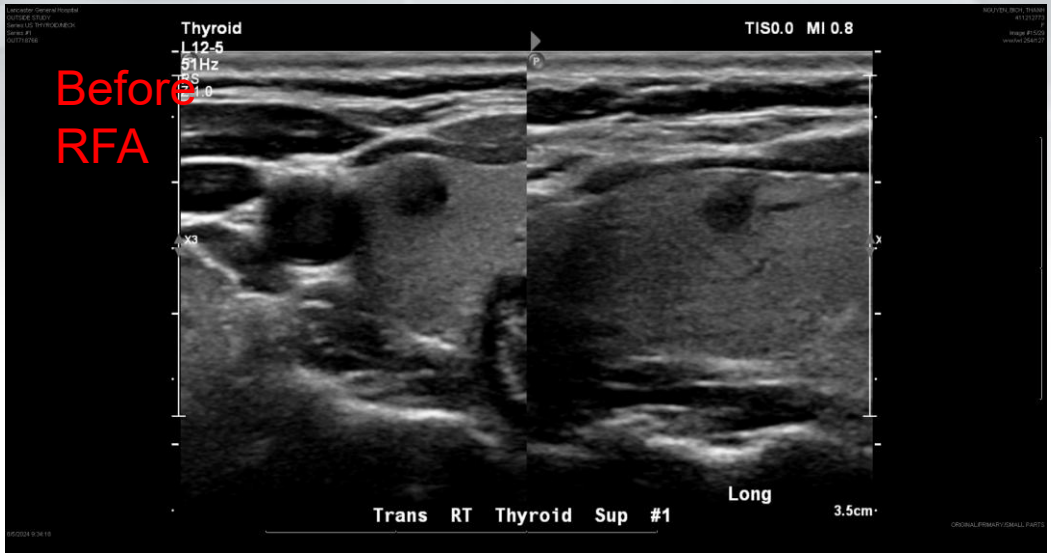
RFA and Thyroid Cancer

- **Primary PTMC**: Intrathyroidal papillary thyroid cancers 10 mm (T1a), located >5 mm from heat-sensitive structures (trachea, esophagus, recurrent laryngeal nerve)

- **Patient Selection**: Not surgical candidates, refuse surgery, or prefer minimally invasive treatment over active surveillance

- **Recurrent Disease**: NCCN guidelines support RFA for select patients with limited burden nodal disease when available

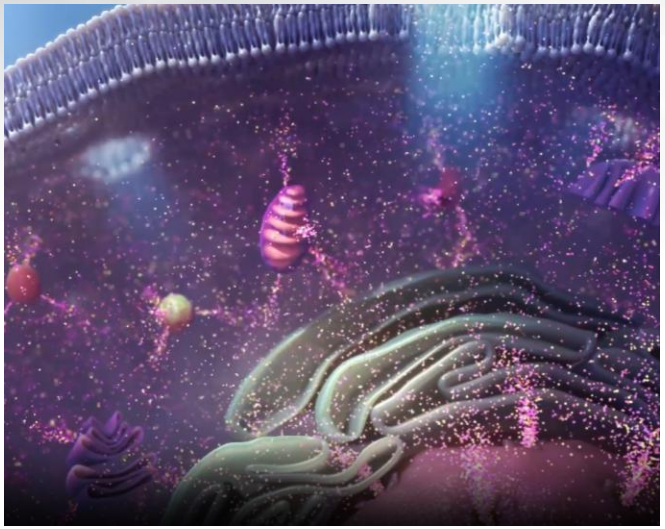
- **Tumor Characteristics**: Unifocal or multifocal low-risk PTMC without lymph node metastasis or extrathyroidal extension



RFA for - Micro Papillary Thyroid Cancer

Nanosecond Pulsed Electric Field Ablation

- **Mechanism of Action**
- Non-thermal ablation using ultrashort pulses of electric energy (nanoseconds)
- Creates membrane nanopores through irreversible electroporation
- Triggers regulated cell death without thermal damage to surrounding structures
- Selectively targets cells while preserving acellular components and structural tissue

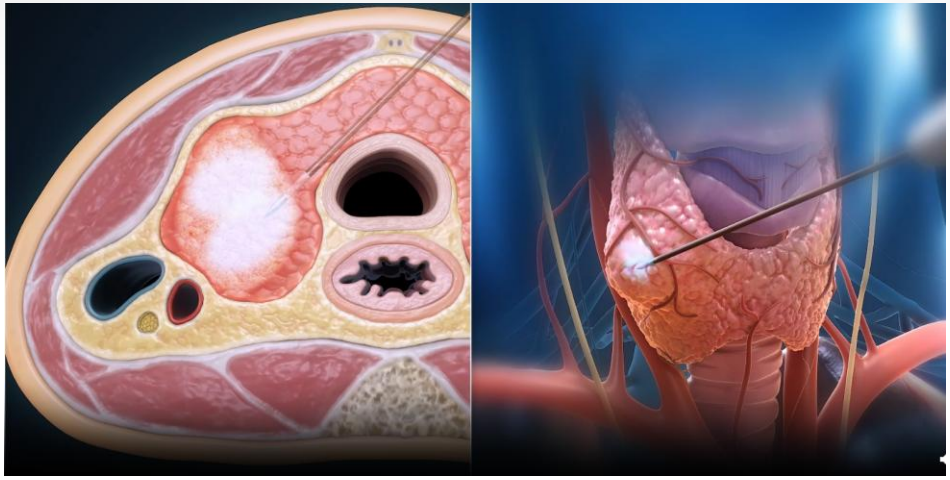


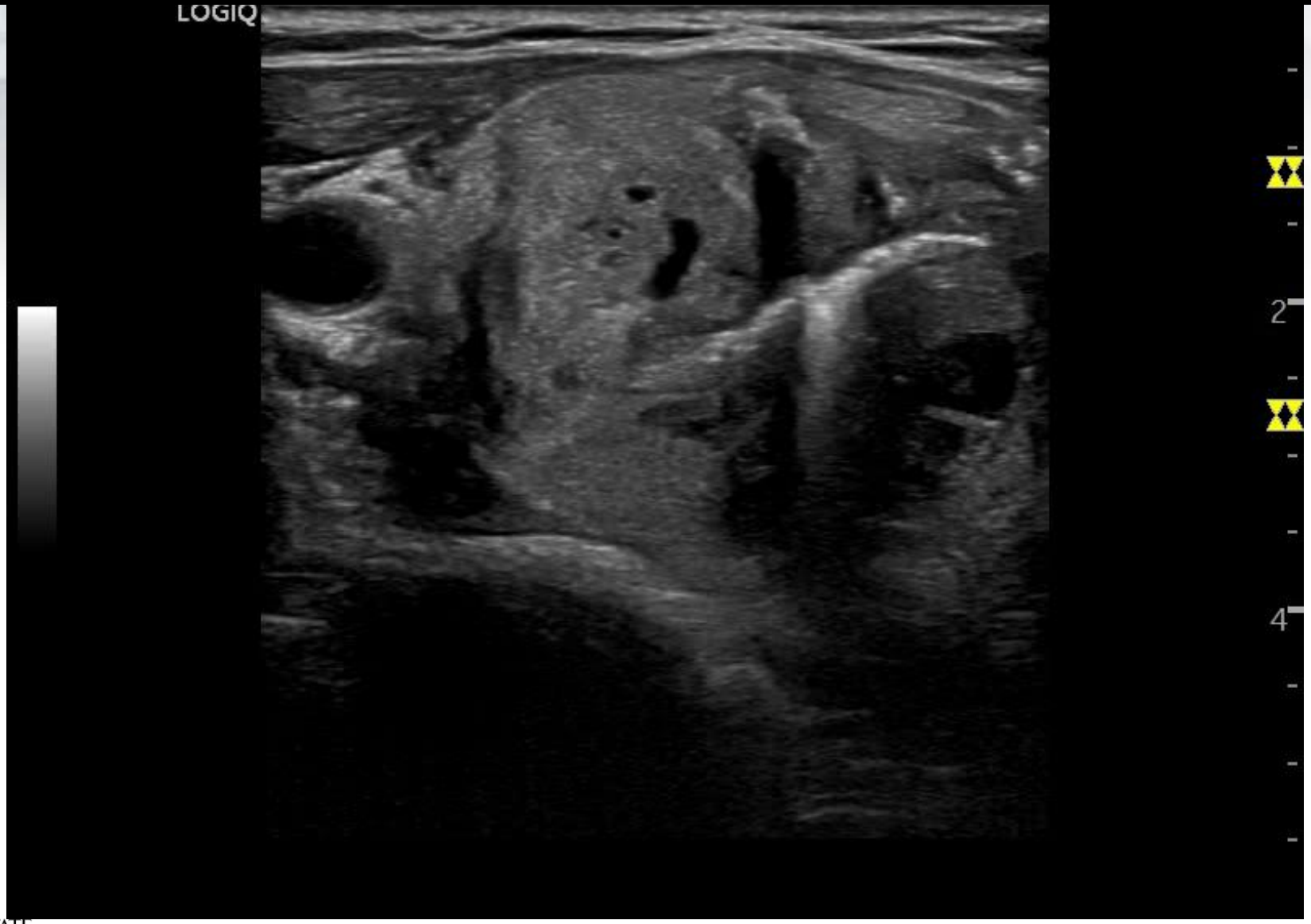
Clinical Efficacy

- *Benign Thyroid Nodules:*
- Volume reduction: 48.2% at 2 weeks, 71.1% at 1 month, 85.8% at 1 year
- Symptom relief as early as 2 weeks post-treatment
- No fibrosis or scarring on follow-up ultrasound
- *Low-Risk Papillary Thyroid Microcarcinoma (PTMC): TRIAL*
- 88% complete disappearance at 12 months (66/75 patients)
- 100% technical success rate in multicenter study (85 patients)
- No recurrence, lymph node metastasis, or distant metastasis during follow-up

Advantages Over Thermal Ablation

- Non-thermal: reduces risk of nerve injury and structural damage
- Minimal scarring and fibrosis
- Rapid volume reduction compared to thermal ablation
- Outpatient procedure under ultrasound guidance



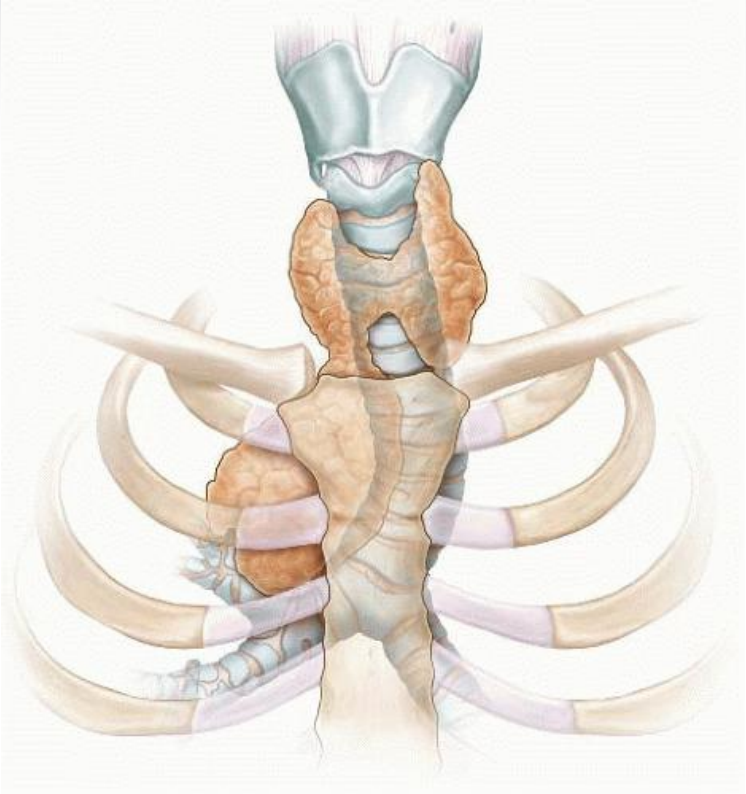

LOGIQ
2
4

Surgical Judgment (i.e. common sense)

Observation

Surgery

Ablation



Conclusions

- Thyroid nodules- Common
- Diagnostic workup- history and PE
- Imaging
- Biopsy
- Interpreting results
- Observation/Surgery/RFA


Thyroid Cancer
Awareness

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