A Practical Approach To Thyroid Nodules

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Disclosures

• None
Objectives

- Thyroid nodule basics
- ATA/AAE Thyroid nodule guidelines
- Long-term follow-up
- Role of molecular testing

Case 1

- 55 yo F presents for annual physical exam. She reports sensation of fullness in her neck with swallowing and intermittent hoarseness.
- FHx: thyroid cancer in sister
- Exam: firm 2cm nodule palpated in right lobe
- TSH 1.4
Ultrasound

Definition

- Thyroid nodule = discrete lesion within the thyroid that is distinct from the surrounding thyroid parenchyma
Incidence of Thyroid Nodules

- 20-76% population have clinically inapparent thyroid nodules
- 3-7% palpable
- 20-40% >1 nodule
- Higher incidence
  - elderly
  - women
  - iodine deficiency
  - h/o radiation exposure

Mazaheri et al. 1993. NEJM

Box 1
Causes of Thyroid Nodules

- Benign nodular goiter
- Chronic lymphocytic thyroiditis
- Simple or hemorrhagic cysts
- Follicular adenomas
- Subacute thyroiditis
- Papillary carcinoma
- Follicular carcinoma
- Hurthle cell carcinoma
- Poorly differentiated carcinoma
- Medullary carcinoma
- Anaplastic carcinoma
- Primary thyroid lymphoma
- Sarcoma, teratoma, and miscellaneous tumors
- Metastatic tumors

AACE/AME/ETA Thyroid Nodule Guidelines, (Editor's Report, 2019)
Increasing Incidence of Thyroid Cancer

Figure 2. Increasing Incidence of Thyroid Cancer

Increasing Incidence of Thyroid Cancer

Original Contribution | May 10, 2006
Increasing Incidence of Thyroid Cancer in the United States, 1973-2002

Louise Davies, MD, MS; M. Shibata, MD, MPH

All Author Affiliations

Clinical Evaluation

- History
  - Family history of thyroid cancer
  - Previous head or neck irradiation
  - History of radiation exposure
  - Rate of neck mass growth
  - Dysphonia, dysphagia, dyspnea
  - Symptoms of hyperthyroidism or hypothyroidism
- Most nodules are asymptomatic
Clinical Evaluation

- Physical exam
  - Location, consistency, and size of nodule(s)
  - Neck tenderness or pain
  - Cervical lymphadenopathy
  - Vocal fold paresis on laryngoscopy

Box 2
Factors Suggesting Increased Risk of Malignant Potential

- History of head and neck irradiation
- Family history of medullary thyroid carcinoma, multiple endocrine neoplasia type 2, or papillary thyroid carcinoma
- Age <14 or >70 years
- Male sex
- Growing nodule
- Firm or hard consistency
- Cervical adenopathy
- Fixed nodule
- Persistent dysphonia, dysphagia, or dyspnea
Evaluation

- **TSH**
  - If TSH is elevated or normal —
    > Neck US
  - If TSH is low or suppressed —>
    FT4/FT3 and Thyroid Uptake and Scan first!
    - “Hot” nodules have low probability of malignancy
    - “Cold” nodules should be biopsied—risk of malignancy is 3-15%
  - Thyroglobulin—Not recommended

- **Calcitonin**
  - FHx Medullary thyroid cancer (MTC) or Multiple Endocrine Neoplasia 2 (MEN2)
  - FNA results suggestive of MTC
  - Consider for all pts with nodular goiter undergoing surgery to avoid risk of inadequate surgery
Thyroid Incidentaloma

- Thyroid nodule found incidentally on physical exam or imaging study performed for unrelated reason
- Thyroid nodules noted on CT or MRI
  - Uncertain risk of malignancy
  - Neck US, then determine if biopsy indicated
- Thyroid nodules noted on PET
  - High risk of malignancy (~33%), more aggressive
  - Neck US followed by biopsy

Thyroid US

- Most sensitive test available to evaluate thyroid nodule
- Not recommended as a screening test
- Recommended for patients with
  - high risk for thyroid cancer
  - palpable thyroid nodules
  - lymphadenopathy suggestive of malignancy
US Characteristics Associated with Malignancy

- hypoechoic pattern
- irregular infiltrative margins
- microcalcifications
- increased intranodular vascularity
- taller than wide transversely
- enlarged lymph nodes with no hilum, cystic changes, and microcalcifications

![Image of US Characteristics](image)

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![Graph of US Characteristics](graph)
# Table 3. Sonographic and Clinical Features of Thyroid Nodules and Recommendations for FNA

<table>
<thead>
<tr>
<th>Nodule sonographic or clinical features</th>
<th>Recommended nodule threshold size for FNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk history$^9$</td>
<td></td>
</tr>
<tr>
<td>Nodule WITH suspicious sonographic features$^9$</td>
<td>&gt;5 mm</td>
</tr>
<tr>
<td>Nodule WITHOUT suspicious sonographic features$^9$</td>
<td>&gt;5 mm</td>
</tr>
<tr>
<td>Abnormal cervical lymph nodes</td>
<td>AIF</td>
</tr>
<tr>
<td>Microcalcifications present in nodule</td>
<td>2 cm</td>
</tr>
<tr>
<td>Solid nodule</td>
<td>≥1 cm</td>
</tr>
<tr>
<td>AND hypoechoic</td>
<td>≥1-1.5 cm</td>
</tr>
<tr>
<td>AND iso- or hypoechoic</td>
<td>≥1-1.5 cm</td>
</tr>
<tr>
<td>Mixed cystic-solid nodule</td>
<td>≥1.5-2.0 cm</td>
</tr>
<tr>
<td>WITH any suspicious ultrasound features</td>
<td>≥2.0 cm</td>
</tr>
<tr>
<td>WITHOUT suspicious ultrasound features</td>
<td>≥2.0 cm</td>
</tr>
<tr>
<td>Spongiform nodule</td>
<td>≥2.0 cm$^a$</td>
</tr>
<tr>
<td>Purely cystic nodule</td>
<td>FNA not indicated$^b$</td>
</tr>
</tbody>
</table>

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$^9$High-risk history: History of thyroid cancer in one or more first degree relatives; history of external beam radiation as a child; exposure to ionizing radiation in childhood or adolescence; prior hemithyroidectomy with discovery of thyroid cancer. $^a$FOG: fluid on FUE imaging; MNG: microcalcification; RET: retinoblastoma mutation, calcitonin >300 pg/mL. $^b$MEN: multiple endocrine neoplasia; FNU: fine-needle ultrasound.

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$^a$Cystic features: microcalcifications; hypoechoic; increased nodular vascularity; infinitive margins. $^b$FNA: cytology may be obtained from the abnormal lymph node in lieu of the thyroid nodule. $^c$Cytologic evaluation of fine-needle aspiration biopsy may be an acceptable alternative (see text) [48].
Table 1
Summary Characteristics for Thyroid Fine-Needle Aspiration: Results of Literature Survey

<table>
<thead>
<tr>
<th>Feature, %</th>
<th>Mean</th>
<th>Range</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>83</td>
<td>63-98</td>
<td>Likelihood that patient with disease has positive test result</td>
</tr>
<tr>
<td>Specificity</td>
<td>92</td>
<td>72-100</td>
<td>Likelihood that patient without disease has negative test results</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>75</td>
<td>50-96</td>
<td>Fraction of patients with positive test results who have disease</td>
</tr>
<tr>
<td>False-negative rate</td>
<td>5</td>
<td>1-11</td>
<td>Fine-needle aspiration negative; histology positive for cancer</td>
</tr>
<tr>
<td>False-positive rate</td>
<td>5</td>
<td>0-7</td>
<td>Fine-needle aspiration positive; histology negative for cancer</td>
</tr>
</tbody>
</table>


Table 3
AACE/AME/ETA Classification for Cytologic Diagnosis of Thyroid Nodule

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Suggested Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1. Nondiagnostic (inadequate-massive)</td>
<td>Repeated US-guided FNA biopsy, unless pure cyst</td>
</tr>
<tr>
<td>Class 2. Benign (non-neoplastic)</td>
<td>Clinical and US follow-up, FNA biopsy repetition if nodule size increases or according to clinician's or cytopathologist's judgment</td>
</tr>
<tr>
<td>Class 3. Follicular lesion/infiltration</td>
<td>Surgery for most, frozen section usually not recommended. In some cases follow-up on the basis of a multidisciplinary team evaluation</td>
</tr>
<tr>
<td>Class 4. Suspicious</td>
<td>Surgery, frozen section recommended. Repeated FNA biopsy only if more material is needed</td>
</tr>
<tr>
<td>Class 5. Positive for malignant cells</td>
<td>Surgery for differentiated carcinomas. Further diagnostic workup for anaplastic carcinomas, lymphomas, and metastatic lesions</td>
</tr>
</tbody>
</table>

Abbreviations: AACE, American Association of Clinical Endocrinologists; AME, Associazione Medici Endocrinologi; ETA, European Thyroid Association; FNA, fine-needle aspiration.

*This proposed classification is based on the results of the British Thyroid Association Thyroid Cancer Guidelines (2002-2006) (62) and the Italian SHAPEC-IAP Working Group for the Consensus on Classification of Thyroid Cytology (2008) (63).
Surgical Indications

- Suspicious, Malignant, or Indeterminate cytology
- History of previous external neck radiation
- Progressive nodule growth
- Suspicious US features
- Cosmetic
- Compressive symptoms
Case Continued

- FNA is benign, consistent with benign colloid nodule
- What is appropriate follow-up?


The Natural History of Benign Thyroid Nodules

Cosimo Durante, MD, PhD; Giuseppe Costante, MD; Giuseppe Lucisano, MSc STAT; Rocco Bruno, MD; Domenico Meringolo, MD; Alessandra Pacaroni, MD; Efisio Puexeddu, MD, PhD; Massimo Torlontano, MD; Salvatore Tumino, MD; Marco Attard, MD; Livia Lamartina, MD; Antonio Nicolucci, MD; Sebastiano Filetti, MD

- Objective: determine frequency, magnitude, and factors associated with changes in thyroid nodule size
- Design: prospective, multicenter, observational including 992 pts
- Outcomes: baseline nodule growth with yearly US
Nodule growth occurred in 15.4% pts; 11.1% nodules

Nodule growth associated with presence of multiple nodules, larger nodules, nulliparity, and male sex

Age>60 associated with lower risk of growth than <45

New nodules developed in 9.3% pts

Thyroid cancer diagnosed in 5 original nodules (0.3%); only 2 had grown

CONCLUSION: among pts with asymptomatic cytologically benign nodules, majority showed no significant size increase in 5 years of follow-up and thyroid cancer rare

Thyroid Nodule Follow-up

AAE 2010:
- repeat US and TSH in 6-18 months
- repeat UGFNA if >50% increase in volume
- High suspicion—consider repeat UGFNA even if first benign

ATA 2009:
- repeat US in 6-18 months
- repeat UGFNA if >50% increase in volume or >20% increase in at least 2 nodule dimensions of solid nodule or solid portion of solid-cystic nodules, with minimal increase of 2mm in 2 dimensions
- if stable, repeat US every 3-5 years
Alternative Case continued

- Cytology reveals follicular lesion of undetermined significance (FLUS)
- What next?

Diagnostic Ambiguity

- 15-30% Thyroid nodule FNAs “Indeterminate”
- Atypia of undetermined significance/Follicular lesion of undetermined significance (AUS/FLUS, Bethesda III)
- Follicular neoplasm/Suspicious for follicular neoplasm (FN/SFN, Bethesda IV)
- 20-30% of these nodules are malignant on surgical pathology
- 70-80% of these nodules are benign
- Long-term morbidity from surgery 2-10%
Molecular Testing

- “Rule in” = confirm FNA malignant
- Informs extent of surgery
- Currently available assays miss ~50% cancers with indeterminate cytology
- “Rule out” = confirm FNA benign
- Prevents unnecessary surgery
- Requires high sensitivity and high negative predictive value (NPV)

“Rule out” Test

- Alexander et al. “Preoperative Diagnosis of Benign Thyroid Nodules with Indeterminate Cytology.” 2012. NEJM
- Large, prospective and double blind, multi center study
  - 49 clinical sites, 3789 patients, 4812 FNA nodules >1cm
  - 577 indeterminate aspirates, 413 surgical path specimens
  - After inclusion criteria met, 265 underwent novel test
- Study designed by 2 principal academic investigators and 2 employees of Veracyte
- Cytologically indeterminate nodules underwent novel diagnostic test —gene expression classifier (GEC)

GEC Study

- When indeterminate FNA reclassified as benign by GEC, sample had <6% likelihood of being malignant (>94% NPV)
- Result comparative to benign cytopathology diagnosis
- Benign GEC result combined with clinical judgement allowed pts to be followed and observed, sparing stress and risk of diagnostic surgery

JL Jameson. 2012. NEJM
Limitations of GEC

- 5-10% of nodules classified as benign (false negative) may be malignant
- Thus, for those pts with benign result who are being monitored, it is important to have low threshold to repeat FNA

“Rule In” Test

A Clinical Algorithm for Fine-Needle Aspiration Molecular Testing Effectively Guides the Appropriate Extent of Initial Thyroidectomy


- Molecular testing of indeterminate cytology for BRAF, RAS, PAX8-PPAR, RET-PTC promotes initial total thyroidectomy for clinically significant thyroid cancer and correctly limits surgery to lobectomy when appropriate

TABLE 2. Histology of Patients by Cohort and Initial Operation

<table>
<thead>
<tr>
<th></th>
<th>TT</th>
<th>Lobectomy</th>
<th>P</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort 1</td>
<td>Cohort 2</td>
<td></td>
<td>Cohort 1</td>
<td>Cohort 2</td>
<td></td>
</tr>
<tr>
<td>Histology, all FNAB categories, n</td>
<td>202</td>
<td>241</td>
<td></td>
<td>120</td>
<td>108</td>
<td></td>
</tr>
<tr>
<td>Benign, n (%)</td>
<td>85 (42)</td>
<td>112 (46)</td>
<td>0.35</td>
<td>79 (66)</td>
<td>65 (60)</td>
<td>0.38</td>
</tr>
<tr>
<td>Cancer, n (%)</td>
<td>117 (58)</td>
<td>129 (54)</td>
<td>0.35</td>
<td>41 (34)</td>
<td>44 (60)</td>
<td>0.38</td>
</tr>
<tr>
<td>sTCC, n (%)</td>
<td>66 (33)</td>
<td>51 (21)</td>
<td>0.006</td>
<td>21 (18)</td>
<td>27 (30)</td>
<td>0.03</td>
</tr>
<tr>
<td>PTMC, n (%)</td>
<td>51 (25)</td>
<td>78 (32)</td>
<td>0.10</td>
<td>20 (17)</td>
<td>11 (10)</td>
<td>0.15</td>
</tr>
<tr>
<td>Histology, only FLUS and FN, n</td>
<td>173</td>
<td>123</td>
<td></td>
<td>117</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Benign, n (%)</td>
<td>77</td>
<td>52</td>
<td>0.7</td>
<td>78</td>
<td>25</td>
<td>0.003</td>
</tr>
<tr>
<td>Cancer, n (%)</td>
<td>96 (58)</td>
<td>71 (58)</td>
<td>0.7</td>
<td>36 (33)</td>
<td>33 (37)</td>
<td>0.003</td>
</tr>
<tr>
<td>sTCC, n (%)</td>
<td>49 (28)</td>
<td>31 (25)</td>
<td>0.6</td>
<td>20 (17)</td>
<td>24 (28)</td>
<td>0.001</td>
</tr>
<tr>
<td>PTMC, n (%)</td>
<td>47 (27)</td>
<td>40 (33)</td>
<td>0.4</td>
<td>19 (16)</td>
<td>8 (14)</td>
<td>0.3</td>
</tr>
<tr>
<td>Permanent complications</td>
<td>3 (1.4)</td>
<td>5 (2)</td>
<td>0.5</td>
<td>3 (2.5)</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>Hypoparathyroidism, n (%)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
<td>NS</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>RLN paralysis, n (%)</td>
<td>3 (1.5)</td>
<td>4 (1.7)</td>
<td>NS</td>
<td>3 (2.5)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Postoperative L-T4, %</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>49</td>
<td>46</td>
<td>0.7</td>
</tr>
</tbody>
</table>

L-T4 indicates larynx; NA, not available; NS, not significant; RLN, recurrent laryngeal nerve.
Conclusions

- Thyroid nodules are common
- Neck US is most sensitive test to evaluate thyroid nodule
- If TSH is suppressed → thyroid uptake and scan first!
- Fine needle aspiration recommended for suspicious nodules, particularly if high risk history
- Monitor with serial neck US based on level of suspicion
- Molecular testing for indeterminate cytology may help deciding which patients need surgery

Thank you!