Evaluation and Management of Thyroid Nodules

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Disclosure

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Objectives

• Understand the significance of incidental thyroid nodules
• Review thyroid nodule evaluation algorithm
• Identify the indications for thyroid biopsy
• Describe the management and monitoring of thyroid nodules
Epidemiology

- Prevalence increases with age
- Women more than men
- 20-76% of women have at least one nodule by US
- 37-57% of patients on autopsy studies have thyroid nodule
- 5% of thyroid nodules are cancerous in the general population
- 90% of thyroid cancers are differentiated (papillary, follicular)
Clinical Implication of Nodule

- Is the nodule malignant?
- Are there compressive symptoms?
- Is the nodule autonomous and causing thyrotoxicosis?
Benign Causes of Thyroid Nodules

- Multinodular goiter
- Hashimoto’s thyroiditis
- Cysts: colloid, simple, or hemorrhagic
- Follicular adenoma
- Hurthle-cell adenoma
Risk of Malignant Thyroid Nodules

- Children (risk of nodule being malignant 2x adult)
- Men (risk 2x women)
- Adults less than 30 years or over 60 years old at increase risk
- Patients with a history of head & neck irradiation
- Whole body irradiation for bone marrow transplant
- Patients with a family history of thyroid cancer
Malignant Causes of Thyroid Nodules

- Thyroid follicular epithelial-derived cancers:
  - Papillary thyroid carcinoma
  - Follicular thyroid carcinoma
  - Anaplastic thyroid carcinoma
- Medullary thyroid cancer
  - Familial, part of MEN2 syndrome
  - Sporadic
- Primary thyroid lymphoma
- Metastatic carcinoma
  - Breast, renal, melanoma, and colon
Thyroid Nodule Evaluation

- History
- Physical Examination
- Laboratory Testing
- Thyroid Ultrasound
- Fine Needle Aspiration Biopsy
History

- Childhood head and neck irradiation
- Total body irradiation for bone marrow transplantation
- Family history of thyroid cancer
- Rapid growth of a neck mass
- Compression symptoms (dysphagia, hoarseness, stridor, choking sensation)
High-Risk History

- History of thyroid cancer in one or more first degree relatives
- Exposure to ionizing radiation in childhood or adolescence
- Prior hemithyroidectomy with discovery of thyroid cancer
- Focal FDG avidity on PET scanning
- MEN2/FMTC-associated RET proto-oncogene mutation
Physical Examination

• Size, texture of the thyroid and nodules
• Concerning findings:
  • Fixed mass
  • Cervical lymphadenopathy
  • Evidence of vocal cord paralysis
Laboratory Testing

• Laboratory testing is helpful to evaluate the function of the gland

• Serum TSH:
  – Required in all patients
  – Independent risk factor for predicting malignancy

• Calcitonin level:
  – Not indicated for routine thyroid nodule evaluation
  – Consider if risk factors or concern for medullary thyroid carcinoma exist

• TPO antibody, thyroglobulin antibody
  – It is not helpful in initial nodule evaluation
Normal TSH

• Normal TSH is the most common scenario
• Biopsy is indicated if patient meet the US criteria
Elevated TSH

- Evaluate for hypothyroidism
- Biopsy is still indicated if based on US criteria
- Thyroiditis can present as pseudo-nodule
Suppressed TSH

• It indicates overt or subclinical hyperthyroidism
• Thyroid scintigraphy (RAI uptake and scan) should be performed next
• Cold nodule should be biopsied
I-123 Radioactive Iodine Uptake and Scan

• Test used to determine the functional status of a nodule
• Only useful in patients with hyperthyroidism on laboratory testing (suppressed TSH)
• It should not be done to evaluate thyroid nodules in patient with normal or elevated TSH
RAI Uptake and Scan

• Non-functional nodule ("cold nodule")
  – Uptake is less than surrounding thyroid tissue
  – Nodule requires FNA biopsy

• Autonomous nodule ("hot nodule")
  – Uptake is greater than surrounding thyroid tissue with suppressed uptake in the rest of the gland
  – Generally does not require FNA biopsy
RAI Uptake and Scan

• Indeterminate Nodule
  – Uptake is the same as surrounding thyroid tissue
  – Can represent either small non-functioning nodules anterior or posterior to normally functioning thyroid tissue or autonomous nodules that do not produce sufficient thyroid hormone to suppress the surrounding thyroid tissue
  – Indeterminate nodules require FNA biopsy if US features warrant
Thyroid Ultrasonography

• Thyroid ultrasound should be performed in all patients with a suspected thyroid nodule or nodular goiter on physical examination or with nodules incidentally noted on other imaging studies (carotid ultrasound, CT, MRI, or FDG-PET scan)

• Ultrasound findings can be used to select nodules for FNA biopsy
Ultrasound Features Associated with Low Risk of Thyroid Carcinoma

- Hyperchoic
- Spongiform appearance
- Predominately cystic, purely cystic
- Large, coarse calcifications
- Peripheral vascularity
- Colloid ("comet tail" artifact)
- Egg shell calcification
Ultrasound Features Associated with an Increased Risk of Thyroid Carcinoma

- Hypoechoic
- Microcalcification
- Central vascularity
- Irregular border
- Incomplete rim calcifications
- Nodule is taller than wide
- Documented enlargement of the nodule
<table>
<thead>
<tr>
<th>Sonographic pattern</th>
<th>US features</th>
<th>Estimated risk of malignancy, %</th>
<th>FNA size cutoff (largest dimension)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High suspicion</td>
<td>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</td>
<td>&gt;70–90&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Recommend FNA at ≥1 cm</td>
</tr>
<tr>
<td>Intermediate suspicion</td>
<td>Hypoechoic solid nodule with smooth margins without microcalcifications, ETE, or taller than wide shape</td>
<td>10–20</td>
<td>Recommend FNA at ≥1 cm</td>
</tr>
<tr>
<td>Low suspicion</td>
<td>Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, without microcalcification, irregular margin or ETE, or taller than wide shape.</td>
<td>5–10</td>
<td>Recommend FNA at ≥1.5 cm</td>
</tr>
<tr>
<td>Very low suspicion</td>
<td>Spongiform or partially cystic nodules without any of the sonographic features described in low, intermediate, or high suspicion patterns</td>
<td>&lt;3</td>
<td>Consider FNA at ≥2 cm Observation without FNA is also a reasonable option</td>
</tr>
<tr>
<td>Benign</td>
<td>Purely cystic nodules (no solid component)</td>
<td>&lt;1</td>
<td>No biopsy&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

US-guided FNA is recommended for cervical lymph nodes that are sonographically suspicious for thyroid cancer (see Table 7).<sup>a</sup>

<sup>a</sup>The estimate is derived from high volume centers, the overall risk of malignancy may be lower given the interobserver variability in sonography.

<sup>b</sup>Aspiration of the cyst may be considered for symptomatic or cosmetic drainage.

ETE, extrathyroidal extension.
Follow-Up

• Nodules not selected for FNA
  • 6-12 months for sub-cm nodule with suspicious features
  • 12-24 months for nodules with low to intermediate risk feature
  • 2-3 years for very low-risk nodule
  • Sub-cm nodules that increase to >1 cm may be selected for FNA depending on features
  • Nodules that grow significantly or develop concerning radiographic features may be selected for FNA
FNA Pathology Result

- **Cytology Bethesda system (R9)**
  - **Nondiagnostic**
    - Repeat FNA (R10)
  - **Benign**
    - No Surgery (R11, 23)
  - **AUS/FLUS**
  - **FN/FSN**
    - See Recommendations 13-17
  - **Suspicious**
  - **Malignant**
    - Surgery (R12)
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<th>Diagnostic category</th>
<th>Estimated/predicted risk of malignancy by the Bethesda system, %&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Actual risk of malignancy in nodules surgically excised, % median (range)&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
<td>Nondiagnostic or unsatisfactory</td>
<td>1–4</td>
<td>20 (9–32)</td>
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<tr>
<td>Benign</td>
<td>0–3</td>
<td>2.5 (1–10)</td>
</tr>
<tr>
<td>Atypia of undetermined significance or follicular lesion of undetermined significance</td>
<td>5–15</td>
<td>14 (6–48)</td>
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<td>Follicular neoplasm or suspicious for a follicular neoplasm</td>
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<td>25 (14–34)</td>
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<tr>
<td>Suspicious for malignancy</td>
<td>60–75</td>
<td>70 (53–97)</td>
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<tr>
<td>Malignant</td>
<td>97–99</td>
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<sup>a</sup>As reported in The Bethesda System by Cibas and Ali (1076).

<sup>b</sup>Based on the meta-analysis of eight studies reported by Bongiovanni et al. (103). The risk was calculated based on the portion of nodules in each diagnostic category that underwent surgical excision and likely is not representative of the entire population, particularly of nondiagnostic and benign diagnostic categories.
Management of Benign Thyroid Nodules

- Thyroid ultrasound in 6 to 12 months after the initial diagnosis to monitor nodule size then once a year
- Re-biopsy if nodule:
  - Increased in nodule volume by more than 50%, or
  - Development of new, concerning US features
  - New symptoms attributed to the nodule
- Re-biopsy of thyroid nodules that are unchanged is not indicated
- Stable nodules could be reassessed at increasing intervals (e.g. 3-5 years)
Management of Benign Thyroid Nodules

• Thyroid hormone suppressive therapy is not effective in majority of benign thyroid nodule
• Consider thyroid hormone replacement if TSH is elevated (hypothyroidism or subclinical hypothyroidism)
Classification of Thyroid Malignancy

- Thyroid follicular epithelial-derived cancers:
  - Papillary thyroid carcinoma
  - Follicular thyroid carcinoma
  - Anaplastic thyroid carcinoma
- Medullary thyroid cancer
- Primary thyroid lymphoma
- Metastatic carcinoma
  - Breast, renal, melanoma, and colon
Management of Malignant Nodules

• Thyroidectomy is the standard of care for differentiated thyroid carcinoma
• Good prognosis for differentiated thyroid carcinoma with overall 20 years survival of 90%
Management of Indeterminate Thyroid Nodules
Table 8. The Bethesda System for Reporting Thyroid Cytopathology: Diagnostic Categories and Risk of Malignancy

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Indeterminate Nodules

- Diagnostic lobectomy
- Repeat FNA
- Molecular Diagnostic Testing
  - Mutational analysis
  - mRNA genomic expression classifier
  - miRNA Gene Expression with Mutational Analysis
Approach to the adult with a thyroid nodule with indeterminate cytology

1. FNA results showing any of the following:
   - AUS (nuclear atypia)
   - FLUS (follicular lesion)
   - Malignant

   Was an entire FNA sample collected for molecular testing at the time of the initial biopsy?

2. Yes
   - Repeat FNA in 6 to 12 weeks or newer (collect extra sample for molecular testing, if available)
   - AUS or follicular lesion
   - What is the TSH?
     - i.e., > 5 mIU/L
     - < 1 mIU/L

     Some experts perform a thyroid radioactive scan, if not previously obtained.

     Is molecular testing available?

     If molecular testing is available:
     - Yes: Molecular diagnostic testing
       - Mutational analysis
       - NfiR/BRCA1/BRCA2 sequencing
       - Combined miRNA and methylation analysis
     - No: Suspicious pattern

     Suspicious pattern

3. No
   - Benign
   - Observation
   - Repeat ultrasound in 12 to 24 months to assess stability

   Suspicious pattern

   Suspicious pattern

   Molecular diagnostic testing:
   - Mutational analysis
   - NfiR/BRCA1/BRCA2 sequencing
   - Combined miRNA and methylation analysis
   - Diagnostic surgery (thyroidectomy)

   Diagnostic surgery (thyroidectomy)

   Thyroid surgery (Choice of thyroidectomy in intermediate depends on higher risk: the presence of abnormal lymph nodes or contralateral nodules on ultrasound)

   Suspicious pattern

   Diagnostically biopsy (biopsy: thyroidectomy is an option if a high-volume physical surgeon is available)

   Suspicious pattern

   Diagnostically biopsy (biopsy: thyroidectomy)

   This algorithm is intended to be used in conjunction with additional UpToDate content on thyroid nodules.

   1. FNA: Fine-needle aspiration; AUS: atypia of undetermined significance; FLUS: follicular lesion of undetermined significance; THS: thyroid-stimulating hormone; mIU/L: micro International units/L; T4: thyroxine; T3: triiodothyronine.
   2. If TSH below lower limit of reference range, measure free T4 and total T3. Refer to UpToDate content on diagnosis and treatment of hyperthyroidism.
   3. Other experts proceed directly to molecular testing, if available. If molecular testing is not available or not desired by the patient, repeat aspirates show atypical cells or follicular neoplasm, diagnostic surgery is performed.
   4. The decision to perform lobectomy or total thyroidectomy is based upon clinical grounds (eg, size, growth patterns) and/or sonographic features.
FNA for Specific Gene Mutation

- Papillary and medullary thyroid cancers harbor RAS, RET, and BRAF genetic mutations
- Follicular thyroid cancers harbor translocations and fusions of certain genes (PAX 8 and PPAR-gamma)
- ThyroSeq® v3
  - gene expression, mutations, insertions/deletions, fusions, and copy number variations in 112 thyroid-related genes
  - NPV 97 and 98 percent, and PPV 64 and 68 percent for FLUS/AUS and follicular neoplasm, respectively
mRNA Genomic Expression Classifier

• Afirma® Genomic Expression Classifier reclassifies indeterminate FNAs as benign or suspicious
• NPV 96% and PPV 47% percent
• High NPV helps in identifying benign nodule with high confidence
• PPV near 50% means that a substantial number of patients undergoing thyroidectomy will prove to have a benign nodule
miRNA Gene Expression with Mutational Analysis

• ThyraMIR and ThyGenX® tests for expression of 10 miRNA genes and mutational analysis to detect the presence of eight oncogene

• 97% and 91% NPV for FLUS/AUS and follicular neoplasm, respectively, and a PPV for malignancy of 68% and 82%, respectively
Summary

- Identify clinical impact
- Identify risk factors for malignancy
- TSH to assess function
- US to characterize non-functioning nodules and identify those requiring FNA based on US features/size
- Determine follow-up plan for benign nodules or nodules not meeting criteria for biopsy
- Thyroidectomy for malignant nodules
- Determine appropriate plan for indeterminate nodules
Questions?