Texas Tech University Health Sciences Center El Paso
Neoplastic Diseases: Update for Practitioners
June 14th, 2019

“Evaluation and Management of Thyroid Nodules by Fine Needle Aspiration Cytology, Endocrine Perspective”

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Disclosures

None
Objectives

• Understand the diagnostic approach and evaluation of thyroid nodules

• Recognize the utility of molecular testing in the management and follow up of thyroid nodules with indeterminate cytology
Background

- Thyroid nodules are common and most of the time benign.
- Prevalence: depends on the population studied and the methods used to detect nodules:

<table>
<thead>
<tr>
<th>Method</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpation</td>
<td>2-6%</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>19-35%</td>
</tr>
<tr>
<td>Autopsy</td>
<td>8-65%</td>
</tr>
</tbody>
</table>

1- Dean DS et al. Best Pract Res Clin Endocrinol Metab. 2008 Dec;22(6):901-11
Background

• Incidence is higher in women and increases with:
  – Age, Iodine deficiency, and after radiation exposure.\(^1\)

• Overall malignancy rate: 5-10%.\(^2\)

• Lifetime risk of being diagnosed with thyroid cancer = 1.1\(^3\)

1- Dean DS et al. Best Pract Res Clin Endocrinol Metab. 2008 Dec;22(6):901-11
3- Howlander et al. SEER Cancer Review 1975-2012. SEER Web Site, 04/2015
Background

NEW!

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated New Cases in 2019</td>
<td>52,070</td>
</tr>
<tr>
<td>% of All New Cancer Cases</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated Deaths in 2019</td>
<td>2,170</td>
</tr>
<tr>
<td>% of All Cancer Deaths</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

Percent Surviving 5 Years

<p>| |</p>
<table>
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<tr>
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<tbody>
<tr>
<td>2009-2015</td>
</tr>
<tr>
<td>98.2%</td>
</tr>
</tbody>
</table>

1- National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER)
• Seventy recommendations for Differentiated Thyroid Cancer!
Thyroid Nodules - How to differentiate between benign and suspicious?

- Complete history
- Identify risk factors:
  - Childhood head and neck radiation therapy
  - Total body radiation for bone marrow transplantation
  - Exposure to ionizing radiation from fallout in childhood or adolescence
  - Familial thyroid carcinoma
  - Excess of thyroid hormone
- Physical examination focusing on the thyroid gland and cervical lymph nodes
- Labs
Thyroid Nodules - Management

1. Physical exam
2. Labs
3. Thyroid ultrasound
4. FNA?
ATA Nodule Sonographic Patterns and Risk of Malignancy

2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

Haugen BR et al. Thyroid. 2016 Jan;26(1):1-133.
Do all thyroid nodules need a biopsy?

- Depends on US findings, size and suspicion
- NO biopsy
  - Size: <1 cm
  - Purely cystic

- YES biopsy
  - >1 cm with intermediate and high suspicion
  - >1.5 cm with low suspicion

- CONSIDER biopsy
  - >2cm with very low suspicion
Algorithm for evaluation and management of patients with thyroid nodules based on US pattern and FNA cytology

Haugen BR et al. Thyroid. 2016 Jan;26(1):1-133.
2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer
Thyroid Nodules - Management

The Bethesda System for Reporting Thyroid Cytopathology with implied risk of malignancy and recommended clinical management

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Risk of malignancy (%)</th>
</tr>
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<tbody>
<tr>
<td>I. Nondiagnostic or unsatisfactory</td>
<td>1-4</td>
</tr>
<tr>
<td>II. Benign</td>
<td>0-3</td>
</tr>
<tr>
<td>III. AUS or FLUS</td>
<td>5-15</td>
</tr>
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<td>IV. Follicular neoplasm or suspicious for a follicular neoplasm</td>
<td>15-30</td>
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<tr>
<td>V. Suspicious for malignancy</td>
<td>60-75</td>
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<td>VI. Malignant</td>
<td>97-99</td>
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AUS: Atypia of undetermined significance, FLUS: Follicular lesion of undetermined significance, FNA: Fine needle aspiration

1- As reported in The Bethesda System by Cibas and Ali (1076).
FNA cytology results

- If initial nondiagnostic cytology result --> Repeat FNA
- Repeatedly nondiagnostic nodules might have indication for surgical excision for histopathologic diagnosis
- If the nodule is benign on cytology, further *immediate* diagnostic studies or treatment are not required
- If a cytology result is diagnostic for primary thyroid malignancy --> surgery

Haugen BR et al. Thyroid. 2016 Jan;26(1):1-133.
2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer
Malignant FNA cytology results

- Surgery.
  - Active surveillance management approach can be considered:
    - Patients with very low risk tumors (e.g., papillary microcarcinomas without clinically evident metastases or local invasion, and no convincing cytologic evidence of aggressive disease)
    - Patients at high surgical risk because of comorbid conditions
    - Patients expected to have a relatively short remaining life span (e.g., serious cardiopulmonary disease, other malignancies, very advanced age), or
    - Patients with concurrent medical or surgical issues that need to be addressed prior to thyroid surgery.

Haugen BR et al. Thyroid. 2016 Jan;26(1):1-133.
2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer
FNA cytology results

Haugen BR et al. Thyroid. 2016 Jan;26(1):1-133.

2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer
FNA cytology results

- Traditionally, patients with AUS or FLUS would undergo repeat FNA.

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- Cytology results with Follicular neoplasms or suspicious for follicular neoplasms would be referred for diagnostic surgery.

- 70% to 80% of these nodules ultimately prove to be benign by surgical histopathology.

- Patients with confirmed thyroid cancer may not receive the surgery they need.  

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Indeterminate FNA cytology results

- Diagnostic uncertainty
- Often resulting in repeat FNA and/or unnecessary diagnostic surgery
- These limitations have led to the emergence of molecular testing to improve diagnostic accuracy of FNA cytology
Role of molecular studies in Indeterminate FNA cytology results

- To identify patients who can avoid unnecessary surgery – while minimizing the risk of missing cancer.\(^1\)

- Many markers are in development

1- Shanik, M. How Might Molecular Testing Advances the Care of Patients with Thyroid Nodules?
Role of molecular studies in Indeterminate FNA cytology results

- Two principal tests are currently in the market to improve the malignancy risk assessment of "indeterminate" cytology:
  - "Rule In" → attempt to confirm the presence of cancer in a thyroid nodule.
    - Assess for the presence of single gene point mutations (BRAF or RAS) or gene rearrangements (RET/PTC, PAX8/PPARγ) known to increase the ability to predict cancer
  - "Rule Out" → attempt to exclude the presence of cancer in a thyroid nodule.
    - Proprietary gene expression classifier (RNA expression) designed to maximize the ability to define a process as benign

1- Woeber KA . Writing Group for the AACE Thyroid Scientific Committee
Role of molecular studies in Indeterminate FNA cytology results

- Rule out test: Afirma®
Role of molecular studies in Indeterminate FNA cytology results

• Retrospective, blinded study conducted on 49 academic and community centers in the United States. FNA samples from June 2009 and December 2010.

• All patients underwent surgery without genomic information and were assigned a histopathology diagnosis by an expert panel blinded to all genomic information.

• 210 potentially eligible thyroid biopsy samples with Bethesda III or IV indeterminate cytopathology.

• The genomic sequencing classifier had a sensitivity of 91% (95% CI, 79-98) and a specificity of 68% (95% CI, 60-76).

• At 24% cancer prevalence, the negative predictive value was 96% (95% CI, 90-99) and the positive predictive value was 47% (95% CI, 36-58).

Role of molecular studies in Indeterminate FNA cytology results
Role of molecular studies in Indeterminate FNA cytology results

• Rule in test: ThyroSeq v3®
Role of molecular studies in Indeterminate FNA cytology results

• Prospective, blinded cohort study conducted at 10 medical centers, with 782 patients with 1013 nodules enrolled.

• Total of 286 FNA samples from thyroid nodules underwent molecular analysis using the multigene GC (ThyroSeq v3).

• In Bethesda III and IV nodules combined, the test demonstrated a 94% sensitivity and 82% specificity.

• With a cancer/NIFTP prevalence of 28%, the negative predictive value (NPV) was 97% (95% CI, 93%-99%) and the positive predictive value (PPV) was 66% (95% CI, 56%-75%).

Role of molecular studies in Indeterminate FNA cytology results

• Highest NPV and PPV among well validated tests

• Highest reduction in diagnostic surgery – allowing avoidance of surgery for up to 61% of all Bethesda III/IV nodules and 82% of indeterminate nodules with benign pathology

• Reliable detection of all types of thyroid tumors including Hurthle cell cancer

• Reports probability of cancer and predicted risk of cancer recurrence, empowering individualized patient management

<table>
<thead>
<tr>
<th>Study type</th>
<th>ThyroSeq GC&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Afirma GSC&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type</td>
<td>Multicenter, prospective, double-blind</td>
<td>Multicenter, retrospective, double-blind</td>
</tr>
<tr>
<td>Total number, samples</td>
<td>247</td>
<td>191</td>
</tr>
<tr>
<td>Nodule size by ultrasound, median (range), cm</td>
<td>2.1 (0.5-7)</td>
<td>2.6 (1.0-9.1)</td>
</tr>
<tr>
<td>Disease prevalence</td>
<td>27.5%</td>
<td>23.7%</td>
</tr>
<tr>
<td>Sensitivity, (95%CI)</td>
<td>94.1% (86-98%)</td>
<td>91.1% (79-98%)</td>
</tr>
<tr>
<td>Specificity, (95%CI)</td>
<td>81.6% (75-87%)</td>
<td>68.3% (60-76%)</td>
</tr>
<tr>
<td>NPV</td>
<td>97.3% (93-99%)</td>
<td>96.1% (90-99%)</td>
</tr>
<tr>
<td>PPV</td>
<td>65.9% (56-75%)</td>
<td>47.1% (36-58%)</td>
</tr>
<tr>
<td>Benign call rate</td>
<td>61%</td>
<td>54%</td>
</tr>
<tr>
<td>Avoidable surgeries for histologically benign nodules with indeterminate cytology</td>
<td>82%</td>
<td>68%</td>
</tr>
</tbody>
</table>
Initial follow-up of nodules with benign FNA cytology

- Follow-up should be determined by risk stratification based upon US pattern.


  - Nodules with low to intermediate suspicion US pattern: repeat US at 12–24 months. If sonographic evidence of growth (20% increase in at least two nodule dimensions) or new suspicious sonographic features, the FNA could be repeated or observation continued with repeat US, with repeat FNA in case of continued growth.

  - Nodules with very low suspicion US pattern: If US is repeated, it should be done at ≥24 months.
Follow-up of nodules with two benign FNA cytology results

• If a nodule has undergone repeat US-guided FNA with a second benign cytology result, US surveillance for this nodule for continued risk of malignancy is no longer indicated.
Take home points

- Thyroid nodules are common but just a very small percentage are malignant.
- Not all thyroid nodules have indication for biopsy.
- Molecular markers are promising to decrease rate of unnecessary thyroid surgeries.
- More advances in the molecular testing field will provide additional valuable diagnostic information to guide appropriate treatment for patients with thyroid nodules and will likely aim to guide surgical management in a considerable number of cases.