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

The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer


2015 American Thyroid Association Thyroid Nodule and Cancer Guidelines

Angela M. Leung, MD, MSc, ECNU

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Outline

• Workup of nontoxic thyroid nodule(s)
  – Ultrasound
  – FNAB
• Management of FNAB results
• Preoperative tests
• Surgical management
• Postoperative staging
  – Recurrence/persistence
  – Mortality
Outline

• Workup of nontoxic thyroid nodule(s)
  – Ultrasound
  – FNAB

• Management of FNAB results

• Preoperative tests

• Surgical management

• Postoperative staging
  – Recurrence/persistence
  – Mortality
Introduction

- Thyroid nodules are increasingly common
  - Palpable nodules present in up to 5% of pts
  - Nodules found by ultrasound present in up to 68% of pts

- Thyroid cancer risk is up to 15% of all nodules

- Thyroid cancer subtypes
  - Papillary
  - Follicular
  - Medullary
  - Anaplastic
  - Others/Variants

Differentiated thyroid cancers (DTC)
2015 ATA Recommendations for New Thyroid Nodules

• Laboratory tests:
  – Obtain TSH
  – Tg not recommended
  – Calcitonin controversial (not cost-specific, issues with sensitivity/specificity)

• Imaging:
  – Perform thyroid ultrasound for any suspected nodules
Ultrasonographic Patterns of Nodules

- **High Suspicion 70-90%**
  - Microcalcifications, hypoechoic nodule, microlobulated
  - Hypoechoic, irregular margins
  - Hypoechoic, taller than wide
  - Hypoechoic, irregular margins, extrathyroidal extension
  - Hypoechoic, interrupted rim calcification with soft tissue extrusion
  - Nodule with irregular margins, suspicious left lateral lymph node

- **Intermediate Suspicion 10-20%**
  - Hypoechoic solid regular margin
  - Hypoechoic solid regular margin

- **Low Suspicion 5-10%**
  - Hypoechoic solid regular margin
  - Isoechoic solid regular margin
  - Partially cystic with eccentric solid area
  - Partially cystic with eccentric solid areas

- **Very Low Suspicion <3%**
  - Spongiform
  - Partially cystic no suspicious features
  - Partially cystic no suspicious features

- **Benign <1%**
  - Cyst
Sonographically Suspicious Characteristics of Thyroid Nodules

<table>
<thead>
<tr>
<th>Sign</th>
<th>Reported sensitivity, %</th>
<th>Reported specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcalcifications</td>
<td>5–69</td>
<td>93–100</td>
</tr>
<tr>
<td>Cystic aspect</td>
<td>10–34</td>
<td>91–100</td>
</tr>
<tr>
<td>Peripheral vascularity</td>
<td>40–86</td>
<td>57–93</td>
</tr>
<tr>
<td>Hyperechogenicity</td>
<td>30–87</td>
<td>43–95</td>
</tr>
<tr>
<td>Round shape</td>
<td>37</td>
<td>70</td>
</tr>
</tbody>
</table>
FNA Thyroid Biopsy

• Biopsy recommended for:
  ✓ Nodules > 1cm with high suspicion sonographic pattern
  ✓ Nodules > 1 cm with intermediate suspicion sonographic
  ✓ Nodules > 1.5cm with low suspicion sonographic pattern
  ✓ Nodules > 2cm with very low suspicion sonographic pattern (e.g. - spongiform)
  ✓ Any incidental nodules >1 cm with positive PET uptake

• Biopsy not recommended for:
  ✗ Purely cystic nodules
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• Surgical management
• Postoperative staging
  – Recurrence/persistence
  – Mortality
Bethesda System for Reporting Thyroid Cytopathology

<table>
<thead>
<tr>
<th>Class</th>
<th>Category</th>
<th>Prevalence of all thyroid nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Nondiagnostic/Unsatisfactory</td>
<td>5-11%</td>
</tr>
<tr>
<td>II</td>
<td>Benign</td>
<td>55-74%</td>
</tr>
<tr>
<td>III</td>
<td>Atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS)</td>
<td>2-18%</td>
</tr>
<tr>
<td>IV</td>
<td>Follicular neoplasm/suspicious for follicular neoplasm (FN)</td>
<td>2-25%</td>
</tr>
<tr>
<td>V</td>
<td>Suspicious for malignancy</td>
<td>1-6%</td>
</tr>
<tr>
<td>VI</td>
<td>Malignant</td>
<td>2-5%</td>
</tr>
</tbody>
</table>
## Bethesda System for Reporting Thyroid Cytopathology

<table>
<thead>
<tr>
<th>Class</th>
<th>Category</th>
<th>Prevalence of all thyroid nodules</th>
<th>Estimated risk of malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Nondiagnostic/Unsatisfactory</td>
<td>5-11%</td>
<td>1-4%</td>
</tr>
<tr>
<td>II</td>
<td>Benign</td>
<td>55-74%</td>
<td>0-3%</td>
</tr>
<tr>
<td>III</td>
<td>Atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS)</td>
<td>2-18%</td>
<td>5-15%</td>
</tr>
<tr>
<td>IV</td>
<td>Follicular neoplasm/suspicious for follicular neoplasm (FN)</td>
<td>2-25%</td>
<td>15-30%</td>
</tr>
<tr>
<td>V</td>
<td>Suspicious for malignancy</td>
<td>1-6%</td>
<td>60-75%</td>
</tr>
<tr>
<td>VI</td>
<td>Malignant</td>
<td>2-5%</td>
<td>97-99%</td>
</tr>
</tbody>
</table>
Bethesda Class I (Nondiagnostic/Unsatisfactory)

• Defined as failure to meet the following criteria:
  – Presence of at least 6 groups of follicular cells
  – Each group containing at least 10 cells
  – All of the above preferably on a single slide
Bethesda Class I (Nondiagnostic/Unsatisfactory)

• Repeat ultrasound-guided FNAB, preferably with on-site cytology if available (after >3 months)

• Close observation or refer to surgery

• Refer to surgery if:
  – Highly suspicious sonographic pattern
  – Growth of nodule
  – Clinical risk factors for malignancy are present
Bethesda Class II (Benign)

• No other studies or treatment necessary
• False negative rate of benign cytology only 1-2% in large series
Bethesda Class VI (Malignant)

- Usually refer to surgery

- Rarely, observation can be recommended for:
  - Low risk tumors (papillary microcarcinomas without invasion)
  - High surgical risk patients
  - Patients with short lifespan
  - Patients with concurrent and more pressing medical or surgical issues
Bethesda Class III/IV/V
(AUS/FLUS, FN, SUSP)

- For AUS/FLUS (III), consider molecular marker testing if available, or repeat FNA
  - Refer to surgery if either are not performed or are inconclusive

- For FN and SUSP (IV/V), surgery has been the long-established standard of care
  - Molecular marker testing can be used to provide additional information
  - FN: Estimated risk of malignancy is 15-30%
  - SUSP: Estimated risk of malignancy is 60-75%

- Thyroid lobectomy usually recommended for indeterminate (III/IV/V) cytologies
<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Proportion of patients with a disease who test positive</td>
<td>Proportion of patients without the disease who test negative</td>
</tr>
<tr>
<td><strong>100% (1.0) Means</strong></td>
<td>The test correctly identify every person who has the target disorder</td>
<td>The test correctly identify every person who does not have the target disorder</td>
</tr>
<tr>
<td><strong>Statistical Outcome</strong></td>
<td>True Positive</td>
<td>True Negative</td>
</tr>
<tr>
<td><strong>Ideal Test Result</strong></td>
<td>Negative Test Result</td>
<td>Positive Test Result</td>
</tr>
<tr>
<td><strong>Test Interpretation</strong></td>
<td>They are definitely not positive → They DON’T have it</td>
<td>They are definitely not negative → They DO have it</td>
</tr>
<tr>
<td><strong>The Rule</strong></td>
<td>Rule Out (SnOut)</td>
<td>Rule In (SpIn)</td>
</tr>
</tbody>
</table>
Test Performance Characteristics

• NPV: How likely the negative test really is negative
  – Ideal NPV of a test = good “rule out” test

• PPV: How likely the positive test really is positive
  – Ideal PPV of a test = good “rule in” test
Molecular Markers for Cytologically-Indeterminate Thyroid Nodules

**Veracyte Afirma GEC**

- Measures the mRNA expression of 142 genes
- High sensitivity (92%)
- High NPV (93%)
- Low specificity (48-53%)

**Mutational Testing (e.g. Thyroseq)**

- Measures presence of BRAF, NRAS, HRAS, KRAS, RET/PTC1, RET/PTC3, PAX8/PPARc genetic mutations and rearrangements
- High specificity (86-100%)
- High PPV (84-100%)
- Variable sensitivity (44-100%)

Utility of tests dependent on prevalence of thyroid cancer in the nodules tested

At present, no single test can reliably rule in or rule out thyroid cancer
Multiple Nodules

- Patients with multiple nodules should receive the same evaluation as those with a solitary nodule
  - Each nodule >1cm carries its own independent risk of malignancy
Nodules with a Suppressed TSH

• Autonomy must be ruled out with a thyroid nuclear scan
  – 99-Tc technetium pertechnetate
  – I-123

• Results should be compared against a thyroid ultrasound
## Follow Up of Aspirated Benign Nodules

<table>
<thead>
<tr>
<th>Sonographic Pattern</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High suspicion</td>
<td>Repeat ultrasound and FNAB</td>
</tr>
<tr>
<td>Low/Intermediate suspicion</td>
<td>Repeat ultrasound at 12-24 months</td>
</tr>
<tr>
<td></td>
<td>Repeat FNAB when there is growth, defined as:</td>
</tr>
<tr>
<td></td>
<td>- 20% increase in at least 2 of 3 dimensions</td>
</tr>
<tr>
<td></td>
<td>- Increase of ≥50% volume</td>
</tr>
<tr>
<td>Very low suspicion (i.e. spongiform nodules)</td>
<td>Repeat at ≥24 months, if at all</td>
</tr>
</tbody>
</table>
Follow Up of Aspirated Benign Nodules

• After 2 FNABs yielding a benign cytology, ultrasound surveillance no longer indicated
## Follow up of Never Aspirated Nodules

<table>
<thead>
<tr>
<th>Sonographic Pattern</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High suspicion</td>
<td>Repeat ultrasound at 6-12 months</td>
</tr>
<tr>
<td>Low/Intermediate suspicion</td>
<td>Repeat ultrasound at 12-24 months</td>
</tr>
<tr>
<td>Very low suspicion (i.e. spongiform or purely cystic nodules)</td>
<td>Repeat ultrasound at ≥24 months</td>
</tr>
<tr>
<td>Nodules &lt;5 mm</td>
<td>Do not require repeat ultrasound ever, but if done, should be ≥24 months</td>
</tr>
</tbody>
</table>
Other Therapies for Benign Thyroid Nodules

• TSH suppression with thyroid hormone *not* recommended in iodine-sufficient areas
  – Modest response
  – Potential harms outweighs the benefits

• Adequate iodine intake recommended (150 mcg oral daily) to suppress thyroid hyperplasia

• Refer to surgery if causing compressive symptoms

• Consider percutaneous ethanol injection (PEI) for recurrent cystic nodules causing compressive symptoms
Thyroid Nodules in Pregnancy

• Euthyroid or hypothyroid women with a nodule
  – FNAB recommended

• Suppressed TSH during pregnancy beyond 16 weeks with a nodule
  – Defer until after delivery
  – Then perform a thyroid nuclear scan to rule out autonomy before FNAB
Malignant or Indeterminate Cytology During Pregnancy

• Consider surgery if significant growth before 24-26 weeks gestation or suspicious lymph nodes present
• Otherwise defer until after delivery surgery
• Target TSH 0.1-1.0 mIU/L during pregnancy if malignancy confirmed or suspected
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Preoperative Imaging

• Gold standard is the **preoperative neck ultrasound**, including lateral compartments
  – If suspicious lymph nodes >8-10mm found, perform FNAB
  – Also consider FNA-Tg washout

• Preoperative CT/MRI to confirm ultrasound *if there is significant bulky disease*

• Preoperative PET *not* recommended
Preoperative Labs

- Serum Tg or Tg Ab are not recommended
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# Extent of Thyroid Surgery

<table>
<thead>
<tr>
<th>Recommended Surgery</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Near-total or total thyroidectomy</td>
<td>- Thyroid cancer &gt;4 cm</td>
</tr>
<tr>
<td></td>
<td>- Gross extrathyroidal extension (ETE)</td>
</tr>
<tr>
<td></td>
<td>- Metastatic disease to lymph nodes or distant sites</td>
</tr>
<tr>
<td>Near-total or total thyroidectomy OR</td>
<td>- Thyroid cancer 1-4 cm</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>- No ETE</td>
</tr>
<tr>
<td></td>
<td>- No mets</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>- Thyroid cancer &lt;1 cm</td>
</tr>
<tr>
<td></td>
<td>- No ETE</td>
</tr>
<tr>
<td></td>
<td>- No mets</td>
</tr>
</tbody>
</table>
# Extent of Lymph Node Dissection

<table>
<thead>
<tr>
<th>Recommended Dissection</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic central neck (level VI) dissection</td>
<td>Clinically involved central lymph nodes</td>
</tr>
<tr>
<td>Propylactic central neck (level VI) dissection</td>
<td>Clinically uninvolved central lymph nodes with:</td>
</tr>
<tr>
<td></td>
<td>- Advanced primary tumors</td>
</tr>
<tr>
<td></td>
<td>- Clinically involved lateral nodes</td>
</tr>
<tr>
<td>Lateral neck dissection</td>
<td>Metastatic lateral lymph nodes (confirmed by biopsy)</td>
</tr>
</tbody>
</table>
Completion Thyroidectomy

• Recommend completion for patients in whom a bilateral thyroidectomy would have been recommended if diagnosis had been available preoperatively

• RAI ablation not recommended in lieu of completion thyroidectomy
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  - Mortality
### 2009 ATA Risk of Recurrence Stratification System (after total thyroidectomy and RAI remnant ablation)

<table>
<thead>
<tr>
<th>Recurrence Risk</th>
<th>Definition</th>
</tr>
</thead>
</table>
| **Low**         | - Papillary thyroid cancer with no local or distant metastases, complete resection of macroscopic tumor, no invasion, no aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma)  
- If I-131 is given, there are no RAI avid metastatic foci outside the thyroid bed on the first post-treatment whole-body RAI scan  
- Intrathyroidal papillary microcarcinoma (unifocal or multifocal, including V600E BRAF if positive) |
| **Intermediate**| - Microscopic invasion  
- RAI avid metastatic foci in the neck on post-treatment WBS  
- Aggressive histology  
- PTC with vascular invasion |
| **High**        | - Macroscopic invasion  
- Incomplete tumor resection  
- Distant mets |
2015 ATA Risk of Recurrence Stratification System (after total thyroidectomy and RAI remnant ablation)

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%)
# AJCC TNM Classification System for Risk of Mortality from DTC

<table>
<thead>
<tr>
<th>Definition</th>
<th>Patient age &lt; 45 years</th>
<th>Patient age 45 years or older</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>T1 N0 , M0</td>
<td>T1 N0 , M0</td>
</tr>
<tr>
<td>T2</td>
<td>T2 N0 , M0</td>
<td>T2 N0 , M0</td>
</tr>
<tr>
<td>T3</td>
<td>T3, N0, M0</td>
<td>T1, N1a, M0</td>
</tr>
<tr>
<td>T4a</td>
<td>T4a, N0, M0</td>
<td>T4a, N1a, M0</td>
</tr>
<tr>
<td>T4b</td>
<td>T4a, N1a, M0</td>
<td>T4b, Any N, M0</td>
</tr>
<tr>
<td>TX</td>
<td>Any T, any N, M0</td>
<td>Any T, any N, M1</td>
</tr>
<tr>
<td>N0</td>
<td>No metastatic lymph nodes</td>
<td>No metastatic lymph nodes</td>
</tr>
<tr>
<td>N1a</td>
<td>Metastases to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)</td>
<td>Metastases to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)</td>
</tr>
<tr>
<td>N1b</td>
<td>Metastases to unilateral, bilateral, contralateral cervical or superior mediastinal lymph node metastases</td>
<td>Metastases to unilateral, bilateral, contralateral cervical or superior mediastinal lymph node metastases</td>
</tr>
<tr>
<td>NX</td>
<td>Lymph nodes not assessed at surgery</td>
<td>Lymph nodes not assessed at surgery</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastases</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastases</td>
<td>Distant metastases</td>
</tr>
<tr>
<td>MX</td>
<td>Distant metastases not assessed</td>
<td>Distant metastases not assessed</td>
</tr>
</tbody>
</table>

AJCC Cancer Staging Manual, 2010
Postoperative Staging for Mortality Risk

• Many thyroid cancer staging systems have been proposed

• **AJCC/UICC TNM** staging recommended in patients with DTC
  – Used to predict mortality (not very well though)
  – Applicable to most patient cohorts
  – Validated in retrospective studies and prospectively in clinical practice

• None of the current staging systems incorporate molecular testing results
<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>No clinical, biochemical or structural evidence of disease <em>(Suppressed Tg &lt;0.2 or stimulated Tg &lt;1)</em></td>
<td>• 1-4% recurrence</td>
</tr>
<tr>
<td>Biochemical incomplete</td>
<td>Abnormal thyroglobulin or rising anti-thyroglobulin antibody levels in the absence of localizable disease <em>(Suppressed Tg &gt;1, stimulated Tg &gt;10, or rising Tg Ab)</em></td>
<td>• 20% develop structural disease</td>
</tr>
<tr>
<td>Structural incomplete</td>
<td>Persistent or newly identified loco-regional or distant metastases</td>
<td>• 50-85% with persistent disease</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Non-specific biochemical or structural findings which cannot be confidently classified as either benign or malignant.* <em>(Suppressed Tg 0.2-1 or stimulated Tg 1-10)</em> <em>(Stable or declining anti-thyroglobulin antibody levels without definitive structural evidence of disease)</em></td>
<td>• 15-20% develop structural disease</td>
</tr>
</tbody>
</table>
# TSH Targets Based on Mortality Risk Estimates

<table>
<thead>
<tr>
<th>Increasing Risk of TSH Suppression</th>
<th>Excellent</th>
<th>Indeterminate</th>
<th>Biochemical Incomplete **</th>
<th>Structural Incomplete</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Known Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopause</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Tachycardia</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Osteopenia</td>
<td></td>
<td></td>
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<tr>
<td>Age &gt; 60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td></td>
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</tbody>
</table>

* 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
Take-Home Points

• Thyroid cancer incidence is rising
• A normal serum TSH needed before FNAB is to be considered
• The decision to perform an FNAB depends on both ultrasound characteristics and nodule size
• Molecular markers may be helpful in nodules with indeterminate cytology
• Preoperative ultrasound with lateral neck lymph nodes should be done before every thyroid surgery
• Overall, less aggressive extent of surgery is now recommended
• Assessments of thyroid cancer patients should include:
  – **AJCC (TNM) staging** to predict mortality risks post-thyroid surgery
  – **ATA risk** for structural recurrence of disease after surgery and RAI ablation
  – **Response to therapy over time** to predict mortality risks during continued monitoring