Highlights of the 2015 ATA Guidelines for Differentiated Thyroid Cancer – Histologic & Molecular Approach to Staging

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Disclosures:
Over the past 10 years, I have received research support, served as a consultant or scientific advisory board member for: Veracyte, Inc., Asuragen, Inc., Genzyme, Inc., and NPS Pharma.

Outline:

Highlight the new ATA 2015 Guidelines:
To discuss the approach to a patient with typical, well-differentiated, generally low-risk thyroid cancer. (Papillary and Follicular Thyroid Carcinoma)

I. Staging & Risk Assessment
II. Initial Surgical Treatment
III. Decisions for 131I Therapy
IV. Long-term TSH suppression
V. Molecular Testing
VI. Follow up

A Typical Patient:
• 43yo male found to have an incidental thyroid nodule on CAT-scan of the Chest
• Ultrasound confirms a well-circumscribed, 3.2cm solid nodule. No lymphadenopathy
• FNA Cytology – Positive for Papillary Carcinoma.
• He is asymptomatic and otherwise healthy.

How should he be managed?

The Standard Approach to Differentiated Thyroid Cancer:

1. Thyroid Surgery
2. 131I (Radioactive Iodine) Ablation
3. Long-Term TSH Suppression

While the standard approach remains unchanged, the recommended management of affected patients is increasingly conservative & acknowledges that disease lies on a spectrum. We must Individualize Care.

Individualized Care begins with Individualized Staging:

2015 ATA Guidelines –

Staging is a Continuum of 3 Processes:

➢ AJCC/UICC staging
➢ ATA Initial Risk Stratification (Introduced 2005, Modified 2015)
➢ ATA Response to Therapy (New 2015)
Why 3 Staging Systems?

AJCC/UICC staging System → predicts disease mortality

ATA Initial Risk Stratification System → predicts structural disease recurrence and/or persistence

ATA Response to Therapy System → acknowledges that risk changes over time (reassessment of risk is required)

Central to Risk Stratification - improved (& standardized) Histopathologic Assessment

Former System:
- Primary tumor type & description
- Tumor Size
- Resection Margins
- Lymph Node Involvement
- Distant Metastasis

2015 ATA Guidelines:
- Histologic Variants of Thyroid CA
- Vascular Invasion & number of invaded vessels
- Multifocality
- Number of lymph nodes examined and involved
- Size of the largest metastatic focus to the lymph node
- Extracapsular extension

All of the above

Histologic Variants of Papillary Carcinoma
Standardized and Recommended Reporting:

Lower Risk:
- Follicular Variant, PTC
- Classical Variant, PTC
- Minimally Invasive, PTC

Higher Risk:
- Tall-cell or Columnar Variant, PTC
- Hobnail Variant, PTC
- Widely Invasive, PTC
- ** Diffuse Sclerosing Variant, PTC

Staging Thyroid Cancer:
I. AJCC 7th Edition/ TNM System

Traditional Staging, Tumor Size & Presence of Lymph Nodes

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>Tumor &lt;1 cm, NO extrathyroid extension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor 1-2 cm, NO extrathyroid extension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor 2-4 cm, NO extrathyroid extension</td>
</tr>
<tr>
<td>N0</td>
<td>No metastatic lymph nodes</td>
</tr>
<tr>
<td>N1a</td>
<td>Lymph node Metastases to Level II (central neck)</td>
</tr>
</tbody>
</table>

30 year survival >95%

The Primary Utility of AJCC Staging is to:
- Identify High-Risk Patients in whom mortality may be increased
- Allow Accurate Communication
- Maintain Common Cancer Registries

Staging Thyroid Cancer:
II. ATA Initial Risk Stratification - 2009
Based upon clinicopathologic features available at the time of initial treatment:

Post-operatively, classify each patient as:

- Low Risk for Recurrence
  - Intrafollicular differentiated Thyroid Cancer < 4 cm
  - No ETE, Vascular Invasion or LN Metastasis
- Intermediate Risk for Recurrence
  - Everything else
- High Risk for Recurrence
  - Gross extrathyroid extension
  - Incomplete Tumor Resection
  - Distant Metastasis

Staging Thyroid Cancer:
II. ATA Initial Risk Stratification - 2015
Based upon clinicopathologic features available at the time of initial treatment:

Post-operatively, classify each patient as:

- No Evidence of Disease following Thyroidectomy & 131 I ablation
  - ~85%
- Low Risk for Recurrence
  - Intrafollicular differentiated Thyroid Cancer < 4 cm
  - No ETE, Vascular Invasion or LN Metastasis
  - Gross extrathyroid extension (< 0.5 cm)
  - Minimally invasive Papillary Carcinoma (CT only)
- Intermediate Risk for Recurrence
  - Everything else
  - Higher risk variants of PTC (tall-cell variants, etc.)
- High Risk for Recurrence
  - Gross extrathyroid extension
  - Incomplete Tumor Resection
  - Distant Metastasis

Cortesio, Le J. (2016) Torts, Thyroid 2016 volume, One node 2016/Provo, Thyroid 2014
I. Should this patient have Surgery?  
What is the optimal extent of Surgery?  
43yo Male – 3.2cm follicular variant PTC, No adenopathy

**Answer:**

- Previous Guidelines: >>> Near Total Thyroidectomy
- 2015 ATA guidelines: <<< Hemi- <<< Near-Total Thyroidectomy

**Why?**

When ATA low to intermediate risk patients can be identified:

- Clinical Outcomes are very similar
- Surgery carries risk
- In some cases, 131I may not be necessary

II. Should this patient have 131I?

3.2cm PTC, follicular variant; No LAD, No Invasion; No ETE

**Answer:**

- Previous Guidelines: >>> Recommend 131I Therapy
- 2015 ATA guidelines: <<< Not Routine – may be considered ATA Intermediate risk

**Why?**

For TNM Stage I / ATA Low-Risk Patients:

- 131I does not improve disease specific survival
- 131I does not improve disease free survival
- Radiation carries a cumulative lifetime risk

III. Should you suppress TSH?

3.2cm PTC, follicular variant; No LAD, No Invasion; No ETE

**Answer:**

- No suppression – TSH target: 2-4 mIU/L
- Mild suppression – TSH target: 0.1-2 mIU/L
- Moderate or Complete suppression – TSH target: <0.1 mIU/L

**The Standard Approach to Differentiated Thyroid Cancer:**

- **2015 ATA Guidelines – Provide Better Guidance for Low-Risk Thyroid Cancer**
  - by improving histopathologic interpretation  
  - by better understanding the meaning of lymph node disease  
  - by continually assessing response to therapy

1. Thyroid Surgery – Consider hemi?
2. 131I (Radioactive Iodine) Ablation – Only Intermediate & High Risk patients
3. Long-Term TSH Suppression – Less Often
IV: Should you perform Molecular Analysis:
3.2cm PTC, follicular variant; No LAD; No Invasion; No ETE

**Diagnostic Use:**
- BRAF mutation (V600E)
- TERT mutations
- TP 53 mutations
- 5 HCTA mutations
- 7 PIK3CA mutations

**Guidelines Committee:**
- Recognition that this is rapidly evolving space
- Recognition that multiple genes may require mutational testing
- Recognition that specific histology correlates with specific mutations

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Molecular Analysis of Thyroid Cancer:
The Anticipation:

1991: 
2003:

**Molecular Analysis of Thyroid Cancer:**
The Reality - 2016

- In the post surgical setting, whole genome sequencing (DNA) can identify the Causative Mutation of most Thyroid Cancers:
- In the diagnostic setting, Gene Expression Profiling (RNA) can accurately identify the most benign disease:

Thyroid Cancer Gene Atlas (PTC, PTC, ATC)

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**Molecular Analysis of Thyroid Cancer:**

Disclaimer: I'm a believer in molecular medicine. It is helpful, provides novel information, synergistic, and benefits care. But: Molecular Medicine is moving very fast. Molecular/Genetic testing is now widely available - for anything, & everything.

**CAUTION**

- Molecular Analysis can accurately assess malignancy (or benignity) in ALL nodules
- A genetic mutation means malignancy
- We understand the meaning of all that we data we are uncovering.

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**Molecular Analysis of Thyroid Cancer:**

Discordant Data?

Thyroid Cancer Gene Atlas (PTC, PTC, ATC)

**Highly Selected:**

- 161 RNA and Histo (4 benign; 1 cancer)
- 814 mutations; 133 fusions (mirrors TCGA)

**Test Performance:**

- PPV: 73%
- NPV: 60%

Boswell et al. 2003
- 105 Indeterminate Nodules; 51 finals
- Clinical, Biased
- 17 Mutations - BRAF, NAC, FGFR, PRK, RET

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**Molecular Analysis of Thyroid Cancer:**

Real-World

- Pagan et al.
- 511 Indeterminate Nodules; 17 cancers
- Dissimilar to above
- Retrospective, Not Biased
- 17 Mutations - BRAF, NAC, FGFR, PRK, RET, PTV

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**Molecular Analysis of Thyroid Cancer:**

1991: 
2003:
IV: Molecular Analysis of Thyroid Cancer:
If the lesion harbors a genetic mutation, what does that mean?

RAS Mutations:
- BRAF (V600E) mutations are detected in 30% of FTCs.
- A majority of these mutations result in a hyperactive RAS protein.

BRAF Mutations:
- BRAF (V600E) mutations are detected in 40% of FTCs.
- The majority of these mutations result in a hyperactive BRAF protein.

IV: Molecular Analysis of Thyroid Cancer:
A Clinician's Story... (my story)

Brigham & Women's Hospital
Dana Farber Cancer Institute
Oncopanel
Whole Exome Sequencing of 100 cancer-associated genes

BRAF (V600E) mutational testing -
For prognostic & staging purposes:

Strong Evidence: BRAF V600E + PTC is associated with higher risk of recurrence.

BRAF mutation +
- ~25-30% risk

BRAF wild-type
- ~10-12% risk

Aggressive Disease: BRAF + PTC is tightly linked to aggressive histologic phenotypes.

Higher risk phenotypes
- Lymph Node Metastasis
- Extrathyroidal Extension

But:
- BRAF positivity is not independently associated with disease mortality.
- BRAF does not affect prognosis of very low risk tumors (<1cm).
- Most of the attributable risk is conveyed by histologic interpretation.
- Largest Meta-analysis: BRAF positivity only 25% predictive of recurrence.

V: How Should this Patient be Followed:
3 cm PTC, follicular variant, No LAD, No Invasion, No ETE
Received 30mcg T4 – No local or distant metastatic disease

Measurement of Thyroglobulin & Thyroglobulin Ab

Determining Response to Therapy:
- A) During initial follow-up, serum Tg on thyroid therapy should be measured every 6-12 months.
- B) In ATA low and intermediate risk patients that achieve an excellent response to therapy, the utility of subsequent Tg testing is not established. The time interval between serum Tg measurements can be lengthened to at least 12-24 months.
- C) In high risk patients (regardless of response to therapy) and all patients with biochemical/complete/structural/ incomplete, or indeterminate response, should continue to have Tg measured at least every 6-12 months for several years.
V: How Should this Patient be Followed:
3.2cm PTC, follicular variant, No LAD, No Invasion, No ETE
Received 30mCi 1131 – No local or distant metastatic disease

<table>
<thead>
<tr>
<th>Measurement of Thyroglobulin &amp; Thyroglobulin Ab</th>
<th>Then...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroglobulin&lt;2 microg/L</td>
<td>High Risk No Cancer</td>
</tr>
<tr>
<td>Thyroglobulin 2 - 3 microg/L</td>
<td>Yes, US to assess</td>
</tr>
<tr>
<td>TNM 1 - 2, a US + no钛</td>
<td>No US, Low Risk No Cancer</td>
</tr>
<tr>
<td>Thyroglobulin &gt; 3 microg/L and/or increasing</td>
<td>US</td>
</tr>
<tr>
<td>Antibodies to Thyroglobulin → ↑ TSH or decreasing</td>
<td>Additional imaging</td>
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IV: How Should this Patient be Followed:
3.2cm PTC, follicular variant, No LAD, No Invasion, No ETE
Received 30mCi 1131 – No local or distant metastatic disease

**Should a Neck Ultrasound be Performed?**

- **Initially:** Yes, a cervical US should evaluate the thyroid bed and central and lateral cervical nodal compartments, typically 6-12 months after therapy.
- **Subsequent:** Repeated US examinations are not recommended for all patients, especially when low-risk patients have had a previous negative cervical US and have a low serum Tg (<1.0 ng/ml) or after TSH-stimulation (Tg <1 ng/ml) (Weak recommendation, Low-quality evidence)

Continually reassess your patient’s response to therapy.

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To discuss the approach to a patient with typical, well-differentiated, generally low-risk thyroid cancer. (Papillary and Follicular Thyroid Carcinoma)

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**Conclusions:**

- Well-Differentiated Thyroid Cancer is increasingly common, yet carries very low morbidity & mortality – especially low-risk pts.
- Our ability to define ‘low-risk’ patients has improved substantially. Initial evaluation should seek to categorize all patients into an ATA Risk of Recurrence Category.
- The benefits of extensive initial surgery, and in particular adjunctive ¹³¹I ablation and long-term TSH suppression is questionable in most ATA low-risk patients. Increasingly a more conservative approach to care should be considered.
- Individual assessment is paramount, and should be reassessed frequently to determine response to therapy.
- Molecular analysis is helping us better care for patients. Complex. Avoid assumptions. Space is moving very fast.