Surgery for known or suspected thyroid cancer in 2018

September 2018

Michael W. Yeh, MD
Professor of Surgery and Medicine
Chief, Section of Endocrine Surgery
David Geffen School of Medicine at UCLA
www.endocrinesurgery.ucla.edu
Evolution of thyroid surgery: 2011-2018

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No disclosures
Thyroid nodule mgmt within UCLA Health

- 1 million lives/year
- 1200 biopsies/year
- 25 endocrinologists
- Centralized pathology
- Indeterminate (Bethesda 3+4) rate ~15%
- Reflex molecular testing
  - Advanced analytics (URSA Health, xDR)
- Population health considerations
Molecular testing: Malignant Yield of Diagnostic Thyroid Lobectomy

![Graph showing malignancy found on histopathology over time.](attachment:image.png)
A pragmatic randomized trial comparing molecular markers for indeterminate thyroid nodules: an interim analysis

Masha J. Livhits, MD, Eric J. Kuo, MD, Angela M. Leung, MD, Kyle A. Zanocco, MD, Dianne S. Cheung, MD, Yaroslav Gofnung, MD, Michael W. Yeh, MD

Background
There are no studies directly comparing Afirma Gene Expression Classifier (GEC) vs ThyroSeq v2 gene mutation panel.

Specific Aims
Directly compare GEC and ThyroSeq performance:
- Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)
- Diagnostic lobectomies avoided

Methods

Results
1372 nodules → Benign: 75.1%
  → Indeterminate: 13.0%
  → Malignant: 5.9%

Figure 1. Study cohort

Table 1. Baseline characteristics

Table 2. Results of surgery

<table>
<thead>
<tr>
<th>Molecular test</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Malignant</td>
</tr>
<tr>
<td>GEC</td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>0</td>
</tr>
<tr>
<td>Suspicious</td>
<td>10</td>
</tr>
<tr>
<td>ThyroSeq</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
</tr>
<tr>
<td>Positive</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 3. Performance of GEC vs. ThyroSeq

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV**</th>
<th>NPV**</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEC</td>
<td>100.00%</td>
<td>65.96%</td>
<td>38.46%</td>
<td>100.00%</td>
</tr>
<tr>
<td>ThyroSeq</td>
<td>100.00%</td>
<td>90.63%</td>
<td>57.14%</td>
<td>100.00%</td>
</tr>
</tbody>
</table>

*Assuming nodules with negative molecular test are truly benign
**Prevalence of malignancy, 12.0%
RECOMMENDATION 35

(A) For patients with thyroid cancer >4 cm, or with gross extrathyroidal extension (clinical T4), or clinically apparent metastatic disease to nodes (clinical N1) or distant sites (clinical M1), the initial surgical procedure can be a near-total or total thyroidectomy. Thyroid lobectomy alone may be insufficient initial treatment for low-risk papillary and follicular carcinomas; however, the treatment team may choose total thyroidectomy to enable RAI therapy or to enhance follow-up based upon disease features and/or patient preferences.

(B) For patients with thyroid cancer >1 cm and <4 cm without extrathyroidal extension, and without clinical evidence of any lymph node metastases (cN0), the initial surgical procedure can be either a bilateral procedure (near-total or total thyroidectomy) or a unilateral procedure (lobectomy). Thyroid lobectomy alone may be sufficient initial treatment for low-risk papillary and follicular carcinomas; however, the treatment team may choose total thyroidectomy to enable RAI therapy or to enhance follow-up based upon disease features and/or patient preferences.
Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma
A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

Yuri E. Nikiforov, MD, PhD; Raja R. Seethala, MD; Giovanni Tallini, MD; Zubair W. Baloch, MD, PhD;
Fulvio Basolo, MD; Lester D. R. Thompson, MD; Justine A. Barletta, MD; Bruce M. Wenig, MD; Abir Al Ghuzlan, MD;
Kennichi Kakudo, MD, PhD; Thomas J. Giordano, MD, PhD; Venancio A. Alves, MD, PhD;
Elham Khanafshar, MD, MS; Sylvia L. Asa, MD, PhD; Adel K. El-Naggar, MD; William E. Goode, MS;
Steven P. Hodak, MD; Ricardo V. Lloyd, MD, PhD; Guy Maytal, MD; Ozgur Mete, MD; Marina N. Nikiforova, MD;
Vania Nosé, MD, PhD; Mauro Papotti, MD; David N. Poller, MB, ChB, MD, FRCPATH; Peter M. Sadow, MD, PhD;
Arthur S. Tischler, MD; R. Michael Tuttle, MD; Kathryn B. Wall; Virginia A. LiVolsi, MD; Gregory W. Randolph, MD;
Ronald A. Ghossein, MD

**IMPORTANCE** Although growing evidence points to highly indolent behavior of encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC), most patients with EFVPTC are treated as having conventional thyroid cancer.

**OBJECTIVE** To evaluate clinical outcomes, refine diagnostic criteria, and develop a nomenclature that appropriately reflects the biological and clinical characteristics of EFVPTC.

**DESIGN, SETTING, AND PARTICIPANTS** International, multidisciplinary, retrospective study of patients with thyroid nodules diagnosed as EFVPTC, including 109 patients with noninvasive EFVPTC observed for 10 to 26 years and 101 patients with invasive EFVPTC observed for 1 to 18 years. Review of digitized histologic slides collected at 13 sites in 5 countries by 24 thyroid pathologists from 7 countries. A series of teleconferences and a face-to-face conference were used to establish consensus diagnostic criteria and develop new nomenclature.
PTC risk order: Tall cell > classic >> FVPTC

Shi and Xing, Differential Clinicopathological Risk and Prognosis of Major Papillary Thyroid Cancer Variants, J Clin Endocrinol Metab 2016
Thyroid surgery: Less is more

- Reduction in frequency and extent of surgery for known or suspected thyroid malignancy
- Molecular testing: Fewer diagnostic lobectomies
- 2015 ATA guidelines: TTx \(\rightarrow\) lobectomy
- 2015 ATA guidelines + Shi + NIFTP: Fewer completion thyroidectomies
- 2012 ATA statement on nodal metastases: Greater selectivity for LND
Talking to patients about change
Conceptual separation of suspicious/malignant nodules

**RAS-driven**
- Isoechoic
- Well-demarcated
- No calcifications
- Negative nodes
- Bland nuclei
- Bethesda 3+4
- Soft
- Fleshy
- Tan
- Min invas FTC
- FVPTC
- NIFTP

**RTK-driven**

**BRAF-driven**
- Hypoechoic
- Irregular borders
- Microcalcifications
- Positive nodes
- Nuclear grooves/
Pseudoinclusions
- Psammoma bodies
- Bethesda 5+6
- Hard
- Gritty
- White
- Classic PTC
- Tall-cell variant

**Low recurrence risk**
- Less surgery

**High recurrence risk**
- More surgery
Implementing a strategy of less surgery:

A tale of two Bethesda 6 nodules
Lobectomy appropriate

Total Tx appropriate
Adaptation of surgical management

• **APPROPRIATE SELECTION** of patients for lobectomy, TTx, or TTx+LND

• Driven by (surgeon-performed) **ultrasound** and molecular profiling

• Requires high sensitivity to detect:
  • Abnormal lymph nodes
  • Extrathyroidal extension
“In comparison to a strategy of routine total thyroidectomy, a detailed sonographic assessment reduced the rate of unnecessary total thyroidectomy from 57% to 31%.”

Table 1. Comparison to strategies of routine lobectomy and routine total thyroidectomy

<table>
<thead>
<tr>
<th></th>
<th>Routine lobectomy</th>
<th>Routine TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate lobectomy</td>
<td>20 (57.1%)</td>
<td>-</td>
</tr>
<tr>
<td>Inadequate lobectomy</td>
<td>15 (42.9%)</td>
<td>-</td>
</tr>
<tr>
<td>Potentially avoidable TT</td>
<td>-</td>
<td>20 (57.1%)</td>
</tr>
<tr>
<td>Necessary TT</td>
<td>-</td>
<td>15 (42.9%)</td>
</tr>
</tbody>
</table>

Table 2. Performance of ultrasound in assessment of ETE

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>36.4%</td>
<td>100%</td>
<td>51.5%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Conclusions

- A detailed sonographic assessment of ETE can reliably rule out ETE, permitting patients to undergo lobectomy with minimal risk of requiring completion thyroidectomy.
But beware multiple mutations...

DTC, n=469

Melo M et al. JCEM (2014)

PTC, n=507

Xing M et al. JCO (2014)

DTC, n=551

Song YS et al. Cancer (2016)

DTC, n=551

Song YS et al. Cancer (2016)
Past paradigm: Suspicious/malignant nodules

- Biopsy
- Uniform treatment
- If malignant: Total Tx ± LND ± RAI
New paradigm: Suspicious/malignant nodules

Biopsy

Molecular profile

Ultrasound features

Individualized treatment

Surgery avoided

Active surveillance

Lobectomy

Total Tx

Total Tx LND + RAI

Benign

Very low risk

Low risk

Intermediate risk

High risk
“Only the most wise and most foolish do not change.”

Confucius