Surgery for recurrent thyroid cancer:
When, where, how much?

January 2018
AACE Advances in Medical and Surgical Management of Thyroid Cancer

Michael W. Yeh, MD
Chief, Section of Endocrine Surgery
Professor of Surgery and Medicine
David Geffen School of Medicine at UCLA
www.endocrinesurgery.ucla.edu
No disclosures
Obituary: Jeffrey F. Moley, professor of surgery, cancer researcher, 64

'Masterful surgeon' advanced treatments for thyroid cancer

by Kristina Sauerwein • October 18, 2017

Jeffrey Fletcher Moley, MD, a highly regarded professor of surgery and chief of the Section of Endocrine and Oncologic Surgery at Washington University School of Medicine in St. Louis, died Sunday, Oct. 15, 2017, at his home in Kirkwood. He was 64.

Moley, also an associate director at Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine, died following a sudden cardiac event. He had been married for 30 years to Kelle H. Moley, MD, the university’s James P. Crane Professor of Obstetrics and Gynecology.
Learning Objectives

• How prevalent are cervical recurrences of differentiated thyroid carcinoma?

• What is the strategic framework for managing recurrences?

• If surgery is chosen, what is the optimal approach?
Prevalence of DTC recurrences
Survival and Recurrence in PTC

Adam M, Extent of surgery for papillary thyroid cancer is not associated with survival, Ann Surg 2014
Timing of Recurrences in PTC

Mazzaferri E, Current approaches to primary therapy for papillary and follicular thyroid cancer, J Clin Endo Metab 2001

Mazzaferri E, Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer, Am J Med 1994
Up to 39% of re-operations for thyroid cancer are a direct result of incomplete initial surgery.

Incomplete initial surgery often arises from incomplete pre-operative imaging.

Kouvaraki, Preventable reoperations for persistent and recurrent papillary thyroid carcinoma, Surgery 2004
American Thyroid Association Statement on Preoperative Imaging for Thyroid Cancer Surgery

Michael W. Yeh, Andrew J. Bauer, Victor A. Bernet, Robert L. Ferris, Laurie A. Loevner, Susan J. Mandel, Lisa A. Orloff, Gregory W. Randolph, and David L. Steward

for the American Thyroid Association Surgical Affairs Committee Writing Task Force

Background: The success of surgery for thyroid cancer hinges on thorough and accurate preoperative imaging, which enables complete clearance of the primary tumor and affected lymph node compartments. This working group was charged by the Surgical Affairs Committee of the American Thyroid Association to examine the available literature and to review the most appropriate imaging studies for the planning of initial and revision surgery for thyroid cancer.

Summary: Ultrasound remains the most important imaging modality in the evaluation of thyroid cancer, and should be used routinely to assess both the primary tumor and all associated cervical lymph node basins preoperatively. Positive lymph nodes may be distinguished from normal nodes based upon size, shape, echogenicity, hypervascularity, loss of hilar architecture, and the presence of calcifications. Ultrasound-guided fine-needle aspiration of suspicious lymph nodes may be useful in guiding the extent of surgery. Cross-sectional imaging (computed tomography with contrast or magnetic resonance imaging) may be considered in select circumstances to better characterize tumor invasion and bulky, inferiorly located, or posteriorly located lymph nodes, or when ultrasound expertise is not available. The above recommendations are applicable to both initial and revision surgery. Functional imaging with positron emission tomography (PET) or PET-CT may be helpful in cases of recurrent cancer with positive tumor markers and negative anatomic imaging.
### Table 11. ATA 2009 Risk Stratification System with Proposed Modifications

<table>
<thead>
<tr>
<th>ATA low risk</th>
<th>Papillary thyroid cancer (with all of the following):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- No local or distant metastases;</td>
</tr>
<tr>
<td></td>
<td>- All macroscopic tumor has been resected</td>
</tr>
<tr>
<td></td>
<td>- No tumor invasion of loco-regional tissues or structures</td>
</tr>
<tr>
<td></td>
<td>- The tumor does not have aggressive histology (e.g., tall cell, hoboanl variant, columnar cell carcinoma)</td>
</tr>
<tr>
<td></td>
<td>- If (^{131}\text{I}) is given, there are no RAI-avid metastatic foci outside the thyroid bed on the first posttreatment whole-body RAI scan</td>
</tr>
<tr>
<td></td>
<td>- No vascular invasion</td>
</tr>
<tr>
<td></td>
<td>- Clinical N0 or (\leq 5) pathologic N1 micrometastases (&lt;0.2 cm in largest dimension)(^a)</td>
</tr>
<tr>
<td></td>
<td>- Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer (^a)</td>
</tr>
<tr>
<td></td>
<td>- Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (&lt;4 foci) vascular invasion(^a)</td>
</tr>
<tr>
<td></td>
<td>- Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including (BRAF^{V600E}) mutated (if known)(^a)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATA intermediate risk</th>
<th>Microscopic invasion of tumor into the perithyroidal soft tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RAI-avid metastatic foci in the neck on the first posttreatment whole-body RAI scan</td>
</tr>
<tr>
<td></td>
<td>Aggressive histology (e.g., tall cell, hoboanl variant, columnar cell carcinoma)</td>
</tr>
<tr>
<td></td>
<td>Papillary thyroid cancer with vascular invasion</td>
</tr>
<tr>
<td></td>
<td>Clinical N1 or &gt;5 pathologic N1 with all involved lymph nodes &lt;3 cm in largest dimension(^a)</td>
</tr>
<tr>
<td></td>
<td>Multifocal papillary microcarcinoma with ETE and (BRAF^{V600E}) mutated (if known)(^a)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATA high risk</th>
<th>Macroscopic invasion of tumor into the perithyroidal soft tissues (gross ETE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incomplete tumor resection</td>
</tr>
<tr>
<td></td>
<td>Distant metastases</td>
</tr>
<tr>
<td></td>
<td>Postoperative serum thyroglobulin suggestive of distant metastases</td>
</tr>
<tr>
<td></td>
<td>Pathologic N1 with any metastatic lymph node (\geq 3) cm in largest dimension(^a)</td>
</tr>
<tr>
<td></td>
<td>Follicular thyroid cancer with extensive vascular invasion (&gt; 4 foci of vascular invasion)(^a)</td>
</tr>
</tbody>
</table>

\(^a\)Proposed modifications, not present in the original 2009 initial risk stratification system. See sections [B19]–[B23] and Recommendation 48B.

---

Haugen, 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer, *Thyroid* 2016
Persistent/Recurrent DTC: Scope of the problem

- Single Operation (90%)
- 2 operations (9%)
- >2 operations (1%)
Summary: Prevalence of DTC recurrences

• Recurrence in 10-25% of cases

• Recurrences arise from:
  – Disease biology (unavoidable)
  – Incomplete initial surgery (persistent disease, potentially avoidable)

• Most recurrences are discovered within 10 years of initial diagnosis

• Risk of recurrence may be modified by response to therapy (dynamic risk stratification)
Strategic framework for managing cervical recurrences of DTC
Re-operation is a predictor of mortality

- 11,986 patients over 10 years
- 222 reoperations

Young and Yeh, Effect of reoperation on outcomes in papillary thyroid cancer, Surgery 2013
Does re-operation alter the course of disease?

• If recurrence is merely an indicator of disease biology: NO

• If the recurrence itself is harmful: MAYBE

• Not all recurrences are alike
  – Timing (early vs late)
  – Location (local, nodal, distant)
  – Severity
    • Volume
    • Involvement of vital structures
What are the benefits of re-operation?

- Prolong life?
- Improve quality of life or reduce disability?
- Prevent further spread of tumor?
- Peace of mind
- I would like to be disease-free
Surgical decision-making

RISK

BENEFIT
Surveillance for thyroid cancer

- Blood tumor markers – thyroglobulin
- Anatomic imaging – ultrasound
- (Radioiodine scanning)
- PET scanning – generally insensitive, “flip-flop” phenomenon
- Special case: Tg antibody positive patients
### Informative value of Tg levels

**TABLE 2. Serum Tg and sites of metastases**

<table>
<thead>
<tr>
<th></th>
<th>All bone</th>
<th>Pure bone</th>
<th>All lung</th>
<th>Pure lung</th>
<th>All mediastinum</th>
<th>Pure mediastinum</th>
<th>All cervical</th>
<th>Pure cervical</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>38</td>
<td>7</td>
<td>91</td>
<td>15</td>
<td>74</td>
<td>5</td>
<td>104</td>
<td>31</td>
</tr>
<tr>
<td>Age (yr) Mean</td>
<td>57.4</td>
<td>57.6</td>
<td>53.7</td>
<td>42.7</td>
<td>51.7</td>
<td>41.2</td>
<td>49.8</td>
<td>40.6</td>
</tr>
<tr>
<td>Age (yr) SD</td>
<td>11.2</td>
<td>4.8</td>
<td>17.7</td>
<td>19.1</td>
<td>19.4</td>
<td>19.7</td>
<td>17.8</td>
<td>11.5</td>
</tr>
<tr>
<td>Prestimulated Tg (ng/ml) Median</td>
<td>687</td>
<td>48</td>
<td>34</td>
<td>8</td>
<td>25</td>
<td>4</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Prestimulated Tg (ng/ml) Minimum</td>
<td>5</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Prestimulated Tg (ng/ml) Maximum</td>
<td>65,400</td>
<td>1,000</td>
<td>65,400</td>
<td>1,160</td>
<td>62,000</td>
<td>16</td>
<td>65,400</td>
<td>120</td>
</tr>
<tr>
<td>Poststimulated Tg (ng/ml) Median</td>
<td>2,030</td>
<td>416</td>
<td>246</td>
<td>72</td>
<td>180</td>
<td>16</td>
<td>43</td>
<td>8</td>
</tr>
<tr>
<td>Poststimulated Tg (ng/ml) Minimum</td>
<td>12</td>
<td>12</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Poststimulated Tg (ng/ml) Maximum</td>
<td>97,400</td>
<td>3,000</td>
<td>88,000</td>
<td>2,060</td>
<td>97,400</td>
<td>82</td>
<td>97,400</td>
<td>1,760</td>
</tr>
<tr>
<td>Fold increase Median</td>
<td>2.5</td>
<td>2.4</td>
<td>3.3</td>
<td>5.0</td>
<td>3.2</td>
<td>2.5</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Fold increase Minimum</td>
<td>0.9</td>
<td>1.5</td>
<td>0.8</td>
<td>1.0</td>
<td>1.0</td>
<td>1.7</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Fold increase Maximum</td>
<td>19.2</td>
<td>8.7</td>
<td>34.0</td>
<td>17.0</td>
<td>41.0</td>
<td>41.0</td>
<td>34.0</td>
<td>14.7</td>
</tr>
<tr>
<td>Increment Median</td>
<td>1,032</td>
<td>368</td>
<td>130</td>
<td>42</td>
<td>80</td>
<td>12</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Increment Minimum</td>
<td>-9,720</td>
<td>4</td>
<td>-9,720</td>
<td>4</td>
<td>-600</td>
<td>0.4</td>
<td>-9,720</td>
<td>-1.4</td>
</tr>
<tr>
<td>Increment Maximum</td>
<td>42,400</td>
<td>2,000</td>
<td>26,000</td>
<td>1,940</td>
<td>42,400</td>
<td>80</td>
<td>42,400</td>
<td>1,640</td>
</tr>
</tbody>
</table>

Recurrence Scenario A

- I have a detectable Tg (> 2.0 ng/mL)
- But my doctors can’t find anything on imaging
- Q: What should I do?
  - A: Consider the Tg level and its context (TSH)
  - A: Consider the type of imaging
  - A: It is not worth pursuing a Tg level of zero at all costs
## Classifying response to therapy

<table>
<thead>
<tr>
<th>Response</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Excellent response (50%)</strong></td>
<td>• Recurrence &lt; 5%</td>
</tr>
<tr>
<td>No clinical or radiographic EOD</td>
<td>• Mortality &lt; 1%</td>
</tr>
<tr>
<td>Suppressed Tg &lt; 0.2 or stim Tg &lt; 1</td>
<td></td>
</tr>
<tr>
<td><strong>Biochemical incomplete response (20%)</strong></td>
<td>• 30% resolve spontaneously</td>
</tr>
<tr>
<td>No structural disease</td>
<td>• 20% resolve after further therapy</td>
</tr>
<tr>
<td>Suppressed Tg ≥ 1 or stim Tg ≥ 10</td>
<td>• 20% develop structural recurrence</td>
</tr>
<tr>
<td>TgAb rising</td>
<td>• Mortality &lt; 1%</td>
</tr>
<tr>
<td><strong>Structural incomplete response (10%)</strong></td>
<td>• 50-85% continue to have persistent disease despite additional therapy</td>
</tr>
<tr>
<td>Clinically or radiographically evident disease</td>
<td>• Mortality 11-50%</td>
</tr>
<tr>
<td><strong>Indeterminate response (20%)</strong></td>
<td>• 85% resolve or remain stable</td>
</tr>
<tr>
<td>Nonspecific imaging findings</td>
<td>• 15% develop structural recurrence</td>
</tr>
<tr>
<td>Low but detectable Tg</td>
<td>• Mortality &lt; 1%</td>
</tr>
<tr>
<td>TgAb stable or declining</td>
<td></td>
</tr>
</tbody>
</table>

Haugen, 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer, *Thyroid* 2016
Recurrence Scenario A

- Isolated biochemical recurrence with negative imaging
- Monitor, reassure
- Almost zero mortality
Recurrence Scenario B

• My doctor says there is “something” on my ultrasound. Uh oh.

Frequent Screening With Serial Neck Ultrasound Is More Likely to Identify False-Positive Abnormalities Than Clinically Significant Disease in the Surveillance of Intermediate Risk Papillary Thyroid Cancer Patients Without Suspicious Findings on Follow-Up Ultrasound Evaluation

Samantha Peiling Yang, Ariadne M. Bach, R. Michael Tuttle, and Stephanie A. Fish

Endocrinology Service (S.P.Y., R.M.T., S.A.F.), Department of Medicine, and Department of Radiology (A.M.B.), Memorial Sloan Kettering Cancer Center, New York, New York 10021; and Endocrinology Division (S.P.Y.), Department of Medicine, National University Hospital, Singapore 119228

Context: American Thyroid Association (ATA) intermediate-risk thyroid cancer patients who achieve an excellent treatment response demonstrate a low risk of structural disease recurrence. Despite this fact, most patients undergo frequent surveillance neck ultrasound (US) during follow-up.
Imaging findings during surveillance

• Some of these findings may be false alarms
• Imaging findings should be interpreted in the context of:
  – Original pathology (side and tumor aggressiveness)
  – Tg level
  – Timing of most recent surgery

• Discuss potential management strategies before you biopsy (with patient and surgeon)
Recurrence Scenario B

- Indeterminate imaging finding with low Tg
- Active surveillance is safe
- Many findings (esp nodal) will resolve
- Monitor for growth, persistence
Recurrence Scenario C

- Detectable or increasing Tg
- Suspicious mass on ultrasound
- Consider biopsy if risk/benefit of surgery acceptable
Tg elevated
- Neck ultrasound

Imaging abnormality
- Measure Tg, TgAb, TSH

TgAb present?
- Yes: Measure/trend TgAb by RIA
- No: Scenario compatible w/ isolated cervical disease?

Scenario compatible w/ isolated cervical disease?
- Yes: Extra-cervical imaging:
  1) Thin cut noncontrast CT chest
  2) NM bone survey metastases
  3) Whole body PET-CT

Discussion at multidisciplinary endocrine tumor board

Risk/benefit unfavorable

Risk/benefit favorable
- Consider lesion size <1 cm may be appropriate for observation
- FNA if appropriate
- Surgery

Risk/benefit favorable

Observation with ultrasound/Tg
Re-operations for cervical recurrences of DTC: Outcomes and techniques
Outcomes of re-operation

Lamartina, Surgery for neck recurrence of differentiated thyroid cancer: Outcomes and risk factors, J Clin Endocrinol Metab 2017
Outcomes of re-operation

- 62% initial complete response rate
- Predictors of incomplete response:
  - Age >45
  - Aggressive histology
- 25% rate of subsequent relapse
  - Male sex
  - Aggressive histology
  - >10 positive nodes removed at re-operation
- 9% complication rate

Lamartina, Surgery for neck recurrence of differentiated thyroid cancer: Outcomes and risk factors, J Clin Endocrinol Metab 2017
Risks of re-operation: Frank discussion!

- Generally at least double that of initial surgery
- Scar tissue
- Selection of aggressive tumor cases
- Permanent hoarseness: about 2%
- Permanent hypoparathyroidism: about 2%
- Major vascular injury
- Failure to achieve operative aims: experience-dependent
- Tracheostomy, temporary vs permanent: avoid endangering both recurrent nerves
Re-operation tips (1 of 2)

• Do you really want to do this?

• Are you operating in a previously dissected compartment?
  – No: Achieve compartment-oriented clearance
  – Yes: May settle for focused removal

• Use intraoperative ultrasound
  – Before incision
  – During dissection
  – Proofreading afterwards
Re-operation tips (2 of 2)

• Use frozen section
• Invest time orienting yourself
  – Airway
  – Carotid
• Be opportunistic: Go where the scar isn’t
• Central neck: Work outside in
• Have help nearby (thoracic, vascular)
• Know when to stop operating
Central neck recurrence
Lateral neck recurrence

- 43 yo M, 5.5 cm PTC in right lobe
- 2010: Total thyroidectomy, nerve sacrificed
- Tg elevated, more disease found
- 2010: Right neck dissection
- Tg elevated
Lateral neck recurrence
High-risk cervical recurrences

Contralateral nerve injury
Contralateral nerve injury
Severe recurrent central neck disease
Recurrent DTC: FAQs

• What about Tg-antibody positive patients?
• Do I give RAI after reoperation for DTC?
• What about percutaneous ethanol ablation?
Summary points: Recurrent DTC

• A minority of thyroid cancer patients require re-operation

• Pathway: elevated marker, anatomic target, ?FNA, assess risk/benefit

• Good initial surgery is the best chance for cure

• A little bit of Tg is okay, as are indeterminate US findings

• Re-operations are high-risk and must be carefully considered

• Complete/durable response is achievable in about half of patients who undergo re-operation