Practical Application of Ultrasound and Thyroglobulin for Post-Operative Surveillance of Well Differentiated Thyroid Cancer - 2018

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Surgical Compartments of the Neck

- **Compartment I**
  - Submandibular to the hyoid bone

- **Compartments II, III, IV**
  - From the vascular bundle deep to the SCM
  - Division by hyoid and cricoid

- **Compartment V**
  - Posterior to the SCM

- **Compartment VI**
  - The “central compartment”
Cervical Lymph Nodes

- Approximately 300 lymph nodes in the normal neck.
- Typically can identify 6 – 20 nodes by ultrasound.
- Nodes are more prominent following infections, mononucleosis, dental procedures and in Hashimoto’s thyroiditis.
Differentiated Thyroid Cancer

- 63,000 New cases of DTC in 2014
  - Doubled over last decade
- 1,890 Deaths
- Mortality unchanged over past 30 years
- Unproved assumption: Early detection and treatment of cervical metastases will affect mortality
  - Mortality versus Morbidity
Lymph Node Metastases in WDTC

- Gross lymph node metastases in up to 35%
- Microscopic metastases in up to 80%
- Likelihood of recurrence
  - Clinical stage
  - Extent of initial surgery
  - Modality used to detect recurrence
Risk of Structural Disease Recurrence
(In patients without structurally identifiable disease after initial therapy)

Modified 2009 Risks

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 PMC (≈ 4-6%)
pN1 No extranodal extension, ≤3 LN involved (2%)
Minimally invasive FTC (≈ 2-3%)
Intrathyroidal, < 4 cm, BRAF wild type* (≈ 1-2%)
Intrathyroidal unifocal PMC, BRAF mutated*, (≈ 1-2%)
Intrathyroidal, encapsulated, FV-PTC (≈ 1-2%)
Unifocal PMC (≈ 1-2%)

*While analysis of BRAF and or TERT status is not routinely recommended for initial risk stratification, we have included these findings to assist clinicians in proper risk stratification in cases where this information is available.
Assessing Response to Therapy

<table>
<thead>
<tr>
<th>Excellent Response</th>
<th>Indeterminate (good) Response</th>
<th>Incomplete Response</th>
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</thead>
<tbody>
<tr>
<td>Suppressed Tg</td>
<td>Detectable, but &lt; 1 ng/mL</td>
<td>&gt; 1 ng/mL</td>
</tr>
<tr>
<td>Stimulated Tg</td>
<td>&lt; 10 ng/mL Declining</td>
<td>&gt; 10 ng/mL Stable or rising</td>
</tr>
<tr>
<td>Tg Trend</td>
<td>Absent or declining</td>
<td>Persistent or rising</td>
</tr>
<tr>
<td>Tg antibodies</td>
<td>Normal Indeterminate</td>
<td>Palpable disease</td>
</tr>
<tr>
<td>Neck exam</td>
<td>Clinically Insignificant</td>
<td>Positive</td>
</tr>
<tr>
<td>Imaging</td>
<td></td>
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</tbody>
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Lower Risk Estimate
Stable Risk Estimate
Raise Risk Estimate

Courtesy of RM Tuttle
Application of Dynamic Risk Classification

Risk of Persistent/Recurrent Structural Disease

- initial
- excellent
- indeterminate
- incomplete

Tuttle RM, Thyroid 2010
Tests Used in Post-Operative Thyroid Cancer Surveillance

- Thyroglobulin
- $^{131}$I or $^{123}$I Whole Body Scan
- Ultrasound
Detection of LN metastases
WBS vs. Neck US

Frasoldati et al, Cancer 2003; Pacini et al, J Clin Endocrinol Metab 2003;
Torlontano et al, J Clin Endocrinol Metab 2004
Thyroglobulin for Detection of Recurrence

- Most sensitive marker for recurrence
- Detection limits have improved to <0.1
- High rate of “false positives”
- Difficulty if less than total thyroidectomy
- Difficulty if no RAI ablation

- Trend in TG (or TG Ab) more important for prognostication.
R65A: Following surgery, cervical US to evaluate the thyroid bed and central and lateral cervical nodal compartments should be performed at 6 to 12 months and then periodically, depending on the patients’ risk for recurrent disease and thyroglobulin status. (Strong recommendation, low quality evidence.)
R65B: If a positive result would change management, ultrasonographically suspicious lymph nodes >8-10 mm (see 71) in the smallest diameter should be biopsied for cytology with Tg measurement in the needle washout fluid. (Strong recommendation, low quality evidence.)
R65C: Suspicious lymph nodes less than 8-10 mm in smallest diameter may be followed without biopsy with consideration for FNA or intervention if there is growth or if the node threatens vital structures. (Weak recommendation, low quality evidence.)

(Contrast to 2009 R48C. Suspicious lymph nodes less than 5-8 mm in largest diameter may be followed…)

ATA guidelines 2015
CHANGING PARADIGMS

- Pre-op – Old: Find and detect all thyroid cancer
  New: Diagnose clinically relevant thyroid cancer

- Post surgery – Old: Find and eradicate all recurrences
  - 1990s – Berry picking
  - 2000s – Compartmental dissection
  - 2010s – Active surveillance
  
  New: Treatment of progressive, threatening, or advancing disease
1994 – Dr Mazzaferri’s Thyroid Cancer

- Detected by physical exam
- Most palpable nodules > 1.5 cm
- 20,000 per year
- Treatment: Total thyroidectomy
  - Radioactive iodine
- Surveillance: Physical exam,
  - TG >0.9,
  - Scan (w/d)
- 30% recurrence rate with 20% distant mets
2018 – Our Thyroid Cancer

- Many/most detected incidentally
- 63,000 per year
- 90% less than 1.5 cm (nonpalpable)
- Treatment: Partial thyroidectomy, Selective radioactive iodine
- Surveillance: Ultrasound, TG >0.2 (or >2 stimulated by thyroglobulin).
Factors in decision to resect nodes

- Location – Threatening vital structures
- Age and comorbidities
- Patient emotional concerns
- Adverse histology (tall cell, insular…)
- TG doubling time
- Inability to concentrate RAI
- High SUV on PET scan
- Progressive growth of nodes, extra-nodal extension…

Tufano et al, Thyroid 25(1) 2015
Locations of PTC nodal recurrences

- Ipsilateral ONLY, 12%
- Ipsilateral "skip metastases"
- Central and bilateral, 13%
- Central ONLY, 22%
- Bilateral only, 1%
- Central and ipsilateral, 52%

87% involve Central LNs

Leboulleux J Clin Endocrinol Metab 2005
Node Shape Variations

- Central Compartment
  - Paratracheal nodes
- Post surgical neck
  - Loss of usual tissue planes
- Hashimoto’s
  - Matted Inflammatory
Paratracheal Nodes
Hashimoto’s Thyroiditis
Hashimoto’s Thyroiditis
Node Size Variations

- There is no absolute size limit.
  - Compartments III, IV
    - 5 mm AP (?) NO!!
  - Compartment II
    - 8 – 10 mm AP (?) NO!!

- Role for repeat evaluation over time
  - Reactive nodes vary over time without progressive growth.
Large Benign Node - Compartment 2

D 1: 15.8 mm
D 2: 9.1 mm

D 1: 25.9 mm
D 2: 8.4 mm
Compartment 3 - Benign

D 1:  10.2 mm  
D 2:  5.7 mm  

D 1:  16.4 mm  
D 2:  5.4 mm
Compartment 3 – Benign – 6 months later

D 1: 8.1 mm
D 2: 3.8 mm

D 1: 12.6 mm
D 2: 3.0 mm
Compartment 3 – Benign – 6 months later

10/07

4/08
Compartmental Approach to Comprehensive Neck Ultrasound 1

- Scan the right thyroid bed (VI) from subclavian to thyroid cartilage.
- Center transducer over the right CCA and IJ and sweep from subclavian to submandibular. (IV, III, II)
- Reposition transducer so that the vessels are at the far right of the screen and sweep from subclavian to submandibular. (IV, III, II under SCM)
- Sweep lateral to the SCM (V)
Inspect the submandibular region (I).
Inspect the CCA and IJ and the area between them in the sagittal plane. (IV, III, II)
Repeat above process for the contralateral side.
Note: Perform evaluation of each compartment completely before taking images.
For any abnormal appearing nodes take images in two planes and characterize vascularity, calcification, and cystic degeneration.
Role of cross sectional imaging in setting of rising thyroglobulin:

Neck MRI or CT with contrast for clinically occult nodes
- Retropharynx
- Parapharyngeal space
- Low cervical lymph nodes
- Mediastinum

Consider in patients with prior metastatic LNs in anterior cervical compartments

Kaplan, Mandel J Neuroradiol, 2009
Role of CT and MRI

- Recommendation 69
  Cross-sectional imaging of the neck and upper chest (CT, MRI) with IV contrast should be considered 1) in the setting of bulky and widely distributed recurrent nodal disease where ultrasound may not completely delineate disease, 2) in the assessment of possible invasive recurrent disease where potential aerodigestive tract invasion requires complete assessment or 3) where neck ultrasound is felt to be inadequately visualizing possible neck nodal disease (high TG, negative neck US) (Strong recommendation, Moderate-quality evidence)
History of thyroid cancer, rising thyroglobulin
Left retropharyngeal lymph node

Kaplan, Mandel J Neuroradiol, 2009
Ultrasound in the post-op surveillance of well differentiated thyroid cancer – Conclusions

- Dynamic assessment of risk of recurrence will guide intensity of surveillance.
- Nodal risk factors include numerous (>5) nodes, large nodes (>3cm), aggressive subtypes, and extranodal extension.
- New guidelines recommend close observation of nodes less than 8-10 mm in smallest dimension.