Ultrasound for Pre-operative and Post-operative **Evaluation** of Well Differentiated Thyroid Cancer

Its Not Just About the Nodes

**AACE/ACE Advanced Neck Ultrasound Training Course™**

Robert A. Levine, MD, FACE, ECNU
Thyroid Center of New Hampshire
Geisel School of Medicine at Dartmouth College
No disclosures.
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”
ATA Risk of Recurrence - Stratification Based on Initial Staging - 2009

- LOW RISK
  - Classic PTC / WDTC
  - Complete resection
  - No Extra-thyroidal extension.
  - No vascular invasion

- INTERMEDIATE RISK
  - Microscopic Extra-thyroidal extension
  - Cervical Lymph node Mets
  - Aggressive Histology
  - Vascular invasion

- HIGH RISK
  - Macroscopic gross Extra-thyroidal extension
  - Incomplete tumor resection
  - Thyroglobulin elevation
  - Distant Mets
## 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
- $\leq 5$ LN micrometastases ($< 0.2$ cm)

---

FTC, extensive vascular invasion ($\approx 30-55\%$)
- pT4a gross ETE ($\approx 30-40\%$)
- pN1 with extranodal extension, >3 LN involved ($\approx 40\%$)
- PTC, $> 1$ cm, TERT mutated $\pm$ BRAF mutated* ($>40\%$)
- pN1, any LN $> 3$ cm ($\approx 30\%$)
- PTC, extrathyroidal, BRAF mutated* ($\approx 10-40\%$)
- PTC, vascular invasion ($\approx 15-30\%$)
- Clinical N1 ($\approx 20\%$)
- pN1, $> 5$ LN involved ($\approx 20\%$)
- Intrathyroidal PTC, $< 4$ cm, BRAF mutated* ($\approx 10\%$)
- pT3 minor ETE ($\approx 3-8\%$)
- pN1, all LN $< 0.2$ cm ($\approx 5\%$)
- pN1, $\leq 5$ LN involved ($\approx 5\%$)
- Intrathyroidal PTC, 2-4 cm ($\approx 5\%$)
- Multifocal PMC ($\approx 4-6\%$)
- pN1 with extranodal extension, $\leq 3$ LN involved (2%)
- Minimally invasive FTC ($\approx 2-3\%$)
- Intrathyroidal, $< 4$ cm, BRAF wild type* ($\approx 1-2\%$)
- Intrathyroidal unifocal PMC, BRAF mutated*, ($\approx 1-2\%$)
- Intrathyroidal, encapsulated, FV-PTC ($\approx 1-2\%$)
- Unifocal PMC ($\approx 1-2\%$)

*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.
Pre-operative Comprehensive Neck Ultrasound

- The pre-operative neck US is for more than just cervical lymph nodes.
  - Evaluate thyroid for signs indicative of high risk of aggressive disease
    - Size of primary tumor.
    - Suggestion of multifocality.
    - Location of cancer (Adjacent to trachea or recurrent laryngeal nerve).
    - Suspicion of extrathyroidal extension.
Thyroid sonography with survey of the cervical lymph nodes should be performed in all patients with known or suspected thyroid nodules. (Strong recommendation, High-quality evidence)

Sonographic evaluation of the anterior cervical lymph node compartments (central and lateral) should be performed whenever thyroid nodules are detected. If ultrasound detects cervical lymph nodes that are sonographically suspicious for thyroid cancer (Table 8), FNA of the suspicious lymph node should be performed for cytology and washout for thyroglobulin measurement if indicated. In addition, this scenario also warrants US-guided FNA of a subcentimeter nodule that is likely to represent the primary tumor based upon sonographic features.
RECOMMENDATION 32

A) Preoperative neck US for cervical (central and especially lateral neck compartments) lymph nodes is recommended for all patients undergoing thyroidectomy for malignant or suspicious for malignancy cytologic or molecular findings. (Strong recommendation, Moderate-quality evidence)

B) US-guided FNA of sonographically suspicious lymph nodes > 8-10 mm in the smallest diameter should be performed to confirm malignancy if this would change management. (Strong recommendation, Moderate-quality evidence)

C) The addition of FNA-Tg washout in the evaluation of suspicious cervical lymph nodes is appropriate in select patients, but interpretation may be difficult in patients with an intact thyroid gland. (Weak recommendation, Low-quality evidence)
Characteristics of Benign Lymph Nodes

- Flattened or oval shape
  - Short / long axis < 0.5
- Echogenic (hilar) line
- Vascular flow limited to hilum on Doppler
- Size varies with compartment and is less important than morphology.
- Border characteristics are also less important.
Characteristics of Metastatic Lymph Nodes

- Calcifications
- Cystic necrosis
- Chaotic (peripheral) vascularization
- Rounded appearance
  - Short/Long Axis > 0.5
- Jugular displacement
- Absent echogenic (hilar) line
Table 8: Ultrasound features of lymph nodes predictive of malignant involvement. (adapted with permission from the European Thyroid Association guidelines for cervical ultrasound (20)

<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>
A correlation performed between US findings and pathology at surgery (292) has shown for lymph nodes > 7 mm in the smallest diameter, that a cystic appearance or hyperechoic punctuations in a context of thyroid cancer should be considered as malignant; lymph nodes with a hyperechoic hilum are reassuring; the type of vascularization (central: reassuring; peripheral: concerning) has a high sensitivity/specificity; a round shape, a hypoechoic appearance or the loss of the hyperechoic hilum by themselves does not justify a FNAB.

Interpretation of neck US should take into account all other clinical and biological data.
Disordered (peripheral) vascularity
Size > 3cm is associated with high risk of Recurrent disease
Jugular Displacement
Papillary Carcinoma – Tall Cell – Calcified Node
Papillary Carcinoma – Node – Chaotic Vascularity
Pre-operatively, central compartment lymph nodes are often much more difficult to visualize than lateral nodes, but should be investigated.
Investigation of the central compartment includes inferior to the thyroid.
Prognostic Indicators for Recurrence
Nodal factors

- Lymph node metastases larger than 3 cm
- Extra-nodal extension
- More than 5 lymph nodes involved
- Aggressive Subtype (Tall Cell, TERT)
- High ratio of positive/removed nodes
ATA 2015 Guidelines
Threshold size of Lymph Nodes for Biopsy

RECOMMENDATION 32

A) Preoperative neck US for cervical (central and especially lateral neck compartments) lymph nodes is recommended for all patients undergoing thyroidectomy for malignant or suspicious for malignancy cytologic or molecular findings. (Strong recommendation, Moderate-quality evidence)

B) US-guided FNA of sonographically suspicious lymph nodes $>8-10$ mm in the smallest diameter should be performed to confirm malignancy if this would change management. (Strong recommendation, Moderate-quality evidence)

C) The addition of FNA-Tg washout in the evaluation of suspicious cervical lymph nodes is appropriate in select patients, but interpretation may be difficult in patients with an intact thyroid gland. (Weak recommendation, Low-quality evidence)
Should this solitary <0.7 cm metastatic node undergo biopsy prior to thyroidectomy?
Should this solitary 0.6 cm atypical node undergo biopsy prior to thyroidectomy?
The pre-operative neck US assesses more than just cervical lymph nodes.

- Evaluate the thyroid for signs indicative of high risk of aggressive disease
  - Size of index thyroid lesion.
  - Multifocality.
  - Suspicion of extrathyroidal extension.
- Location of cancer
  - Adjacent to trachea or RLN
  - Isthmus lesions have higher rate of ETE
Preoperative Factors Associated with Higher Risk of Recurrence

- Lesion factors
  - Extrathyroidal Extension (ETE)
  - Location (Adjacent to RLN or trachea)
  - Nodes - Number and size (ENE)
  - Percent of tumor abutting thyroid capsule
- Signs or symptoms of invasion of RLN or trachea
- FNAB findings of high grade malignancy
- Patient factors
  - Familial cancer, radiation
Extra-thyroidal extension is difficult to detect

- 79 Thyroid cancers evaluated for ETE on pre-op ultrasound, both 2D and 3D.
- Mean size 1 cm
  - 71% <1cm
- 52/79 (66%) showed extra-thyroidal extension.
  - ETE ➔ pT3 or pT4
- Accuracy for predicting ETE 61%
  - Increased to 68% if combined with 3D US

Extrathyroidal Extension into Strap Muscles
Suspicious for Extrathyroidal Extension
Suspicious for Extrathyroidal Extension
Extensive abutment of thyroid capsule suggests a high risk for ETE

Pre-operative Ultrasound Conclusions

- A comprehensive central / lateral preoperative ultrasound should be performed in all patients undergoing surgery for thyroid cancer.
- Risk stratification should aid in planning the extent of thyroid surgery, as well as the need for a high volume thyroid surgeon.
- Consider biopsy of ANY suspicious nodes.
- Additional factors including: size, location, extrathyroidal extension and abutment ratio should be considered in surgical planning.
- Provide a detailed pre-operative map.
Comprehensive Post–operative cervical ultrasound evaluation

- 1st evaluation at 4-6 months after surgery.
- Subsequent intervals based on initial risk of recurrence and dynamic risk stratification.
- ATA guidelines: 6-12 months and “then periodically”.
Fig 8. Influence of nodal status at initial operation on cumulative risk of recurrence (any site). Graphs are based on 892 patients without initial distant metastases and with complete tumor resection.
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>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.2 ng/ml</td>
<td>Detectable, but &lt; 1 ng/mL</td>
<td>&gt; 1 ng/mL</td>
</tr>
<tr>
<td>&lt; 1 ng/ml</td>
<td>&lt; 10 ng/mL</td>
<td>&gt; 10 ng/mL</td>
</tr>
<tr>
<td>Low Absent</td>
<td>Declining Absent or declining</td>
<td>Persistent or rising</td>
</tr>
<tr>
<td>Normal Negative</td>
<td>Normal Indeterminate Clinically insignificant</td>
<td>Palpable disease Positive</td>
</tr>
</tbody>
</table>

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
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
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
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.