Ultrasound for Pre-operative and Post-Operative Surveillance of Well Differentiated Thyroid Cancer

AACE/ACE Advanced Endocrine Neck Ultrasound Training Course™
2016
Differentiated Thyroid Cancer

- 62,500 New cases of DTC in 2015
  - Doubled over last decade
- 1,950 Deaths
- Mortality not significantly changed over past 30 years
- Assumption: Early detection and treatment of cervical metastases will affect mortality
  - Mortality versus Morbidity
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.
Preoperative Imaging

- WDTC clinically involves lymph nodes in approximately 20% of patients. (Micrometastases in up to 90%)
- Pre-op US identifies suspicious lateral neck nodes in approximately 14% of cases.
- Surgical management is altered in the presence of lateral neck metastases
  - Total Thyroidectomy
  - Central Neck Dissection! (ATA Guidelines 2015)
  - Lateral Neck Dissection

Kouvaraki, Surgery 2003 134:946; Stulak, Arch Surg 2006 141:489
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 with 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.
ATA Risk of Recurrence - Stratification Based on Initial Staging

- **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
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”
Value of pre-operative US

- 17 patients underwent reoperation for thyroid cancer MD Anderson <6months after initial surgery

- PRE-OP US would have prevented 70% or the reops!!!
Clinical (PE) Lymph Node (LN) Metastases at Presentation: WORSE Outcome

Hay, Surgery 1992

![Graph showing local and nodal recurrence rates](image)

- Local Recurrence
- Nodal Recurrence

Recurrence (%) vs. Years after initial surgery

- LN positive
- LN negative

p<0.001

Hay, Surgery 1992
US Detects about 40% of Pathologically Abnormal LNs

US (-), PATHOLOGY (+) LN Metastases: NO IMPACT on Outcome

Ito, Word J Surg 2004
Recurrences occurred significantly more often if ultrasound demonstrated abnormal nodes preoperatively

460 patients underwent thyroidectomy and modified neck dissection

Recurrence rate

US Neg 3.1%

US Pos 24.8%

US neg LNs 455 pts

US + LNs 105 pts

Recurrences occurred significantly more often if ultrasound demonstrated abnormal nodes preoperatively

Does lateral neck dissection alter the outcome for preoperative US positive for lymph nodes?

Prophylactic lateral neck dissection does NOT improve recurrence free survival for patients with preoperative US negative for lymph nodes

Ito, World J Surg 2004
For “macroscopic” lateral lymph node metastases, modified neck dissection at time of initial thyroidectomy *improves* survival.

Noguchi, Arch Surg, 1998 133 276-280
RECOMMENDATION 6

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)
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.
    - Multifocality.
    - Location of cancer (Not Adjacent to trachea or RLN).
    - Suspicion of extrathyroidal extension.
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
Tests Used in Post-Operative Thyroid Cancer Surveillance

- Thyroglobulin
- $^{131}$I or $^{123}$I Whole Body Scan
- Ultrasound
Diagnosis of Recurrent DTC in 51 of 494 Patients

- $^{131}$I Whole Body Scan 23 (45%)
- Tg > 2ng/ml (off T4 therapy) 29 (57%)
- Tg detectable 34 (67%)
- Ultrasound 48 (94%)

Frasoldati, et al; *Cancer* 2003
RECOMMENDATION 65

A) Following surgery, cervical US to evaluate the thyroid bed and central and lateral cervical nodal compartments should be performed at 6–12 months and then periodically, depending on the patient’s risk for recurrent disease and Tg status. (Strong recommendation, Moderate-quality evidence)

B) If a positive result would change management, ultrasonographically suspicious lymph nodes > 8-10 mm (see Recommendation 71) in the smallest diameter should be biopsied for cytology with Tg measurement in the needle washout fluid. (Strong recommendation, Low-quality evidence)

ATA guidelines 2015
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C) 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)

D) Low-risk patients who have had remnant ablation, negative cervical US, and a low serum Tg on thyroid hormone therapy in a sensitive assay (<0.2 ng/ml) or after TSH-stimulation (Tg <1 ng/ml) can be followed primarily with clinical examination and Tg measurements on thyroid hormone replacement. (Weak recommendation, Low-quality evidence)
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
2016 – 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 >0.1 (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
Where do we look for metastatic lymph nodes?
Locations of PTC nodal recurrences

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

87% involve Central LNs

Leboulleux J Clin Endocrinol Metab 2005
Post-operative Neck
Characteristics of Benign Lymph Nodes

- Flattened or oval shape
  - Short / long axis < 0.5
- Echogenic (hilar) line
- Hilar vascular flow on Doppler
- Size varies with compartment and is less important than morphology.
- Border definition also less important.
The Hilar Line

- A normal node can be split down the central hilum.
- Hilum contains fat and vessels
- A normal hilar line can be thin or thick, and can be central or eccentric/diagonal.
- The presence of a hilar line is reassuring.
Normal lymph node - hilus
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
Compartment 3 – Benign – 6 months later
Compartment 3 – Benign – 6 months later
Characteristics of Metastatic Lymph Nodes

- Absent echogenic (hilar) line
- Rounded appearance - Short/Long Axis > 0.5
- Jugular displacement
- Calcifications
- Cystic necrosis
- Chaotic (peripheral) vascularization
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.
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In low and intermediate risk patients, the risk of lymph node recurrence is low (<2%) in patients with undetectable serum Tg level and is much higher in those with detectable/elevated serum Tg. In fact, 1 g of neoplastic thyroid tissue will increase the serum Tg by ~1 ng/ml during LT4 treatment and by ~2-10 ng/ml following TSH stimulation (788;800). Neck US can detect N1 as small as 2-3 mm in diameter (in whom serum Tg may be low or undetectable), but benefits of their early discovery (<8-10 mm) is not demonstrated.
Figure 4
Risk of Structural Disease Recurrence
(In patients without structurally identifiable disease after initial therapy)

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Central Compartment Node
Disordered (peripheral) vascularity
Jugular Displacement
Papillary Carcinoma – Tall Cell – Calcified Node
Papillary Carcinoma – Node – Chaotic Vascularity
Soft-tissue metastasis
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)
Compartmental Approach to Comprehensive Neck Ultrasound 2

- Inspect the submandibular region (I).
- Inspect the CCA and IJ and the area between them in the sagital 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.
Thyroid bed
Along vascular bundle
Lateral Compartments II, II, IV
Under SCM
(Far) Lateral compartments
Role of cross sectional imaging in setting of rising thyroglobulin:

Neck 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

CT guided FNA

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, but numerous factors need to be considered in the decision regarding observation versus resection.