Metastatic Lymph Nodes in Thyroid Cancer: Why they matter, how to find them

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• I have no disclosures related to this presentation
US and LNs in Papillary Thyroid Cancer Pts

- Features of metastatic lymph nodules that impact prognosis
- Ultrasound imaging
  - Normal lymph nodes
  - Metastatic lymph nodes
  - Minimal residual disease . . .
- What to do?

Randolph GW 2012 Thyroid 22:1144
A case to start:

43 y.o. woman with 3.2cm right sold nodule, detected by palpation and confirmed by US
FNA → papillary thyroid cancer
Does she need any pre-op testing?
R21. Preoperative neck ultrasound for . . . cervical (central and especially lateral neck compartments) lymph nodes is recommended for all patients undergoing thyroidectomy for malignant cytologic findings on biopsy. Recommendation B

ATA Guidelines 2006, 2009 www. thyroid.org
AACE/AME/ETA Guidelines 2010  www.aace.com
Consensus Statement on the Terminology and Classification of Central Neck Dissection for Thyroid Cancer

Carty et al Thyroid Nov 2009
Pre-op US changes surgery by detection of abnormal NONpalpable LATERAL LN

Kouvaraki, Surgery 2003; Stulak, Arch Surg 2006
Do cervical lymph node metastases at presentation make a difference?
TNM: Initial disease stage predicts OVERALL SURVIVAL

Jonklaas, Thyroid 2006

Stage I LN+ <45
Stage II
Stage III Central LNs+ >45
Stage IV IVa Lateral LNs+ ≥45

Survival
Year

p<0.001
But, lymph nodes NOT in other survival scoring systems

- AMES (age, mets, size)
- AGES (age, grade, extent, size)
- MACIS (mets, age, completeness of surgery, invasiveness, size)
Spectrum of LN metastases

- Spectrum from micrometastasis to gross bulky adenopathy
- Number dependent upon extent of surgery and pathologic dissection
- "clinically apparent" metastatic LNs definition: palpation v.s. ultrasound
Micromet

LN almost replaced by tumor

Extranodal extension
Lymph node mets at presentation predict recurrence

Size of metastases
Number
Location
Patient factors
SIZE of LN metastasis predicts RECURRENCE

- If routine neck dissection performed, small volume microscopic LNs present
  - Up to 80% central neck
  - ~35% lateral neck
- However, if not performed, this is NOT incidence of clinical recurrence
- Detection by
  - Palpation examination (intraop, preop)
  - Ultrasound
  - Pathologic examination
SIZE of LN metastasis predicts recurrence. Micromet on pathology.

170 pts: near total thyrx, central and ipsilateral neck dissection, I-131 Rx

- macro mets: n=49
- micro mets (<2mm): n=20
- no mets: n=101

Recurrence (%)

p=0.015 univariate

Cranshaw Surg Oncol 2008 17:253-258
SIZE of LN metastasis predicts RECURRENT
Ultrasound detection

460 pts → thyrx, LATERAL neck dissection

Disease-free survival (%)

US neg LNs
455 pts

US+ LNs
105 pts

57% path pos
43% path neg

P < 0.0001
univariate

11%

25%

SIZE of LN metastasis predicts \textbf{RECURRENCE}

Ultrasound detection

Central neck dissection in:
79 pts with US pos LNs and 119 pts with US neg LNs

\textbf{Disease Free Survival (\%)}

\begin{itemize}
\item Normal US, NO dissection (n=133)
\item Normal US, prophylactic dissection (n=119) 71\% LN+, 29\% LN neg
\item Abnormal US, therapeutic dissection (n=79)
\end{itemize}

\textbf{Years after surgery}

\textbf{Moreno et al 2012 Thyroid 22: 347-55}
SIZE of LN metastasis predicts recurrence
Ultrasound detection

US only detects about 30% of pathologically abnormal central and lateral LNs
BUT, if LNs are NOT ABNORMAL on US, lateral neck dissection does not change recurrence

US NEGATIVE, PATHOLOGY+ lateral neck LN mets: NO IMPACT on outcome

NUMBER of Lymph node mets at presentation predict RECURRENCE

Risk stratification by number of met LNs
Sugitani > 5
Leboulleux >10

Log-Rank p<0.0001

n= 2070
Follow-up Years
Multivariable analysis
p=0.043

Leboulleux J Clin Endocrinol Metab 2005 90:5723
LOCATION: LATERAL neck lymph node mets at presentation predict RECURRENCE

Intrathyroidal tumor

Multivariable analysis
p=0.02

Central neck LNs

Lateral neck LNs

n= 522

Cumulative Disease-Free Survival

P<.001

P=.15

months 10 yrs

Beasley Arch Otolaryngol 2002
But with the advent of US, US detected CENTRAL neck lymph node mets at presentation predict **RECURRENTNESS**

![Graph showing disease free survival](image)

- **US neg LNs** $n=252$
- **US pos LNs** $n=79$

$p <0.05$ bivariate with age

$n= 331$

**Moreno 2012 Thyroid 22:347**
Patients OLDER \( \geq 45 \text{yo} \) with macroscopic LN mets have a high risk for **RECURRENT**E than younger patients.

**Palpable Lymphadenopathy at Presentation**

- **NO** (n=201)
  - If \( \geq 45 \text{yo} \): 42% recurrence
  - If \(< 45 \text{yo} \): 27% recurrence

- **YES** (n=30)

Multivariable analysis

\( p = <0.005 \)

Wada Eur J Surg Oncol 2008 34:202
Disease specific mortality

• Analysis in few studies with variable results
• SEER—older pts with more metastatic LNss
So, if lymph nodes predict increased risk for recurrence and maybe death\(^1\), does lymph node resection improve **RECURRENCE rates** and/or **SURVIVAL**?

\(^1\) Mazzaferri, Am J Med 1994; Mazzaferri, Kloos, J Clin Endocrinol Metab 2001
RECURRENTE lower with comprehensive neck dissection for macroscopic lymph node mets at DX

"Berry picking (n=58)

Systematic LN dissection, II-IV, VI (n=60)

p=0.01 multivariable
Therapeutic central or lateral neck dissection decreases recurrence for US + LN pts

Prophylactic lateral neck dissection does not alter outcome for US negative LN pts

How do we detect recurrence?

80% occur within 10 years of DX

Detection of LN metastases
I-131WBS vs. Neck US

Frasoldati et al, Cancer 2003; Pacini et al, J Clin Endocrinol Metab 2003; Torlontano et al, J Clin Endocrinol Metab 2004
R48a Following surgery, cervical ultrasound 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. Recommendation B
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

Lebouleux J Clin Endocrinol Metab 2005
US of normal cervical lymph nodes

- **Shape**
  - **OVAL** assessed by short to long (S:L) axis ratio
  - S:L is < 0.5 → oval; S:L ≥ 0.5 → round
  - HOWEVER, normal submandibular LN (95%) may be round!

- **Echogenic hilus (hypoechoic cortex)**
  - consists of fatty tissue, sinuses, intranodal vessels
  - visualized in larger nodes (90% with transverse > 5mm)

- **Vascularity**
  - hilar vascularity (90% with transverse > 5mm) or **avascular** (smaller nodes, usually posterior triangle)
Normal lymph node - hilus
Normal lymph node

- Fatty hilus
- Hilar vascularity
Normal lymph node

TRANSVERSE view

Ratio 4mm/10mm=0.4
Right cervical lymph node

PRF: pulse repetition frequency <800Hz
Wall filter: LOW
Two normal lymph nodes right Level IV

heterogeneous

sagittal

fatty hilus

Absent vascularity
US of abnormal cervical lymph nodes

- **SHAPE:** Round shape \(-S:L > 0.5\) \(\Rightarrow\) round

- **ECHOGENICITY:** Metastatic papillary thyroid cancer LNs may be **hyperechoic** or **hypoechoic** compared to surrounding strap muscles

- **ABSENCE OF HILUS:** tumor infiltration of sinuses

- **CYSTIC CHANGE**

- **CALCIFICATIONS**

- **VASCULARITY:** aberrant vessels enter **peripherally** in the nodal capsule. With increased tumor infiltration, increased vascularity in both **peripheral** and **central** zones
Right level 4 LN hyperechoic, with calcifications and increased vascularity
Hyper- and hypoechoic vascular left lateral LNs
Cystic Lymph Node
Lymph node with focus of papillary thyroid cancer (normal shape)

Sagittal

superior

inferior

normal hilar vascularity

increased vascularity
Lymph node with metastatic medullary thyroid cancer
What are the best criteria for identification of abnormal LNs?

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral vascularity</td>
<td>86%</td>
<td>82%</td>
</tr>
<tr>
<td>Microcalcifications</td>
<td>46%</td>
<td>100%</td>
</tr>
<tr>
<td>Cystic change</td>
<td>11%</td>
<td>100%</td>
</tr>
<tr>
<td>Absent hilus</td>
<td>~95%</td>
<td>20%</td>
</tr>
<tr>
<td>Hypoechoic</td>
<td>39%</td>
<td>18%</td>
</tr>
</tbody>
</table>

LeBoulleux, J Clin Endocrinol Metab, 2007; Ahuja Clin Radiol 2001
32 yo with PTC, TSH 0.12, Tg 0.3, TgAb <0.4
June 20, 2012
32 yo with PTC, TSH 0.12, Tg 0.3, TgAb <0.4
July 27, 2012

June 20, 2012
Neck anatomy can challenge our ability to detect lymph nodes.

Hiding place
After comprehensive neck dissection, where are the missed nodes???
What do we do when US detects an abnormal LN?

R48b  If a positive result would change management, ultrasonographically suspicious lymph nodes greater than 5 – 8 mm in the smallest diameter should be biopsied for cytology with thyroglobulin measurement in the needle washout fluid. Recommendation A

ATA guidelines 2009
Does re-operative LN dissection do anything?

- After reoperation with compartmental or regional neck dissections, 30-50% of patients have stimulated Tg <1 ng/ml\(^1,2\)
- Post op stimulated Tgs >5 are predictive of additional recurrences\(^2\)

Multiple recurrences decrease survival

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\(^1\)Al-Saif J Clin Endocrinol Metab 2010 95:2187; Yim J Clin Endocrinol Metab 2011 96:2049;
\(^2\)Carsten 2004 Arch Otolaryngol Head Neck Surg 130: 819
What is the significance of minimal disease?

- Recurrence versus residual disease
- Cost/benefit of surgery
Minimal residual/recurrent disease

strap muscle

scar tissue
Do small US suspicious cervical LNs grow?

- 166 PTC patients with sonographically abnl LNs outside thyroid bed followed for >1 yr
  - Increased vascularity (41%), calcifications (40%), cystic (24%), absent hilus (22%), round shape (21%), hypoechoic (18%), heterogeneous (18%)
- Median LN size 1.3cm (range 0.5 to 2.7cm)
- Median f/u 3.5 yrs, median of 6 US exams
  - 33 pts (20%) LN growth ≥ 3mm
  - 15 pts (9%) LN growth ≥5mm
- No sonographic or clinical feature reliably predicted LN growth

Robenshtok et al, J Clin Endocrinol Metab epub May 25 2012
R48c  Suspicious lymph nodes less than 5-8 mm in largest diameter may be followed without biopsy with consideration for intervention if there is growth or if the node threatens vital structures. Recommendation C
To summarize

• In papillary thyroid cancer, prognosis (recurrence, ? Survival) is influenced by metastatic lymph nodes at diagnosis
  – Size (US vs. pathologic detection)
  – Number
  – NOT necessarily location
  – Patient age

• Sonography
  – Recognition of suspicious lymph nodes
    • At initial surgery--implications for prognosis both in central and lateral neck
    • During follow up--uncertain
What to do? The challenge of when to treat

- After initial surgery—is I-131 always required?
  - Definition of micro mets
  - Limited number of involved LNs
- During surveillance, just because we can see it and FNA it, does it need to be removed?
- Patients with multiple recurrences have a reduced disease-specific survival