Integrating guidelines, experience and clinical judgement in the management of thyroid cancer:

How will the guidelines affect surgical management

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Disclosures

• Member, Data Monitoring Committee of the Medullary Thyroid Cancer Consortium Registry, supported by NovoNordisk, GlaxoSmithKline, AstraZeneca, Eli Lilly
Rising incidence of thyroid cancer

- 2.4-fold increase in total thyroid cancer, driven by papillary thyroid cancer (PTC)
- Increasing proportion of smaller vs. larger PTCs over time
- Relatively stable mortality rates
- “We believe increased diagnostic scrutiny is the most likely explanation for the apparent increase in incidence.”

Davies L, Welch HG. JAMA 2006;295:2164-7
But is there more to the story?

Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. JAMA 2017;317(13):1338-48
Thyroid cancer incidence trends (1974-2013), by histology

Total (n=77,276): APC=3.6*

Papillary (n=64,625): APC=4.4*

Follicular (n=8,359): 0.6*

Medullary (n=1,685): 0.7*

Other/unspecified (n=1,632): -0.6

Anaplastic (n=975): -0.1
PTC incidence trends (1974-2013), by SEER stage at diagnosis

Localized (n=45,919): APC=4.6*

Regional (n=25,835): APC=4.3*

Distant (n=3,658): APC=2.4*

Unknown (n=1,864): APC=1.8*
PTC incidence trends (1983-2013), by size at diagnosis

≤1 cm (n=19,943): APC=9.3*
1.1-2.0 cm (n=18,113): APC=5.4*
2.1-4.0 cm (n=16,031): APC=4.5*
>4.0 cm (n=6,713): APC=6.1*
Unknown (n=8,879): APC=-1.8
Thyroid cancer mortality trends (1994-2013), by type and histology

Total U.S. (n=28,652): APC=0.9*
SEER-9 (n=2,596): APC=1.0*
SEER-9 IBM (total, n=2,371): APC=1.1*
Papillary (n=1,063): APC=1.7*
Anaplastic (n=471): APC=0.9
Follicular (n=404): APC=-0.2
Other/unspecified (n=244): APC=2.4
Medullary (n=189): APC=-0.7
PTC mortality trends (1994-2013), by SEER stage at diagnosis

Regional (n=566): APC=1.7
Distant (n=308): APC=2.9*
Localized (n=143): APC=2.1
Unknown (n=46): APC=not reported
PTC mortality trends (1994-2013), by size at diagnosis

≤2.0 cm (n=182): APC=6.8*  
2.1-4.0 cm (n=274): APC=4.3*  
>4.0 cm (n=277): APC=2.8  
Unknown (n=275): APC=-0.6
Conclusions

• Increasing incidence and thyroid cancer mortality rates for advanced-stage PTC suggest overdiagnosis is not the only explanation for rising thyroid cancer incidence.

• Environmental exposures may have contributed.

• Despite excellent prognosis for most thyroid cancer patients, improvements are needed in treating advanced-stage PTC.
Goals of Initial Therapy

• To improve cancer-related survival
• To minimize the risk of disease recurrence and metastatic spread
• To permit accurate long-term surveillance for disease recurrence
• To permit accurate staging of disease
• To minimize treatment-related morbidity

Adapted from ATA Guidelines, Cooper DS, Thyroid, 2006
Updated 2009
Updated 2016
How much surgery is too much, or not enough?

Risks of misdiagnosis, long-term outcome uncertainty
Patient preferences
Medico-legal considerations
Costs to patients and payers

Avoid undertreatment of clinically significant cancer
Avoid overtreatment of indolent lesions
Less is sometimes more, and
More is sometimes less!

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Important surgery-related topics

- Optimal use of preoperative imaging
- Extent of thyroid resection
- Appropriate use of prophylactic central lymph node dissection
- Perioperative management of voice and calcium
A case

38 yo female is referred for an incidental 1-2 cm thyroid nodule on routine exam. No radiation or family history

TSH 1.2 mU/L

US – 1.3 x 1.1x 0.9 cm solid, isoechoic nodule. No other suspicious features or abnormal lymph nodes
Preop imaging: Critical role of ultrasound

• **2009**: Preop US for the contralateral lobe and cervical lymph nodes is recommended for all patients undergoing thyroidectomy for malignant cytologies.

• **2017**: Preop US for cervical lymph nodes is recommended for all patients undergoing thyroidectomy for malignant or suspicious for malignancy cytologic or molecular findings. (Strong recommendation, Moderate quality evidence)
...is unchanged

- 2009 and 2017: US-guided FNA of sonographically suspicious lymph nodes should be performed if this would change management. (Strong recommendation, Moderate quality evidence)
The case, with US limitations

- Now on US, the patient has bulky cervical lymphadenopathy and the inferior border of the involved nodes cannot be appreciated...
In 2009,

- Routine preop use of other imaging studies (CT, MRI, PET) is not recommended. (Recommendation rating: E)
The role of cross-sectional imaging as an adjunct
In 2017,

- Preop use of cross-sectional imaging with IV contrast is recommended as an adjunct to US for patients with clinical suspicion for advanced disease. (Strong recommendation, low-quality evidence)
Combined preop US/CT can enhance detection of macroscopic nodal disease resulting in change of surgical strategy in 25% of patients.

TABLE 3. Group I (primary patients): diagnostic accuracy characteristics of nodal detection tests.

<table>
<thead>
<tr>
<th></th>
<th>Evaluation of lateral neck</th>
<th>Evaluation of central neck</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PE</td>
<td>US</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>38%</td>
<td>79%</td>
</tr>
<tr>
<td>Specificity</td>
<td>93%</td>
<td>87%</td>
</tr>
<tr>
<td>95% CI</td>
<td>79–98</td>
<td>70–95</td>
</tr>
<tr>
<td>PPV</td>
<td>79%</td>
<td>80%</td>
</tr>
<tr>
<td>95% CI</td>
<td>69–89</td>
<td>70–90</td>
</tr>
<tr>
<td>NPV</td>
<td>69%</td>
<td>86%</td>
</tr>
<tr>
<td>95% CI</td>
<td>60–78</td>
<td>78–94</td>
</tr>
</tbody>
</table>

Cross sectional imaging can clarify involvement of:

- Nodal regions difficult to visualize on routine US, including the mediastinum, infraclavicular, retropharyngeal and para-pharyngeal regions.
- Larynx, trachea, esophagus, or blood vessels
When cross-sectional imaging is performed, IV contrast is a useful adjunct.

FIG. 1. (A) The results of urinary iodide in all 25 patients collected in 24 hours (24U) at the baseline, first week, and first, second, and third month after iodinated contrast agents (ICA) (in logarithmic scale). (B) The results of urinary iodide in all 25 patients collected in spot sample (sU) at the baseline, first week, and first, second, and third month after ICA (in logarithmic scale).

-Padovani et al Thyroid 2012
The case: A PTmC

38 yo female is referred for an incidental 7 mm thyroid nodule on routine exam. No radiation or family history

TSH 1.2 mU/L

US – 1.3 x 1.1x 0.9 cm solid, isoechoic nodule. No other suspicious features or abnormal LN

FNAB of nodule is positive for PTC.

How should this be managed?
Surveillance bias:
Incidence of thyroid cancer by size
SEER, 1988-2009
Safety of active surveillance in a large prospective cohort

Tumor enlargement

Nodal metastases

Ito et al, Thyroid 2014
Is PTMC an over-treated entity?
Probably

- More patients are undergoing total thyroidectomy (73 vs 25% lobectomy) and RAI (31%) despite a lack of evidence this translates into survival benefit.
- It is important to distinguish patients with risk factors that predispose for high risk for recurrence.

-Wang et al, WJS 2014
Recommendation

- If surgery is chosen for PTMCs w/o extrathyroidal extension and cN0, initial surgery should be lobectomy unless there are clear indications to remove the contralateral lobe. Lobectomy is sufficient for small, unifocal, intrathyroidal carcinomas in the absence of prior head and neck irradiation, family history, or nodal metastases.
The case: A low-risk PTC

38 yo female is referred for an incidental 1-2 cm thyroid nodule on routine exam. No radiation or family history

TSH 1.2 mU/L

US – 1.3 x 1.1x 0.9 cm solid, isoechoic nodule. No other suspicious features or abnormal LN

FNAB of nodule is positive for PTC.

What thyroid operation should be performed, lobectomy or total thyroidectomy?
Total thyroidectomy

- For thyroid cancer >1 cm, initial surgery should be total thyroidectomy unless there are contraindications. Lobectomy may be sufficient for <1 cm, low-risk, unifocal, intrathyroidal PTCs w/o prior head/neck irradiation or nodal metastases. (Recommendation rating: A) - ATA Guidelines 2009
Bilimoria et al. 2007:

52,173 PTC patients
National Cancer Database (NCDB)
1985-1998

Overall survival:

Total thyroidectomy vs. lobectomy
Total thyroidectomy was associated with improved overall survival ≥1 cm.

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>&lt; 1.0 cm</th>
<th>≥ 1.0 cm</th>
<th>1.0–2.0 cm</th>
<th>2.1–4.0 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>42,952</td>
<td>10,247</td>
<td>32,705</td>
<td>12,778</td>
<td>16,365</td>
</tr>
<tr>
<td>Recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total thyroidectomy</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>1.57 (1.20–2.06)</td>
<td>1.01 (0.77–1.32)</td>
<td>1.15 (1.02–1.30)</td>
<td>1.24 (1.01–1.54)</td>
<td>1.26 (1.03–1.42)</td>
</tr>
<tr>
<td></td>
<td><em>P = 0.001</em></td>
<td><em>P = 0.24</em></td>
<td><em>P = 0.04</em></td>
<td><em>P = 0.04</em></td>
<td><em>P = 0.03</em></td>
</tr>
<tr>
<td>Survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total thyroidectomy</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>1.21 (1.02–1.44)</td>
<td>1.02 (0.74–1.41)</td>
<td>1.31 (1.07–1.60)</td>
<td>1.49 (1.02–2.17)</td>
<td>1.31 (1.01–1.69)</td>
</tr>
<tr>
<td></td>
<td><em>P = 0.027</em></td>
<td><em>P = 0.83</em></td>
<td><em>P = 0.009</em></td>
<td><em>P = 0.04</em></td>
<td><em>P = 0.04</em></td>
</tr>
</tbody>
</table>

Hazard Ratios greater than 1.0 indicate increased risk of recurrence or death.

*Adjusted for gender, age, race, nodal status, distant metastases, socioeconomic factors, RAI administration, year of diagnosis, and hospital volume.*
Thyroid lobectomy advocates

- Less morbidity (hypocalcemia and RLN injury)
- No need for thyroid hormone replacement
- Equivalent survival
Total thyroidectomy is associated with more complications even in the hands of high-volume surgeons.

Figure 1. Risk of complication by surgeon volume and type of thyroidectomy

Low surgeon volume is <10 thyroidectomies/year; intermediate surgeon volume is 10-99 thyroidectomies/year; high surgeon volume is >99 thyroidectomies/year.

Hauch et al SSO 2014
To examine the association between extent of surgery and overall survival among patients with papillary thyroid carcinoma 1-4 cm.
# Tumor/treatment characteristics

<table>
<thead>
<tr>
<th></th>
<th>Lobectomy (N=6849)</th>
<th>Total Thyroidectomy (N=54926)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor size</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0-2.0 cm</td>
<td>60%</td>
<td>59%</td>
<td>NS</td>
</tr>
<tr>
<td>2.1-4.0 cm</td>
<td>40%</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td><strong>Multifocality</strong></td>
<td>29%</td>
<td>44%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Extrathyroidal extension</strong></td>
<td>5%</td>
<td>16%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Nodal metastases</strong></td>
<td>7%</td>
<td>27%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Distant metastases</strong></td>
<td>0.4%</td>
<td>1.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Positive surgical margin</strong></td>
<td>7%</td>
<td>27%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>RAI administration</strong></td>
<td>33%</td>
<td>65%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
## Adjusted survival analysis

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>Total thyroidectomy vs. lobectomy</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjusted hazard ratio</strong> (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0-2.0 cm</td>
<td>1.05 (0.88-1.27)</td>
<td>0.57</td>
</tr>
<tr>
<td>2.1-4.0 cm</td>
<td>0.87 (0.72-1.06)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

*Adjusted for: age, gender, race, annual income, insurance status, hospital volume, patient comorbidities, tumor multifocality, extrathyroidal extension, lymph node involvement, distant metastases, surgical margins, and radioactive iodine (RAI) treatment.
In 2017,

- For patients with thyroid cancer >1 cm and <4 cm w/o extrathyroidal extension, and cN0, the initial surgery can be *either* total thyroidectomy (high-risk tumors with nodal mets, requiring RAI) *or* thyroid lobectomy (low and medium-risk tumors).
The case: pCLND?

38 yo female is referred for an incidental 1-2 cm thyroid nodule on routine exam. No radiation or family history

TSH 1.2 mU/L

US – 1.3 x 1.1x 0.9 cm solid, isoechoic nodule. No other suspicious features or abnormal LN

FNAB of nodule is positive for PTC.

What is the role for routine prophylactic central lymph node dissection?
Compartments of the neck
Debate continues.

- Pro
  - May improve disease-specific survival, local recurrence, post-op Tgb levels
  - Will detect some pN1 disease (but this prognostically is not equivalent to cN1 disease)
  - Can inform use of RAI
  - Can improve risk estimates of recurrence
  - Safe in the hands of high-volume surgeons

- Chisholm 2009
- Bonnet 2009
- Laird 2012
- Moreno 2012
- Barczynski 2013
- Sancho 2014
Consensus is lacking. An RCT has not been done.

- **Cons**
  - No improvement in long-term outcomes, while
  - Increasing the likelihood of short-term post-op morbidity, including hypocalcemia

-Hughes 2010
-Wang 2012
-Yoo 2012
-Raffaelli 2012
Recurrence rate of TT: 7.9%
Recurrence rate of TT/pCCND: 4.7%
Relative risk of recurrent PTC after TT/pCCND: 0.59 (95% CI: 0.33 – 1.07)
Number needed to treat to prevent one recurrence: 31
Postoperative complications

Permanent hypocalcemia: Relative risk 1.82 (95% CI: 0.51 – 6.5)

Permanent RLN injury: Relative risk 1.82 (95% CI: 0.46 – 2.83)
Prophylactic central neck dissection (unchanged from 2009)

• Thyroidectomy \(w/o\) pCLND *may be appropriate* for patients who are cN0 with:
  – Small (T1 or T2) PTCs,
  – Non-invasive PTCs, and
  – Most follicular cancer.

  *(Strong Recommendation, Moderate-quality evidence)*
Prophylactic central neck dissection *(changed from 2009)*

- pCLND *should be considered* for cN0 PTC patients and:
  - Advanced primary tumors (T3 or T4)
  - Clinically involved lateral neck nodes (cN1b)
  - *If the information will be used to plan further steps in therapy.*

  - (Weak Recommendation, Low-quality evidence)
Alternative approaches are acceptable.

• For pts with increased risk of metastasis or recurrence (older or very young age, larger tumors, multifocal dz, extrathyroidal extension, lateral node mets)
• If nodal staging will inform decisions about adjuvant therapy.
• A selective approach for pts with clinically evident disease preop, or intraop demonstration of detectable disease.
Setting Limits: Lymph Node Removal & Thyroid Cancer

A new study seeks to establish a clinical guideline to quantify the risk of metastatic lymph nodes in thyroid cancer patients. The findings should go a long way to help ease the mind of the patients...and the physicians.

With thyroid cancer incidence on the rise, especially papillary thyroid cancer, surgical tumor resection is a critical component of the overall treatment plan, which might also include one or more of several adjuvant treatment options such as concomitant lymph node (LN) dissection.

The American Cancer Society notes that although an estimated 63,450 new cases of

...
How Many Lymph Nodes Are Enough? Assessing the Adequacy of Lymph Node Yield for Papillary Thyroid Cancer

Timothy J. Robinson, Samantha Thomas, Michaela A. Dinan, Sanziana Roman, Julie Ann Sosa, and Terry Hyslop

**Fig 2.** Probability of a false-negative lymphadenectomy as a function of number of lymph nodes examined in a patient with truly lymph node-positive disease.

**Fig 3.** Probability of occult nodal disease on the basis of American Joint Committee on Cancer tumor stage.
What is an adequate lymphadenectomy?
- We estimate that 6, 9, and 18 LN need to be removed to ensure a reasonably adequate LN evaluation for patients with T1b, T2, and T3 disease.
- As few as 3, 4 and 8 LN are needed for patients with T1b, T2, and T3 disease undergoing true pCLND.

Robinson et al, JCO 2016
The case: Voice

38 yo female is referred for an incidental 1-2 cm thyroid nodule on routine exam. No radiation or family history

TSH 1.2 mU/L

US – 1.3 x 1.1 x 0.9 cm solid, isoechoic nodule. No other suspicious features or abn LN

What is the status of their voice?
In 2009
In 2017, All pts undergoing thyroid surgery should have preop voice assessment as part of their physical examination. This should include the patient’s description of vocal changes, as well as the physician’s assessment of voice. (Strong recommendation, Moderate-quality evidence)
The case: Hoarseness

38 yo female is referred for an incidental 1-2 cm thyroid nodule on routine exam and the complaint of subjective raspiness and change in voice over the last 3-4 months.
Indications for preop laryngeal exam

• Pre-op voice abnormalities (Strong recommendation, Moderate-quality evidence)
• B) H/o cervical/upper chest surgery which places the RLN or vagus nerve at risk. (Strong recommendation, Moderate-quality evidence)
• C) Known thyroid cancer with posterior extrathyroidal extension or extensive central nodal metastases. (Strong recommendation, Low-quality evidence)
In other words, selective use of pre-op laryngeal exam.

• Vocal cord paresis/paralysis is seen in
  – 0-3.5% of benign disease
  – Up to 8% of thyroid cancer

• Vocal cord paralysis suggests locally invasive dz.

• 10-15% of thyroid cancers present with extrathyroidal extension; 47% of these involve RLN
A compromised RLN has important implications.

• Undiagnosed preop dysfunction conveys greater risk during total thyroidectomy of postop bilateral nerve paralysis, respiratory distress, and need for tracheostomy.

• Patient counseling is potentially improved.

• Surgical algorithms should incorporate nerve functional status (threshold for sacrificing nerve, anticipation of nerve reconstruction, management of the contralateral lobe).
It is essential to see and protect the RLN.

- Visual identification of the RLN during dissection is required. Steps should be taken to preserve the external branch of the superior laryngeal nerve during dissection of the superior pole. (Strong recommendation, Moderate-quality evidence)
Preservation of the parathyroids

• The parathyroid glands and their blood supply should be preserved during thyroid surgery. (Strong recommendation, High-quality evidence)
Routine post-op voice assessment and selective laryngeal exam.

- Patients should have their voice assessed in the postop period. Formal laryngeal exam should be performed if the voice is abnormal. (Strong recommendation, Moderate-quality evidence)
The case at hand:

- The patient underwent total thyroidectomy and se were任 Level VI nodes, and she has hypopcalcemia that delays discharge and requires calculatingqh iseo calcium in Universidad keep. and high dose calcitriol/calcium supplementation at discharge.
Communication is essential.

- Important intra-op findings and details of postop care should be communicated by the surgeon to the patient and other physicians who are important in the patient’s postop care. *(Strong recommendation, Low-quality evidence)*
The operation should be selected in the setting of the larger overall treatment strategy formulated by the care team.
Alternative causes and prevention!
Management of advanced disease.