Initial surgery for differentiated thyroid cancer: What is the appropriate extent and attendant risks and benefits?

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Disclosure

Member and ATA representative, Medullary Thyroid Cancer Registry Data Monitoring Committee funded by GlaxoSmithKline, Novo Nordisk, Astra Zeneca, and Eli Lilly
Epidemic of thyroid cancer

• Thyroid cancer is the most common endocrine malignancy.
• Fastest increasing cancer
• The 8th (2005) → 5th (2013) most incident cancer among women
• Anticipated to be 3rd (2019)

Women 805,500

- 29% Breast
- 14% Lung & bronchus
- 9% Colon & rectum
- 6% Uterine corpus
- **6% Thyroid**
- 4% Non-Hodgkin lymphoma
- 4% Melanoma of skin
- 3% Kidney & renal pelvis
- 3% Pancreas
- 3% Ovary
- 19% All Other Sites

American Cancer Society 2013; 2005
SEER Stat Fact Sheets 2013: Thyroid Cancer
Cost of care of thyroid carcinoma, 2013-2030

Millions

2013

2030

Lubitz, et al., Cancer 2014
Thyroid Cancer and Bankruptcy

- Any cancer doubles the risk of bankruptcy
- **Thyroid cancer carried one of the highest risks – 3.5X**
- Most patients file bankruptcy in the first year following the cancer diagnosis

The incidence rates of bankruptcy at one year after diagnosis, per 1,000 person-yrs

107% increase in thyroid FNAs, 2006-2011

- Thyroid FNAs more than doubled: 16% compounded annual percentage change
- Thyroid FNAs increased as a percentage of all FNAs, from 49% to 65%.

Sosa et al 2013
ATA guidelines for the management of thyroid nodules and differentiated thyroid cancer

2013
2014
2015
A process of evolution
2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer

- The 4 surgeons:
  David Steward
  Jerry Doherty
  Greg Randolph
  Julie Ann Sosa
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

Risk stratification

Adapted from ATA Guidelines, Cooper DS, *Thyroid*, 2006
Updated 2009
Updated 2015
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
Surveillance bias: Incidence of thyroid cancer by size SEER, 1988-2009

Rate (per 100,000)

0.1-1.0 cm
1.1-2.0 cm
2.1-3.0 cm
>4.0 cm
Is the identification and eradication of all PTMCs a worthwhile goal?
Challenges

• To identify those tumors destined to become aggressive before they develop disease progression or at a point in progression at which intervention will still be very effective.

• Confirmation of appropriateness and safety of observation of PTMCs.
Follow up 1235 patients, 1993-2011 (mean, 75 mos)
- Patients were divided by age (<40, 40-59, ≥60 yrs)
- Disease progression defined by:
  - Size enlargement
  - New lateral nodal mets
  - Progression to clinical dz (Tumor ≥12 mm or lateral mets)
Tumor enlargement

Nodal metastases
The proportion of patients with PTMC progression was lowest in the old patients and highest in the young patients. On multivariate analysis, young age was an independent predictor of PTMC progression.
Conclusion

• Older patients with low-risk PTMC may be the best candidates for observation.

• PTMC in young patients is more progressive, but it might not be too late to perform surgery after subclinical PTMC has progressed to clinical disease, regardless of age.
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.
Extent of surgery: controversy

Total thyroidectomy:

- Eradication of possible bilateral disease
- Ability to use of radioactive iodine
- Easier detection of recurrence

Lobectomy:

- Indolent disease with excellent prognosis
- Higher risks for complications and need for thyroid hormone replacement with more extensive surgery
  
  No survival benefit

Thyroid nodule-related surgery increased 31%, 2006-11

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
Total thyroidectomy

Bilimoria et al. 2007:

52,173 PTC patients from National Cancer Database (1985-1998)
Overall survival benefit with total thyroidectomy for tumors ≥1 cm

American Thyroid Association (ATA) guidelines:

Lobectomy: tumors <1 cm
Total thyroidectomy: tumors >1 cm

Cooper DS, et al. *Thyroid* 2009
Total thyroidectomy was associated with improved survival for tumors $\geq 1$ cm.

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>&lt; 1.0 cm</th>
<th>$\geq 1.0$ 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>$P = 0.001$</td>
<td>$P = 0.24$</td>
<td>$P = 0.04$</td>
<td>$P = 0.04$</td>
<td>$P = 0.03$</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>$P = 0.027$</td>
<td>$P = 0.83$</td>
<td>$P = 0.009$</td>
<td>$P = 0.04$</td>
<td>$P = 0.04$</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

Thyroid lobectomy for treatment of well differentiated intrathyroidal malignancy

Iain J. Nixon, MD, a Ian Ganly, MD, PhD, a Snehal G. Patel, MD, a Frank L. Palmer, BA, a
Monica M. Whitcher, BA, a Robert M. Tuttle, MD, b Ashok Shaha, MD, a and
Jatin P. Shah, MD, a New York, NY

- 889 pts with pT1 and T2 intra-thyroidal WDTCs treated 1986-95 at MSKCC
- 59% had total thyroidectomy, 41% lobectomy
- Median follow up: 99 mos
- OS, DSS, and RFS were measured
There was no difference in locoregional recurrence or DSS between total thyroidectomy and lobectomy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lobectomy n = 361</th>
<th>Total thyroidectomy n = 528</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45 yr</td>
<td>195 (54)</td>
<td>230 (44)</td>
<td>.002</td>
</tr>
<tr>
<td>&gt;45 yr</td>
<td>166 (46)</td>
<td>298 (56)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>82 (23)</td>
<td>106 (20)</td>
<td>.345</td>
</tr>
<tr>
<td>Female</td>
<td>279 (77)</td>
<td>422 (80)</td>
<td></td>
</tr>
<tr>
<td>pT stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT1</td>
<td>249 (69)</td>
<td>388 (73)</td>
<td>.143</td>
</tr>
<tr>
<td>pT2</td>
<td>112 (31)</td>
<td>140 (27)</td>
<td></td>
</tr>
<tr>
<td>RAI</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No</td>
<td>360 (99.7)</td>
<td>333 (63)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (0.3)</td>
<td>195 (37)</td>
<td></td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Papillary Ca</td>
<td>310 (86)</td>
<td>490 (93)</td>
<td></td>
</tr>
<tr>
<td>Follicular Ca</td>
<td>36 (10)</td>
<td>16 (3)</td>
<td></td>
</tr>
<tr>
<td>Hürthle cell Ca</td>
<td>15 (4)</td>
<td>22 (4)</td>
<td></td>
</tr>
<tr>
<td>10-yr local recurrence</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>10-yr neck recurrence</td>
<td>0 (0)</td>
<td>5 (0.8)</td>
<td>.96</td>
</tr>
<tr>
<td>10-yr distant recurrence</td>
<td>0 (0)</td>
<td>5 (3)</td>
<td>.05</td>
</tr>
<tr>
<td>10-yr deaths of any cause</td>
<td>18 (7)</td>
<td>27 (9)</td>
<td>.64</td>
</tr>
<tr>
<td>10-yr disease-specific deaths</td>
<td>0 (0)</td>
<td>1 (1.5)</td>
<td>.246</td>
</tr>
</tbody>
</table>

RAI, Radioiodine ablation.
Thyroid Lobectomy for Papillary Thyroid Cancer: Long-term Follow-up Study of 1,088 Cases


- Retrospective study of 1088 pts with PTC who underwent lobectomy, 1986-95
- No patients received RAI.
- Median follow-up was 17.6 yrs.
Cause-specific survival

(a) CSS rate
CSS rates
10-Year: 99.4%
15-Year: 98.5%
20-Year: 97.8%
25-Year: 95.2%

(b) Age
- < 45 years old (n = 483)
- ≥ 45 years old (n = 605)

(c) Primary tumor size
- ≤ 40 mm (n = 979)
- > 40 mm (n = 109)

(d) Extrathyroidal invasion
- negative (n = 1004)
- positive (n = 84)

(e) Clinical lymph node metastasis
- negative (n = 1019)
- positive (n = 69)

(f) Lymph node dissection
- none (n = 130)
- central (n = 60)
- central and lateral (n = 898)
And more concern...

Concerns regarding Bilimoria et al; exclusion of possible confounders:
  - Patient comorbidities
  - Multifocality
  - Extrathyroidal extension
  - Adequacy of resection

Mendelsohn et al 2010
  - 22,724 patients with PTC
  - No difference in survival between lobectomy and total thyroidectomy

To examine the association between extent of surgery and overall survival among patients with papillary thyroid carcinoma 1-4 cm.
Study variables

National Cancer Data Base

>1500 hospitals

85% of all incident thyroid cancer cases in the U.S.

Independent variables

Demographics: Age, gender, race, income

Patient comorbidities: Charlson Deyo scores

Pathology: Tumor size, multifocality, extrathyroidal extension, nodal/ distant metastases

**Extent of surgery: Lobectomy, total thyroidectomy**

Dependent variable/Outcome

Overall survival
## Patient characteristics (N=61775)

<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>Female</td>
<td>81%</td>
<td>79%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&lt;45</td>
<td>51%</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td>45-64</td>
<td>37%</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>12%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>White</td>
<td>88%</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>7%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>4%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td>0</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**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>1.0-4.0 cm</td>
<td>Adjusted hazard ratio* (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.95 (0.83-1.04)</td>
<td>0.40</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.
Total thyroidectomy (2009)

• ‘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
Total thyroidectomy or lobectomy (2015)

- ‘For patients with thyroid cancer >1 cm and <4 cm w/o extrathyroidal extension, and cN0, the initial surgery can be \textit{either} total thyroidectomy (high-risk tumors with nodal mets, requiring RAI), \textit{or} thyroid lobectomy (low and medium-risk tumors).’

-ATA Guidelines 2015
Less is sometimes more, and
More is sometimes less!
The operation should be selected in the setting of the larger overall treatment strategy formulated by the care team. Patient preference is critical when evaluating relative risks and benefits.
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)*
Medullary thyroid cancer: Differences in extent of initial surgery

Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma

The American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma

ATA Recommendation 24

• Patients with MTC and no evidence of neck lymph node metastases by US examination and no evidence of distant metastases should have a total thyroidectomy and dissection of the lymph nodes in the central compartment (level VI). Grade B Recommendation
ATA Recommendation 25

• In patients with MTC, no evidence of neck metastases on US, and no distant metastases, dissection of lymph nodes in the lateral compartments (levels II–V) may be considered based on serum calcitonin levels.

• The Task Force did not achieve consensus on this recommendation. Grade I Recommendation
ATA Recommendation 26

• Patients with MTC confined to the neck and cervical lymph nodes should have a total thyroidectomy, dissection of the central lymph node compartment (level VI), and dissection of the involved lateral neck compartments (levels II–V).

• When preop imaging is (+) in the ipsilateral lateral neck compartment but (-) in the contralateral neck compartment, contralateral neck dissection should be considered if the basal serum calcitonin level is greater than 200 pg/mL. Grade C Recommendation
Surgeon experience and patient outcomes

When less isn’t more.
Variability in surgeon volume thresholds (20-100 cases/yr)

Annual surgeon volume (continuous variable)

1-9 10-99 ≥100

1-9 9-19 20-50 51-99 ≥100

Variability in surgeon volume thresholds (20-100 cases/yr)

1-9

≥100

Stavrakis A
Is there a minimum number of thyroidectomies a surgeon should perform to optimize patient outcomes?

- On May 18, 2015, leaders at Dartmouth–Hitchcock Medical Center, the Johns Hopkins Hospital and Health System, and the University of Michigan Health System publicly announced a “Take the Volume Pledge” campaign to prevent certain surgical procedures from being performed by their surgeons who perform relatively few of them or at their hospitals where relatively few such procedures are performed.

(Adam et al, American College of Surgeons Clinical Congress, Chicago, 2015)
Annual surgeon volume (range 1-157 cases)
Statistical analysis

1. Unadjusted analysis:
   Chi-square; Wilcoxon

2. Adjusted survival analysis:
   Adjusted Kaplan-Meier
   Cox proportional hazards

3. Number of lymph nodes on survival
   Restrictive Cubic Splines
Non-Linear Association

Mean Daily Temperature in Montreal 2013-2014

Date


Mean Temperature (Celsius)

O Mean Temperature (Celsius) Regression
1. Piecewise polynomial functions
2. Relax the linearity assumption in multivariable regression analyses
3. Examine a relationship between a continuous predictor and an outcome in the setting of a non-linear relationship
Adjusted association of surgeon volume and patient outcomes

Threshold
25 cases/yr
Definition of high-volume surgeons

Cohort
(Total thyroidectomy)

Low-volume
<25 cases/yr

High-volume
≥25 cases/yr
# Adjusted* outcomes in low- vs. high-volume groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Effect</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall complications</td>
<td>OR 1.55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LOS</td>
<td>↑ 23%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inflation-adjusted costs</td>
<td>↑ 7%</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Adjusted for effect of age, gender, race, comorbidities, thyroid diagnosis
Increased risk of complications compared to a high-volume surgeon

<table>
<thead>
<tr>
<th>Cases/yr</th>
<th>Surgeons</th>
<th>Increased complication risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51%</td>
<td>68%</td>
</tr>
<tr>
<td>2-5</td>
<td>34%</td>
<td>55%</td>
</tr>
<tr>
<td>6-10</td>
<td>7%</td>
<td>35%</td>
</tr>
<tr>
<td>11-15</td>
<td>3%</td>
<td>19%</td>
</tr>
<tr>
<td>16-20</td>
<td>1%</td>
<td>9%</td>
</tr>
<tr>
<td>21-24</td>
<td>1%</td>
<td>2%</td>
</tr>
</tbody>
</table>
Conclusions

• Surgeon volume is significantly associated with improved outcomes, shorter hospitalization, and lower costs.

• The threshold number of total thyroidectomy cases for improved outcomes is 25/yr.

• The majority of patients underwent surgery by low-volume surgeons.
Implications

• Value-based care
  • Safe, appropriate, and effective care with good results at optimized cost

• Identification of a threshold for referral criteria and reimbursement

• Surgical education
Acknowledgments

www.dcri.org/our-research/endocrine-neoplasia-research-group