How Will (Should) the Latest Guidelines Affect the Endocrinologist’s Management of Thyroid Cancer?

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Outline

• Some statistics
• New guidelines grading system
• New/changed guidelines
• Summary review of the guidelines

Disclosures

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Consultant for Eisai
# Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States

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<table>
<thead>
<tr>
<th>New cases</th>
<th>Total</th>
<th>Women</th>
<th>Men</th>
</tr>
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<tbody>
<tr>
<td>Thyroid 2010</td>
<td>45,000</td>
<td>34,000</td>
<td>11,000</td>
</tr>
<tr>
<td>2020</td>
<td>92,000</td>
<td>71,000</td>
<td>21,000</td>
</tr>
<tr>
<td>2030</td>
<td>183,000</td>
<td>144,000</td>
<td>39,000</td>
</tr>
</tbody>
</table>

| Breast 2010 | 226,000 |
| 2020 | 262,000 |
| 2030 | 294,000 |

In 2030, Thyroid will be #2 in women and #9 in men

Projected death rate stable at 2,000
### Adapted ACP system

<table>
<thead>
<tr>
<th>Recommendation and Evidence Quality</th>
<th>Description of supporting evidence*</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong Recommendation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-quality evidence</td>
<td>RCT without important limitations or overwhelming evidence from observational studies</td>
<td>Can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>Moderate-quality evidence</td>
<td>RCT with important limitations or strong evidence from observational studies</td>
<td>Can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>Low-quality evidence</td>
<td>Observational studies/case studies</td>
<td>May change when higher-quality evidence available</td>
</tr>
<tr>
<td><strong>Weak Recommendation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-quality evidence</td>
<td>RCT without important limitations or overwhelming evidence from observational studies</td>
<td>Best action may differ based on circumstances or patients’ values</td>
</tr>
<tr>
<td>Moderate-quality evidence</td>
<td>RCT with important limitations or strong evidence from observational studies</td>
<td>Best action may differ based on circumstances or patients’ values</td>
</tr>
<tr>
<td>Low-quality evidence</td>
<td>Observational studies/case studies</td>
<td>Other alternatives may be equally reasonable</td>
</tr>
<tr>
<td><strong>Insufficient</strong></td>
<td>Evidence is conflicting, poor quality or lacking</td>
<td>Insufficient evidence to recommend for or against</td>
</tr>
</tbody>
</table>
Examples of Grading changes

• 2009 Recommendation: Measure serum TSH during the initial evaluation of a patient with a thyroid nodule. (Recommendation A)

• 2015 Recommendation: Measure serum TSH during the initial evaluation of a patient with a thyroid nodule. (Strong recommendation, Moderate-quality evidence)
Are the new guidelines different from the 2009 guidelines?

Goal: To be evidence-based and helpful

<table>
<thead>
<tr>
<th></th>
<th>2009</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendations</td>
<td>80</td>
<td>101</td>
</tr>
<tr>
<td>Sub-recommendations</td>
<td>103</td>
<td>175</td>
</tr>
<tr>
<td>References</td>
<td>437</td>
<td>1078</td>
</tr>
<tr>
<td>Tables</td>
<td>5</td>
<td>17</td>
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<tr>
<td>Figures</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

New questions - 8
New recommendations - 21
Significantly changed recommendations - 21
Haugen BR, Cancer 2016
Examples of Strong Recommendations Based on Low-quality Evidence

**Recommendation 33A:** Preoperative use of cross-sectional imaging studies (CT, MRI) with intravenous (IV) contrast is recommended as an adjunct to US for patients with clinical suspicion for advanced disease.

**Recommendation 33B:** Routine preoperative $^{18}$FDG-PET scanning is not recommended.
Sonographic patterns

• **High suspicion [malignancy risk 70-90%]:** Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with one or more of the following features: irregular margins, microcalcifications, taller than wide shape.

• **Intermediate suspicion [malignancy risk 10-20%]:** Hypoechoic solid nodule without high suspicion features

• **Low suspicion [malignancy risk 5-10%]:** Isoechoic or hyperechoic solid nodule, or partially (> 50%) cystic nodule, with eccentric solid area without high suspicion features

• **Very low suspicion [<3%]:** Spongiform or partially cystic nodules without high or intermediate suspicion features

• **Benign [<1%]:** Purely cystic nodules
Microcalcifications, hypoechoic nodule
irregular margins
irregular margins, taller than wide
irregular margins, extrathyroidal extension
nodule with irregular margins, suspicious left lateral lymph node

Intermediate
10-20%
> 1 cm

Hypoechoic solid regular margin
Hypoechoic solid regular margin
Isoechoic solid regular margin
Partially cystic with eccentric solid area
Partially cystic with eccentric solid areas
Partially cystic no suspicious features
Partially cystic no suspicious features

Low
5-10%
> 1.5 cm

Hyperechoic solid regular margin
Spongiform

Very low
<3%
> 2 cm
If at all

Benign
<1%
Biopsy not needed to r/o malignancy

Risk of malignancy

High
70-90%
> 1 cm

Intermediate
10-20%
> 1 cm

Benign
<1%
Biopsy not needed to r/o malignancy

Figure 2
FNA – PTC 2.7 cm

Thyroidectomy or lobectomy?

2009 Recommendation: Thyroidectomy

Adam M, Ann Surg 2014
Barney BM, Head Neck 2011
Nixon IJ, Surgery 2011
Mendelsohn AH, Arch Otolaryn 2010
Haigh PI, Ann Surg Onc 2005

RECOMMENDATION 35
PTC >1 cm and <4 cm
No extrathyroidal extension, cN0 (preoperative assessment)
NTT/TT or lobectomy
(Strong Recommendation, Moderate-quality evidence)

No need for prophylactic central neck dissection for:
T1/T2 PTC and cN0 and for most FTC.
(Strong Recommendation, Moderate-quality evidence)

Randolph GW, Thyroid 2012
Recommendation 46 (NEW)
Pathology reports should include:
AJCC/TNM criteria
Vascular invasion and number of vessels
Number of LN examined and involved
Size of the largest metastatic LN focus
Extranodal extension
(Strong recommendation, Moderate-quality evidence)

Variants with more favorable and unfavorable outcomes
(Strong recommendation, Low-quality evidence)

Variants associated with familial syndromes
(Weak recommendation, Low-quality evidence)
System for Estimating Risk of Persistent or Recurrent Disease

ATA Guidelines 2009

Low Risk
- Classic PTC
- No local or distant mets
- Complete resection
- No ETE
- No vascular invasion
- If given, no RAI uptake outside TB

78-91% NED
2-7% Structural Incomplete

Cooper et al, Thyroid 2009
Tuttle et al, Thyroid 2010
Vaisman at al, Clin Endo 2012
Pitoia et al, Thyroid 2013

Intermediate Risk
- Microscopic ETE
- Cervical LN mets
- Aggressive Histology
- Vascular invasion

52-63% NED
21-34% Structural Incomplete

High Risk
- Macroscopic gross ETE
- Incomplete tumor resection
- Distant Mets
- Tg elevation

14-31% NED
56-72% Structural Incomplete
Risk of Structural Disease Recurrence
(In patients without structurally identifiable disease after initial therapy)

**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)

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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 without 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%)

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Figure 4
Risk of Structural Disease Recurrence
(In patients without structurally identifiable disease after initial therapy)

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)

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Intrathyroidal unifocal PMC, BRAF mutated*, (∼1-2%)
Intrathyroidal, encapsulated, FV-PTC (∼1-2%)
Unifocal PMC (∼1-2%)
Radioiodine Remnant Ablation/Adjuvant Therapy
RECOMMENDATION 51 (Table 14)

<table>
<thead>
<tr>
<th>ATA recurrence risk TNM Staging</th>
<th>Description</th>
<th>Post-surgical RAI indicated?</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATA Low Risk T1a/N0,NX/M0,MX</td>
<td>T ≤ 1cm (unifocal or multifocal)</td>
<td>No</td>
</tr>
<tr>
<td>ATA Low Risk T1b, T2/N0,NX/M0,MX</td>
<td>T 1-4 cm</td>
<td>Not routine</td>
</tr>
<tr>
<td>ATA Low to intermediate risk T3/N0,NX/M0,MX</td>
<td>T &gt; 4cm or microscopic invasion</td>
<td>Consider</td>
</tr>
<tr>
<td>ATA Low to intermediate risk T1-3/N1a/M0,MX</td>
<td>Central compartment LN metastases</td>
<td>Consider (size and number)</td>
</tr>
<tr>
<td>ATA Low to intermediate risk AnyT1-3/N1b/M0,MX</td>
<td>Lateral compartment LN metastases</td>
<td>Consider (size, number, age)</td>
</tr>
<tr>
<td>ATA High risk T4/any N/any M</td>
<td>Gross extrathyroidal extension</td>
<td>Yes</td>
</tr>
<tr>
<td>ATA High risk M1 (any T, any N)</td>
<td>Distant metastases</td>
<td>Yes</td>
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### Assessing Response to Therapy

<table>
<thead>
<tr>
<th>Excellent Response</th>
<th>Indeterminate (good) Response</th>
<th>Incomplete Response</th>
</tr>
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<tbody>
<tr>
<td>Suppressed Tg</td>
<td>Detectable, but &lt; 1 ng/mL</td>
<td>&gt; 1 ng/mL</td>
</tr>
<tr>
<td>Stimulated Tg</td>
<td>&lt; 10 ng/mL Declining</td>
<td>&gt; 10 ng/mL Stable or rising</td>
</tr>
<tr>
<td>Tg Trend</td>
<td>Absent or declining</td>
<td>Persistent or rising</td>
</tr>
<tr>
<td>Tg antibodies</td>
<td>Normal Indeterminate</td>
<td>Palpable disease Positive</td>
</tr>
<tr>
<td>Neck exam</td>
<td>Clinical Insignificant</td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td></td>
<td></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

Tuttle RM, Thyroid 2010
Management Approaches Based on Response to Therapy
Low to intermediate risk patients

<table>
<thead>
<tr>
<th></th>
<th>Excellent</th>
<th>Indeterminate</th>
<th>Biochemical Incomplete</th>
<th>Structural Incomplete</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH target</td>
<td>0.5-2</td>
<td>0.1-0.5</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Serum Tg</td>
<td>yearly</td>
<td>yearly</td>
<td>6-12 months</td>
<td>3-6 months</td>
</tr>
<tr>
<td>Neck US</td>
<td>5 years</td>
<td>1-3 years</td>
<td>6-12 months</td>
<td>3-6 months</td>
</tr>
<tr>
<td>Stim Tg</td>
<td>No</td>
<td>maybe</td>
<td>consider</td>
<td>consider</td>
</tr>
<tr>
<td>WBS</td>
<td>No</td>
<td>maybe</td>
<td>consider</td>
<td>consider</td>
</tr>
<tr>
<td>Cross-sectional imaging</td>
<td>No</td>
<td>No</td>
<td>consider</td>
<td>yes</td>
</tr>
</tbody>
</table>

More aggressive monitoring for high risk patients
# TSH targets based on benefits vs risks

<table>
<thead>
<tr>
<th>Increasing Risk of TSH Suppression</th>
<th>Excellent</th>
<th>Indeterminate</th>
<th>Biochemical Incomplete **</th>
<th>Structural Incomplete</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Known Risk</td>
<td></td>
<td></td>
<td>Moderate or Complete Suppression</td>
<td>TSH target &lt; 0.1 mU/L</td>
</tr>
<tr>
<td>Menopause</td>
<td></td>
<td></td>
<td>Mild suppression. TSH target 0.1-0.5* mU/L</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteopenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 60</td>
<td></td>
<td></td>
<td>No suppression. TSH target 0.5*-2.0 mU/L</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Atrial Fibrillation</td>
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</table>
Radioidine-refractory DTC

How is radioiodine refractory DTC defined? (new question)

RECOMMENDATION 91 (NEW)

Radioiodine-refractory structurally-evident DTC is defined in patients with appropriate TSH stimulation and iodine preparation in four basic ways:

1) the malignant/metastatic tissue does not ever concentrate radioiodine
2) the tumor tissue loses the ability to concentrate radioiodine
3) radioiodine is concentrated in some lesions but not in others
4) metastatic disease progresses despite significant concentration of radioiodine.

When a patient with DTC is classified as refractory to radioiodine, there is no indication for further radioiodine treatment. (Strong recommendation, Moderate-quality evidence)
Cancer therapy is like beating a dog with a stick to get rid of his fleas.

Anna Deveare Smith, Let Me Down Easy
What to do with patients who have RAI-refractory DTC?

- **Monitor** (New recommendation 92)
- **Directed Therapy** (New recommendation 93)
  - Surgery, EBRT, thermal ablation
- **Clinical trials** (New recommendation 95)
  - Clinicaltrials.gov
- **Systemic therapy** (New recommendations 96-99)
  - Kinase inhibitors, Bone-directed therapy
Summary

- US sonographic risk patterns
- Don’t need to biopsy every nodule > 1 cm
- Don’t have to biopsy any nodule < 1 cm
- Lobectomy may be reasonable approach
- More detailed pathology reports
- New section on voice management
- Use of selective radioiodine, lower doses
- Cross-sectional imaging for higher risk disease
- Stage (AJCC/TNM), ATA recurrence risk, response to therapy
- Radioiodine refractory DTC
  - Definition, monitoring, directed-therapy, clinical trials and systemic therapy
Acknowledgements

Guidelines Task Force
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Steve Sherman
Julie Ann Sosa
Dave Steward
Mike Tuttle
Len Wartofsky
<table>
<thead>
<tr>
<th>2009 Recommendation</th>
<th>2015 Recommendation</th>
<th>Potential Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 3: Biopsy thyroid nodules primarily based on size and individual sonographic features</td>
<td>Recommendation 8, Table 6: Biopsy thyroid nodules primarily based on sonographic pattern, followed by size</td>
<td>Fewer thyroid nodules will require a biopsy</td>
</tr>
<tr>
<td>Recommendations 7-11: Use of a 4-tiered cytology classification</td>
<td>Recommendations 9-12: Use of a 6-tiered Bethesda cytology classification system</td>
<td>Better stratify the likelihood of malignancy for patients with indeterminate cytology</td>
</tr>
<tr>
<td>Recommendation 8: General consideration of the use of molecular markers</td>
<td>Recommendations 13-17: Specific recommendations for the use of molecular markers</td>
<td>Reduce unnecessary surgeries</td>
</tr>
<tr>
<td>Recommendation 22: Routine preoperative use of non-US imaging (MRI, CT, PET) is not recommended</td>
<td>Recommendation 33: Preoperative use of neck CT (with contrast) or MRI is recommended for patients with clinical suspicion of advanced disease</td>
<td>Improve directed surgical therapy for patients with aggressive disease</td>
</tr>
<tr>
<td>Recommendation 26: Thyroidectomy is recommended for all patients with PTC measuring &gt;1 cm</td>
<td>Recommendation 35B: Thyroidectomy or lobectomy can be used in properly selected patients with PTCs measuring 1-4 cm</td>
<td>Reduce surgical hypoparathyroidism, RLN damage, and need for thyroid hormone therapy in some patients with low-risk DTC</td>
</tr>
<tr>
<td>None</td>
<td>Recommendation 39-42: Perioperative management of voice issues</td>
<td>Improve surgical voice outcomes</td>
</tr>
<tr>
<td>None</td>
<td>Recommendation 46: Guidance for an optimal histopathology report</td>
<td>Uniform communication between pathologists and clinicians and better risk stratification</td>
</tr>
<tr>
<td>Recommendation 36: 30–100 mCi of $^{131}$I for remnant ablation</td>
<td>Recommendation 55A: 30 mCi of $^{131}$I for remnant ablation</td>
<td>Reduce potential for RAI toxicity</td>
</tr>
<tr>
<td>Recommendation 37: 100–200 mCi of $^{131}$I for adjuvant therapy</td>
<td>Recommendation 56: &gt;30-150 mCi of $^{131}$I for adjuvant therapy</td>
<td>Reduce potential for RAI toxicity</td>
</tr>
<tr>
<td>Broad recommendations for long-term follow-up</td>
<td>Recommendation 49: Specific recommendations for long-term follow-up based on response to therapy</td>
<td>More personalized follow-up therapy and monitoring</td>
</tr>
<tr>
<td>RAI-refractory disease not specifically defined</td>
<td>Recommendation 91: RAI-refractory disease carefully defined</td>
<td>Fewer patients receiving large administered doses of RAI that will not be helpful</td>
</tr>
<tr>
<td>None</td>
<td>Recommendations 96-98: Series of recommendations regarding the use of kinase inhibitors and the management of toxicities</td>
<td>Use of kinase inhibitors and management/avoidance of toxicities</td>
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</table>