Dynamic Risk Stratification:

Using Risk Estimates to Guide Initial Management

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Disclosures

No relevant conflicts of interest
Defining and Using Initial Risk Estimates

New AJCC 8th Edition Staging System

ATA Risk Classification

Example Cases

Management and Follow-up

Emphasis on “low risk” thyroid cancer
Spectrum of Thyroid Cancer

More than just papillary microcarcinomas
More than just the risk of recurrence & death

Low Risk Thyroid Cancer

Subclinical

Lethal
Potentially Important Risks

- **Primary risks**
  - Recurrence?
  - Death from thyroid cancer?

- **Staging and follow up risks**
  - Distant metastases?
  - Not a good Tg producer?
  - Disease is RAI refractory?
  - FDG PET avid?

- **Treatment related risks**
  - Complications from surgery?
  - Side effects from RAI?
  - Initial therapy will be ineffective?
  - Needing additional therapy?
Differentiated Thyroid Cancer

Mazzaferri. J CEM 2001

Age (yrs) at time of initial therapy

Recurrence

Death

AJCC/TNM
Predict risk of death, not recurrence
8th Edition AJCC/TNM

**Significant Changes**

Jan 2017 for Clinical Care
Jan 2018 for Tumor Registries

- Age at diagnosis cut off raised
  - Was 45 years, now is 55 years old
- New definitions of all stages (I-IV)
  - Minor extrathyroidal extension no longer mandates stage III
  - Lymph node metastases no longer mandates stages III
8th Edition AJCC/TNM

T1 and T2
Intrathyroidal tumors
T3 definition has changed

**T3a**
Intrathyroidal tumors > 4 cm

**T3b**
Gross extrathyroidal extension invading only strap muscles from a tumor of any size
**T4a**

*Gross ETE subcutaneous soft tissues, larynx, trachea, esophagus, or RLN from any size tumor*

**T4b**

*Gross extrathyroidal extension invading pre-vertebral fascia or encasing the carotid or mediastinal vessels from any size tumor*
8th Edition AJCC/TNM

N1a/N1b definition has changed

Central Neck
Levels VI and VII
# 8th Edition AJCC/TNM

## Stage Definitions Have Changed

<table>
<thead>
<tr>
<th>Distant Mets</th>
<th>Gross ETE present?</th>
<th>Tumor Size</th>
<th>LN status</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 55 yrs old</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 55 yrs old</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
8th Edition AJCC/TNM

< 55 years old at diagnosis, Survival Curves

I: No distant mets

II: Distant mets
≥ 55 years old at diagnosis, Survival Curves

I: Intrathyroidal, < 4 cm

II: > 4 cm or N1, or strap mm

III: Gross invasion of larynx, trachea, esoph, or RLN

IV: Gross invasion prevert fascia, carotid encased or distant mets
### 8th Edition AJCC/TNM

**Low risk of death from thyroid cancer**

<table>
<thead>
<tr>
<th>Distant Mets</th>
<th>Gross ETE present?</th>
<th>Tumor Size</th>
<th>LN status</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 55 yrs old</td>
<td>No</td>
<td>Any</td>
<td>Any</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Any</td>
<td>Any</td>
<td>II</td>
</tr>
<tr>
<td>≥ 55 yrs old</td>
<td>No</td>
<td>No</td>
<td>≤4 cm (T1-2)</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N0/Nx</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N1a/N1b</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; 4 cm (T3a)</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N0/Nx/N1a/N1b</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Only strap muscles (T3b)</td>
<td>Any</td>
<td>Any</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>Subq, larynx, trachea, esophagus, RLN (T4a)</td>
<td>Any</td>
<td>Any</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>Prevertebral fascia, encasing major vessels</td>
<td>Any</td>
<td>Any</td>
<td>IVa</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Any</td>
<td>Any</td>
<td>IVb</td>
</tr>
</tbody>
</table>
Differentiated Thyroid Cancer

Mazzaferri. JCEM 2001

Predicting the Risk of Recurrence
Novel staging systems

Recurrence

Death

Age (yrs) at time of initial therapy
Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer

New System for Estimating Risk of Recurrence
2009 Update

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

Intermediate Risk
Microscopic ETE
Cervical LN mets
Aggressive Histology
Vascular invasion

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

Cooper et al, Thyroid 2009
Risk Estimates Using ATA System

Total Thyroidectomy & RRA: 1,194 patients
(Cancer centers, median follow-up 7-10 yrs)

- **MSKCC**
- **INCA, Rio De Janeiro, Brazil**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>MSKCC</th>
<th>INCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>44%</td>
<td>37%</td>
</tr>
<tr>
<td>High</td>
<td>86%</td>
<td>85%</td>
</tr>
</tbody>
</table>

Tuttle et al. *Thyroid* 2010  
Vaisman et al. *Clin Endo* 2012
## Risk Estimates Using ATA System

**Total Thyroidectomy & RRA: 1,194 patients**  
*(Cancer centers, median follow-up 7-10 yrs)*

<table>
<thead>
<tr>
<th>ATA Risk</th>
<th>Study</th>
<th>Remission</th>
<th>Abnormal Tg without structural disease</th>
<th>Structural persistent/recurrent disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>New York, Rio de Janeiro, Brazil</td>
<td>86%</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>88%</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>New York, Rio de Janeiro, Brazil</td>
<td>57%</td>
<td>22%</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>63%</td>
<td>16%</td>
<td>21%</td>
</tr>
<tr>
<td>High</td>
<td>New York, Rio de Janeiro, Brazil</td>
<td>14%</td>
<td>14%</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16%</td>
<td>12%</td>
<td>72%</td>
</tr>
</tbody>
</table>

*References: Tuttle et al. Thyroid 2010, Vaisman et al. Clin Endo 2012*
Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer

2015 Guidelines Strongly Endorse the 2009 System

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

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Cervical LN mets
Aggressive Histology
Vascular invasion

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

Cooper et al, Thyroid 2009
Risk of Structural Disease Recurrence
(In patients without structurally identifiable disease after initial therapy)

High Risk

PTC, 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%)

Intermediate Risk

Low Risk

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%)
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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.
Expanding the Definition of ATA Low Risk

Papillary thyroid cancer (with all of the following):
- No local or distant metastases
- All macroscopic tumor has been resected
- No tumor invasion of loco-regional tissues or structures
- The tumor does not have aggressive histology
- If 131I is given, there are no metastatic foci outside thyroid bed
- No vascular invasion
- Clinical N0 or ≤ 5 pathologic N1 micrometastases (<0.2 cm in largest dimension)

- Intrathyroidal, encapsulated FVPTC

- Intrathyroidal, well differentiated FTC with capsular invasion and no or minimal (<4 foci) vascular invasion

- Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including BRAFV600E mutated (if known)

Haugen et al, ATA Guidelines, Thyroid 2016
### 2015 Definitions of ATA Low Risk

<table>
<thead>
<tr>
<th>ATA Risk Stratification</th>
<th>NED</th>
<th>Indeterminate</th>
<th>Biochemical Incomplete</th>
<th>Structural Incomplete</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009 (n=56)</td>
<td>55%</td>
<td>36%</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Modified-2009 (n=87)</td>
<td>56%</td>
<td>38%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009 (n=395)</td>
<td>43%</td>
<td>33%</td>
<td>6%</td>
<td>19%</td>
</tr>
<tr>
<td>Modified-2009 (n=346)</td>
<td>42%</td>
<td>32%</td>
<td>6%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009 (n=104)</td>
<td>9%</td>
<td>13%</td>
<td>7%</td>
<td>72%</td>
</tr>
<tr>
<td>Modified-2009 (n=122)</td>
<td>12%</td>
<td>15%</td>
<td>7%</td>
<td>66%</td>
</tr>
</tbody>
</table>

Tarasova, Tuttle et al, MSKCC Unpublished data
Non-invasive follicular thyroid neoplasm with papillary like nuclear features (NIFT-P)

Formerly:
Encapsulated, non-invasive FV-PTC
FOLLICULAR TUMORS OF THE THYROID

- Follicular adenoma
- NIFT-P
- Tumor—Uncertain Malignant Potential
- Follicular variant papillary carcinoma, encapsulated
- Grossly encapsulated, minimally invasive follicular carcinoma
- Follicular variant papillary carcinoma, infiltrative
- Grossly encapsulated, angioinvasive follicular carcinoma
- Widely invasive follicular carcinoma
Low Risk Thyroid Cancer

Papillary thyroid cancers
  Classic PTC
  1-4 cm
  +/- small LN mets

Follicular thyroid cancers
  FTC/FVPTC
  Non-invasive
  Encapsulated
  Capsule invasion
  Minor vascular invasion?
Low Risk Thyroid Cancer

37 year old female
Solitary thyroid nodule (other lobe and neck are normal)
  FNA: non diagnostic
Diagnostic lobectomy: 2.4 cm classic PTC
  No vascular invasion or ETE
  2 LN + (1mm and 2 mm)

Risk Assessment
• Risk of death?
• Risk of recurrence?
• Likely site of recurrence?
• Time frame for recurrence?
• Tools to detect recurrence?
• Will recurrence be treatable?

6 weeks post-op,
  TSH is 1.5 mIU/L
  Tg 6 ng/mL
  Neg Tg Ab
  Post-op Neck US?
37 year old female
Solitary thyroid nodule (other lobe and neck are normal)
FNA: non diagnostic
Diagnostic lobectomy: 2.4 cm classic PTC
No vascular invasion or ETE
2 LN + (1mm and 2 mm)

Next steps
- Observation vs completion thyroidectomy?
- Anticipate RAI ablation?
- TSH goal?
- Long term follow-up
  - US?
  - Tg/TgAb?
Low Risk Thyroid Cancer

54 year old male
Solitary thyroid nodule (other lobe and neck are normal)
FNA: non diagnostic
Diagnostic lobectomy: 3.1 cm encapsulated FVPTC
No vascular invasion or ETE
3 foci of invasion through the tumor capsule

Risk Assessment
- Risk of death?
- Risk of recurrence?
- Likely site of recurrence?
- Time frame for recurrence?
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- Will recurrence be treatable?

6 weeks post-op,
TSH is 1.5 mIU/L
Tg 9 ng/mL
Neg Tg Ab
Post-op Neck US?
Low Risk Thyroid Cancer

54 year old male
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- Non-invasive Encapsulated
- Capsule invasion
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