Risk Stratification in Differentiated Thyroid Cancer: New Aspects and Practical Implementation

Overview
Practical approach to utilizing risk estimates in the management of thyroid cancer

Changing Landscape of Thyroid Cancer
New AJCC 8th Edition Staging System
ATA Risk Classification
Using ATA Risk to Refine and Individualize AJCC Predictions
Dynamic Risk Stratification

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?

Disclosures
No relevant conflicts of interest
Risk Stratification in Thyroid Cancer

A dynamic, iterative, active process

AJCC 8th Edition Risk of death
Stage I, II, III, or IV

ATA Risk
Recurrence/Persistent Disease
Low, Intermediate, or High

Response to Therapy
Management recommendations
Excellent, Biocompatible, Incompleteness, Indeterminate

Surgery
Adjuvant Therapy
Follow up

Suspicious Nodule
Diagnosis

Tuttle, Alzahrani, Mini - review, JCEM expected in early 2019

American Joint Committee on Cancer

October 2016, AJCC published the 8th edition staging manual
Effective: 1 Jan 2018
Replaces the 7th edition used since 2009

www.cancerstaging.org

AJCC Staging Philosophy Has Evolved

Beyond Anatomic Staging

8th Edition

• Continues strong emphasis on anatomic staging
  • T, N, and M
• Endorses integration of non-anatomical prognostic variables in an effort to create a more contemporary personalized approach to risk stratification
  • Genetic alterations, tumor markers, response to therapy
• Evolving philosophy reflected stage groups names (I-IV)
  • Anatomic stage groups (1st six editions)
  • Anatomic stage and prognostic groups (7th)
  • Prognostic stage groups (8th edition)

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What were the major changes?

Thyroid - Differentiated and Anaplastic Carcinoma

• Age at diagnosis cut off raised
  • Was 45 years, now is 55 years old
• In older patients
  • Minor extrathyroidal extension no longer mandates stage III
  • Lymph node metastases no longer mandates stages III/IV
• Many patients will be re-classified into lower prognostic stages
• Better separation between the prognostic stage groups

Tuttle, Haugen, Perrier. Thyroid 2017.
Perrier, Britton, Tuttle. CA: A Cancer Journal for Clinicians, 2017
Increasing the age cut off to 55 yrs

Moves many patients to lower prognostic stage groups without worsening the prognosis in the lower stages

Age as a continuous variable

Ten year disease specific survival at different age cutoffs from age 30 to age 70 yrs

Survival from differentiated thyroid cancer: What has age got to do with it? Benly et al, Thyroid 2015.

Increasing the age cut off to 55 yrs

9,484 WDTC Patients, 10 institutions, median follow up 5 yrs

<table>
<thead>
<tr>
<th>Prognostic Stage</th>
<th>Age Cut Off</th>
<th>N (%)</th>
<th>10 yr DSS (Median 5 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>45 yrs</td>
<td>6,600 (70%)</td>
<td>99.7%</td>
</tr>
<tr>
<td></td>
<td>55 yrs</td>
<td>7,736 (82%)</td>
<td>99.5%</td>
</tr>
<tr>
<td>II</td>
<td>45 yrs</td>
<td>741 (8%)</td>
<td>97.3%</td>
</tr>
<tr>
<td></td>
<td>55 yrs</td>
<td>441 (5%)</td>
<td>94.7%</td>
</tr>
<tr>
<td>III</td>
<td>45 yrs</td>
<td>1,230 (13%)</td>
<td>96.6%</td>
</tr>
<tr>
<td></td>
<td>55 yrs</td>
<td>707 (8%)</td>
<td>94.1%</td>
</tr>
<tr>
<td>IV</td>
<td>45 yrs</td>
<td>913 (10%)</td>
<td>76.3%</td>
</tr>
<tr>
<td></td>
<td>55 yrs</td>
<td>600 (6%)</td>
<td>67.6%</td>
</tr>
</tbody>
</table>

Prognosis & LN metastasis

The challenges of LN risk stratification

LN mets are present in 60-80% of papillary microcarcinoma patients implying that small volume disease has little impact on DSS.

Clinically apparent LN mets have an impact on overall survival that is more apparent in older patients than young patients.

Prognosis probably related to lymph node size, number involved, lymph node ratio, extranodal extension, location (N1a vs. N1b), histology, molecular profile and concurrent gross ETE.

Microscopic Extrathyroidal Extension

7th Edition

Classified as T3

Stage III (> 45 yrs old)

Regardless of tumor size

T1 and T2

"Limited to the thyroid"

With or Without Microscopic ETE

Not a major risk factor

Defining ETE "problematic and subjective" (American College of Pathologists)

Incomplete tumor capsule
**Gross Extrathyroidal Extension**

Consistently shown to be risk factor for mortality

T3a

Intrathyroidal tumors > 4 cm (Stage II, >55 yrs)

T3b

Gross extrathyroidal extension invading any strap muscles from a tumor of any size (Stage II, >55 yrs)


**Gross Extrathyroidal Extension**

Invasion of Major Structures in the Neck
Significant Impact on Survival

T4a

Gross ETE subcutaneous soft tissues, larynx, trachea, esophagus, or RLN from any size tumor (Stage III, > 55 yrs)

T4b

Gross extrathyroidal extension invading pre-vertebral fascia or encasing the carotid or mediastinal vessels from any size tumor (Stage IVA, ≥ 55 yrs)


**Molecular Markers and Prognosis**

Multicenter study, 1,849 patients with PTC
56 PTC related deaths, median 3 yr follow-up

<table>
<thead>
<tr>
<th>AJCC 7th Edition</th>
<th>BRAF V600E Mutant (45 deaths)</th>
<th>BRAF V600E Wild Type (11 deaths)</th>
<th>p value</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1/443</td>
<td>1/664</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1/77</td>
<td>0/127</td>
<td>N.S.</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>4/180</td>
<td>0/102</td>
<td>N.S.</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>38/121 (31.4% mortality)</td>
<td>10/77</td>
<td>0.004</td>
<td></td>
</tr>
</tbody>
</table>

Xing, JAMA 2013

**Practical Application**

What information should be used to determine AJCC/TNM Staging?

Suspicious Nodule Identification of metastatic disease (by any modality) within the first 4 months of thyroid surgery should be used to refine the N and M status

Diagnosis Thyroid Surgery Adjuvant Therapy Follow up

AJCC 7th Edition Staging (I-IV)

Based on T, N, and M definitions

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Diagnosis</td>
<td>&gt; 55 yrs</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Distant Mets</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Stage I</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td></td>
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<tr>
<td>Stage III</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td></td>
</tr>
<tr>
<td>Prevertebral fascia, encasing major vessels (T4A)</td>
<td>Yes</td>
</tr>
<tr>
<td>Stage V</td>
<td></td>
</tr>
<tr>
<td>Stage VI</td>
<td></td>
</tr>
<tr>
<td>Stage VII</td>
<td></td>
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<tr>
<td>Stage VIII</td>
<td></td>
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<tr>
<td>Stage IX</td>
<td></td>
</tr>
<tr>
<td>Stage X</td>
<td></td>
</tr>
</tbody>
</table>

Tuttle, Haugen, Perrrier, Thyroid 2017

Perrier, Brierley, Tuttle, CA: A Cancer Journal for Clinicians, 2017
Transition from the 7th edition to the 8th edition

Validation of 8th Edition AJCC/TNM
3,176 patients, Samsung Medical Center, Seoul, Korea

Differentiated Thyroid Cancer
Mazzaferri. JCEM 2001

Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer
New System for Estimating Risk of Recurrence 2009 Update
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 NO or ≤ 5 pathologic NI 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)

Integrating AJCC and ATA Risk Categories

<table>
<thead>
<tr>
<th>Age at Diagnosis</th>
<th>AJCC 8th Edition Stage</th>
<th>ATA Low</th>
<th>ATA Intermediate</th>
<th>ATA High</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 55 yrs old</td>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 55 yrs old</td>
<td>II</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

ATA Risk

<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</td>
<td>86%</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Rio de Janeiro, Brazil</td>
<td>88%</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>New York</td>
<td>57%</td>
<td>22%</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>Rio de Janeiro, Brazil</td>
<td>63%</td>
<td>16%</td>
<td>21%</td>
</tr>
<tr>
<td>High</td>
<td>New York</td>
<td>14%</td>
<td>14%</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td>Rio de Janeiro, Brazil</td>
<td>16%</td>
<td>12%</td>
<td>72%</td>
</tr>
</tbody>
</table>

Integrating AJCC and ATA Risk Categories

18-44 yrs: m=3167 (65%) 45-54 yrs: n=1714 (35%)

Risk of Structural Disease Recurrence

(In patients without structurally identifiable disease after initial therapy)

High Risk
- Ftc extends vascular invasion (> 30-55%)
- pN1 with extranodal extension, > 1 LS involved (>45%)
- FTC, > 1 cm, TERT mutated*, BRAF mutated* (>40%)
- pN1, any LN 3 cm (>30%)
- FTC, extrathyroidal, BRAF mutated* (>10-40%)
- FTC, vascular invasion (> 10-30%)
- Clinical N1 (20%)
- pN1, > 5 LS involved (20%)
- Intrathyroidal FTC, > 4 cm, BRAF mutated* (>20%)
- FTC, tumor ETE (p < 3-5%)
- pN1, > 5 LS involved (10%)
- Intrathyroidal FTC 2-4 cm (<5%)
- Intrathyroidal FTC, any LN > 3 cm (<5%)
- Intrathyroidal, any LN > 2 cm (<5%)
- IntrathyroidalFTC, > 2 cm, extrathyroidal extension (<1-2%)

Intermediate Risk
- Minimally invasive FTC (< 2-5%)
- Intrathyroidal, < 4 cm, BRAF wild type* (< 1-2%)
- Intrathyroidal microcarcinoma, FTC, BRAF mutated* (< 1-2%)
- Intrathyroidal, encapsulated FTC, < 4 cm (< 1-2%)
- Clinical FTC (< 1-2%)

Low Risk
- FTC, any LN involvement (<1%)
- FTC, any LN involvement (<1%)
- FTC, any LN involvement (<1%)
- FTC, any LN involvement (<1%)
- FTC, any LN involvement (<1%)

*While analysis of BRAF and or TERT information is available.

10 year Disease Specific Survival

4,881 DTC patients < 55 yrs old at diagnosis

- 100% DSS
- 97% DSS*
- 99% DSS
- 98% DSS
- 96% DSS
- 95% DSS
- 93% DSS
- 92% DSS
- 91% DSS
- 90% DSS
- 89% DSS
- 88% DSS
- 87% DSS
- 86% DSS
- 85% DSS
- 84% DSS
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- 11% DSS
- 10% DSS
- 9% DSS
- 8% DSS
- 7% DSS
- 6% DSS
- 5% DSS
- 4% DSS
- 3% DSS
- 2% DSS
- 1% DSS
- 0% DSS

*At 5 years, AJCC stage I had a lower rate of structural disease recurrence compared to ATA (72% vs. 78%), but at 10 years, stage I had similar disease recurrence rates to ATA (87% vs. 90%).
Real Time Prognostication
Response to Therapy Assessment
Delayed Risk Stratification
Dynamic Risk Stratification
Ongoing Risk Assessment

Risk Estimates Change Over Time
The concept of dynamic risk assessment (Response to therapy assessment)

Depending on the clinical course of the disease and response to therapy, the risk of recurrence and the risk of death may change over time.

Appropriate management requires an ongoing reassessment of the risk of recurrence and the risk of disease-specific mortality as new data are obtained during follow-up.

Risk Adapted Approach to Management

"Reconfiguring the Course"
Picture by C. Emerson
Editor, Thyroid, 2010

Results That Modify Risk
Clinical utility far beyond simple disease detection

Change in serum thyroglobulin over time
Change in serum Tg antibodies over time
Results of stimulated thyroglobulin determinations
Results of follow up Neck US
Results of RAI scanning
Other cross sectional imaging
Results of FDG PET imaging
Physical examination

Expected Response to Therapy Outcomes

<table>
<thead>
<tr>
<th>Response</th>
<th>Expected Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>1-4% recurrence</td>
</tr>
<tr>
<td></td>
<td>&lt;1% death</td>
</tr>
<tr>
<td>Biochemical</td>
<td>&gt;30% spontaneously resolve</td>
</tr>
<tr>
<td>Incomplete</td>
<td>20% develop structural disease</td>
</tr>
<tr>
<td>Structural</td>
<td>50-85% will have persistent disease despite additional treatments</td>
</tr>
<tr>
<td>Incomplete</td>
<td>Nearly all deaths arise from this group</td>
</tr>
<tr>
<td></td>
<td>20% develop structural disease</td>
</tr>
<tr>
<td></td>
<td>&lt;1% death</td>
</tr>
</tbody>
</table>

Four Possible Clinical Outcomes

Excellent Response
No clinical, biochemical, or structural evidence of disease

Biochemical Incomplete Response
Persistent abnormal thyroglobulin or rising anti-thyroglobulin values in the absence of localizable disease

Structural Incomplete Response
Persistent or newly identified loco-regional or distant metastases

Indeterminate Response (Acceptable)
Non-specific biochemical or structural findings which cannot be confidently classified as either benign or malignant

Using Response to Therapy Categories to Describe Clinical Status at Any Time Point

25 yr old male
Total thyroidectomy & RAI ablation
3.5 cm tall cell variant FTC, 14/19 LN + (2.5 cm, +ENE)
ATA 2009 Intermediate Risk Patient
AJCC Stage II

3 mo
Tg 0.3
TgAb +

Indeterminate Response

6 mo
Tg 4
TgAb rising
US neg

Biochemical Incomplete Response

12 mo
Tg 8
TgAb rising
Imaging +

Structural Incomplete Response
Using Response to Therapy to Guide Clinical Management

<table>
<thead>
<tr>
<th>Response</th>
<th>Expected Outcomes</th>
<th>Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>1-4% recurrence</td>
<td>Decrease intensity and frequency of follow up and degree of TSH suppression.</td>
</tr>
<tr>
<td>Biochemical Incomplete</td>
<td>&gt;30% spontaneously resolve 20% develop structural disease</td>
<td>Observation with stable/decreasing Tg and TgAb. Rising Tg or TgAb should prompt additional investigations.</td>
</tr>
<tr>
<td>Structural Incomplete</td>
<td>50-85% will have persistent disease despite additional treatments</td>
<td>Some require additional treatments.</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>20% develop structural disease</td>
<td>Continued observation with mild TSH suppression.</td>
</tr>
</tbody>
</table>


Risk Stratification in Thyroid Cancer

Initial Static Risk Assessments
Guide initial treatment and early follow-up recommendations
Focus of Yeh

Dynamic Risk Stratification
Continually modify those risk estimates as new data becomes available
Re-evaluate Management Plans
Stay the course
Testing strategy
Interventions

A Note of Caution

Detectable Findings
Differentiate
"Detectable Findings" from
"Actionable Findings"

Detectable Findings
Non-Actionable Findings
Actionable Findings

ATA guidelines endorsed observation of small volume disease in several clinical situations

Early Diagnosis and immediate therapy is not always the best management approach

- FNA is not required for high suspicion thyroid nodules
  - < 5 mm (2009, 2016)
  - < 10 mm (2015, 2016)

- Active Surveillance "can be considered"
  - Intrathyroidal papillary microcarcinomas (2015 p16 text, R12)

- Small volume cervical lymph node metastasis
  - Abnormal cervical lymph nodes >6-10mm (2009 text, 2015 R60, R71)
  - "probably best managed with active surveillance (observation)..."

- Biochemical incomplete response
  - Stable or declining abnormal Tg or Tg antibodies (2015 R29)

- Distant metastases
  - Stable or slowly growing (2015 R29, R64)
  - Asymptomatic (2015 R29, R64)

Factors that determine whether or not a finding is actionable

- Tumor Size (Volume)
- Tumor growth rate (Doubling Time)
- Location
- Symptoms
- Patient Preference

Differentiating “detectable disease” from “actionable disease”

- Important Clinical Implications
- Diagnostic Implications: Goal should be to identify only “actionable findings”
- Therapeutic Implications: Recommend intervention only for “actionable findings”, recommend against intervention for “non-actionable findings”, transition some of the active surveillance recommendations from “not required” to “not recommended”

Risk Stratification in Thyroid Cancer

A dynamic, iterative, active process

- Peri-Diagnostic Risk Assessment
  - Candidates for Minimalistic Management
    - Ideal
    - Appropriate
    - Inappropriate

- Suspicious Nodule
- Diagnosis
- Thyroid Surgery
- Adjuvant Therapy
- Follow up

- AJCC 8th Edition
  - Risk of death: Stage I, II, III, or IV

- ATA Risk
  - Recurrent/Persistent Disease: Low, Intermediate, or High

- Response to Therapy
  - Management recommendations: Excellent, Incomplete
  - Biochemical: Incomplete
  - Structural: Incomplete
  - Indeterminate

Tuttle, Alizahm, Neri-review, JCEM expected in early 2019

Welcome to NYC