Risk Stratification in Differentiated Thyroid Cancer:

New Aspects and Practical Implementation

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Memorial Sloan Kettering Cancer Center
Professor of Medicine
Weill Medical College of Cornell University
October 2016, AJCC published the 8th edition staging manual
Effective: 1 Jan 2018
Replaces the 7th edition used since 2009

Major Re-write

- Evidenced based medicine principles
- 18 expert panels: 420 contributors,
  181 institutions, and 22 countries
- Expanded multispecialty editorial board supported by six core committees: content harmonization, precision medicine, evidence based medicine/statistics, imaging, data collection, professional organization/corporate relationships, and administration
AJCC Staging Philosophy Has Evolved

8th Edition

Beyond Anatomic Staging

- 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)

www.cancerstaging.org

Amin et al, CA Cancer J Clin 2017
8th Edition Thyroid Cancer Staging

Endocrinology Panel
Nancy Perrier, MD Anderson Cancer Center (Chair)
Herb Chen, Univ Alabama Birmingham (Vice-Chair)

Thyroid – Differentiated and Anaplastic Carcinoma
R. Michael Tuttle, Lilah F. Morris, Bryan R. Haugen,
Jatin P. Shah, Julie A. Sosa, Eric Rohren,
Rathan M. Subramaniam, Jennifer L. Hunt,
and Nancy D. Perrier

Thyroid – Medullary
Jennifer E. Rosen, Ricardo V. Lloyd, James D. Brierley,
Raymon H. Grogan, Robert Haddad, Jennifer L. Hunt,
John A. Ridge, Raja R. Seethala, Julia A. Sosa,
Rathan M. Subramaniam, Tracy S. Wang, Lori J. Wirth,
and Nancy D. Perrier

What were the major changes?

- **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, Brierley, 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

Identifying the most appropriate age threshold for TNM stage grouping of well-differentiated thyroid cancer

J. Hendrickson-Rebizant, H. Sigvaldason, R.W. Nason, K.A. Pathak

Establishment of an Intraoperative Staging System (iStage) by Improving UICC TNM Classification System for Papillary Thyroid Carcinoma

Yasuhiro Ito1, Kiyoshi Ichihara2, Hiroo Masutaka1, Mitsuhiko Fukushima2, Hiroyuki Inoue3, Masaru Kihara2, Chisato Tominaga2, Takuya Higashiyama3, Yusuke Takamura4, Kaoru Kobayashi5, Akihiro Miyazaki5, Akira Miyashita5

The age factor in survival of a population cohort of well-differentiated thyroid cancer

Andrea Mazurat, Andrea Torroni, Jane Hendrickson-Rebizant, Harbinder Benning, Richard W Nason and K Alok Pathak

An International Multi-Institutional Validation of Age 55 Years as a Cutoff for Risk Stratification in the AJCC/UICC Staging System for Well-Differentiated Thyroid Cancer


Optimal Cutoff Age for Predicting Mortality Associated with Differentiated Thyroid Cancer

Su-jin Kim, Jun Pyo Myong, Hyunsuk Suh, Kyu Eun Lee, Yeo-Kyu Youn

1 Department of Surgery, Seoul National University Hospital & College of Medicine, Seoul, Korea, 2 Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea, 3 Division of Surgery, Thyroid Center, Seoul National University Cancer Hospital, Seoul, Korea, 4 Department of Occupational and Environmental Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University, Seoul, Korea, 5 Department of Surgery, Mount Sinai Beth Israel Hospital, Icahn School of Medicine at Mount Sinai, New York, United States of America
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? Ganly 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></th>
<th>Younger</th>
<th>Older</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 45 yrs</td>
<td>4,546 patients (48%)</td>
<td>4,938 patients (52%)</td>
</tr>
<tr>
<td>≥ 55 yrs</td>
<td>6,648 patients (70%)</td>
<td>2,836 patients (30%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>≥ 45 yrs</th>
<th>≥ 55 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,102 pts (22%)</td>
<td>2,102 pts (22%)</td>
<td>2,836 patients (30%)</td>
</tr>
</tbody>
</table>

Nixon et al, Thyroid 2016
<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>1230 (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>

Nixon et al, Thyroid 2016
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.

Young patients N1a/N1b → Stage I
Older patients N1a/N1b → Stage II

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

Issues
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 only 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: BRAF V600E Mutations and Prognosis

<table>
<thead>
<tr>
<th>AJCC 7th Edition</th>
<th>BRAF V600E Mutate (45 deaths)</th>
<th>BRAF V600E Wild Type (11 deaths)</th>
<th>p value Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1/443</td>
<td>1/664</td>
<td>0.02</td>
</tr>
<tr>
<td>II</td>
<td>1/77</td>
<td>0/127</td>
<td>NS</td>
</tr>
<tr>
<td>III</td>
<td>4/180</td>
<td>0/102</td>
<td>NS</td>
</tr>
<tr>
<td>IV</td>
<td>38/121 (31.4% mortality)</td>
<td>10/77 (13% mortality)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

(deaths/total number of patients)

Xing, JAMA 2013
Based on T, N, and M definitions

### AJCC Prognostic Stage Groups

#### Differentiated

<table>
<thead>
<tr>
<th>When age at diagnosis is...</th>
<th>And T is...</th>
<th>And N is...</th>
<th>And M is...</th>
<th>Then the stage group is...</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;55 years</td>
<td>Any T</td>
<td>Any N</td>
<td>M0</td>
<td>I</td>
</tr>
<tr>
<td>&lt;55 years</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>II</td>
</tr>
<tr>
<td>≥55 years</td>
<td>T1</td>
<td>N0/NX</td>
<td>M0</td>
<td>I</td>
</tr>
<tr>
<td>≥55 years</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td>≥55 years</td>
<td>T2</td>
<td>N0/NX</td>
<td>M0</td>
<td>I</td>
</tr>
<tr>
<td>≥55 years</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td>≥55 years</td>
<td>T3a/T3b</td>
<td>Any N</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td>≥55 years</td>
<td>T4a</td>
<td>Any N</td>
<td>M0</td>
<td>III</td>
</tr>
<tr>
<td>≥55 years</td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
<td>IVA</td>
</tr>
<tr>
<td>≥55 years</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>IVB</td>
</tr>
</tbody>
</table>

Differentiated Thyroid Cancer
8th Edition AJCC Staging

Age at Diagnosis

≤ 55 years

< 55 years

No

Yes

Stage I

Stage II

Distant Mets

≥ 55 years

Distant Mets

No

Yes

Stage IVb

Stage II

Gross ETE

No

≤ 4 cm N0/Nx

Stage I

> 4 cm or N1a/N1b

Stage II

Yes

Strap Muscles Only (T3b)

Stage II

Subcutaneous, larynx, trachea, esophagus, recurrent laryngeal nerve (T4a)

Stage III

Prevertebral fascia, encasing major vessels (T4b)

Stage IVa

Tuttle, Haugen, Perrier. Thyroid 2017.
Perrier, Brierley, Tuttle. CA: A Cancer Journal for Clinicians, 2017
Practical Application

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

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.

Tuttle, Haugen, Perrier. Thyroid 2017.
Perrier, Brierley, Tuttle. CA: A Cancer Journal for Clinicians, 2017
8th edition of the AJCC/TNM staging system of thyroid cancer: what to expect (ITCO#2)
Transition from the 7th edition to the 8th edition

Tam et al, Thyroid 2018

MD Anderson Cancer Center
Validation of 8th Edition AJCC/TNM

3,176 patients, Samsung Medical Center, Seoul, Korea

Kim et al, Oral Oncology, 2017

AJCC 7th Edition

AJCC 8th Edition

10 yr DSS

99%

94%

80%

67%

65%
Projecting Survival in Papillary Thyroid Cancer: A Comparison of the 7th and 8th Editions of the AJCC/UICC Staging Systems in Two Contemporary National Patient Cohorts

SEER
64,342 patients

7th Edition

8th Edition

Disease Specific Survival

Time from Diagnosis (Months)

P < 0.001

Pontius et al, Thyroid 2017
Differentiated Thyroid Cancer
8th Edition AJCC Staging

Age at Diagnosis

< 55 years

Distant Mets

No

Stage I

Yes

Stage II

≥ 55 years

Distant Mets

No

Stage II

Yes

Stage IVb

Gross ETE

No

≤ 4 cm N0/Nx

Stage I

> 4 cm or N1a/N1b

Stage II

Yes

Strap Muscles Only (T3b)\(^1\)

Stage II

Subcutaneous, larynx, trachea, esophagus, recurrent laryngeal nerve\(^2\)

(T4a)

Stage III

Prevertebral fascia, encasing major vessels (T4b)

Stage IVa

Possible Areas for Improvement

1. Amit et al, Ann Surgical Oncol 2018
2. Randolph, personal communication, 2018
3. Kim et al, Oral Oncology, 2018
4. Shteinshnaider et al, Thyroid 2018
5. Rosario, Endocrine 2017

Tuttle, Haugen, Perrier. Thyroid 2017.
8th Edition AJCC Staging

< 55 years old
Stage I includes all patients without distant mets

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

Haugen et al, ATA thyroid cancer guidelines, Thyroid 2016
# 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>Gross ETE Incomplete resection Large N1 FTC, extensive vascular inv</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td></td>
<td></td>
<td>DM present Tg suggestive of DM</td>
</tr>
<tr>
<td>≥ 55 yrs old</td>
<td>I</td>
<td></td>
<td></td>
<td>Gross ETE into strap muscles</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td></td>
<td></td>
<td>Gross ETE into subq, larynx, trachea, esophagus, RLN</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td></td>
<td></td>
<td>Gross ETE into prevertebral fascia, encasing major vessels and/or DM</td>
</tr>
</tbody>
</table>
10 year Disease Specific Survival
4,881 DTC patients < 55 yrs old at diagnosis

4,881 patients

AJCC Stage I
98% DSS

ATA Low
100% DSS

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

ATA Intermediate
98% DSS

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

ATA High
92% DSS

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

AJCC Stage II
68% DSS

ATA High
68% DSS

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

S Ghaznavi, RM Tuttle, et al.  Thyroid Oct 2018

Compared to younger group, Log Rank Test: *p<0.0001, †p=0.002, ‡p=0.044
10 year Disease Specific Survival
4,881 DTC patients < 55 yrs old at diagnosis

S Ghaznavi, RM Tuttle, et al. Thyroid Oct 2018
Risk Stratification in Thyroid Cancer

Dynamic, iterative, active process

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

Risk of Death
8th Edition TNM/AJCC

Response to Therapy

Excellent Biochemical Incomplete Structural Incomplete Indeterminate

Recurrent/Persistent Disease
ATA Risk Stratification

Haugen et al, ATA thyroid cancer guidelines, Thyroid 2016
Welcome to NYC