Risk Stratification in the Management of Differentiated Thyroid Cancer

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DIPLOMATE OF THE AMERICAN BOARD OF INTERNAL MEDICINE; ENDOCRINOLOGY, DIABETES AND METABOLISM, AND THE AMERICAN BOARD OF CLINICAL LIPOIDOLOGY
Disclosures

None
Learning Objectives

➢ Discuss the incidence and mortality of thyroid cancer in PR
➢ Discuss the concept of peri-diagnostic risk assessment in addition to intraoperative and post surgical stratification
➢ Evaluate the ideal candidates for a minimalistic approach
➢ Distinguish the differences in the AJCC 8th edition from 7th edition for disease mortality
➢ Discuss the ATA Risk stratification system for disease recurrence
➢ Discuss the dynamic risk assessment in the long-term follow-up
➢ Discuss the role of TSH suppression according to response to therapy categories
➢ Role of the molecular markers to the dynamic risk assessment
Thyroid Carcinoma 2020 PR Estimates

- 5-10% of thyroid nodules are malignant\(^1\)
- Based on GLOBOCAN 2020\(^2\), PR has the highest incidence rate of thyroid cancer in the Americas and the 4th highest rate worldwide.
- 3\(^{rd}\) most common cancer in women.
- A rapid increase in the incidence has been observed during the last decade in both, men and women.

1. HEGEDUS, L. NEJM, 2004. 2. GLOBOCON, 2020
Incidence of Thyroid Cancer in PR

Age-standardized (World) incidence rates per sex, top 10 cancers
Mortality of Thyroid Cancer in PR

During the period 1987 to 2015 mortality rates from thyroid cancer declined 1.2% per year in women and 1.6% per year in men.
Incidence of Thyroid Cancer in Puerto Rico and the US by racial/ethnic group, 2011–2015

Fig. 1 Age-Adjusted Incidence Rates of PTC by Sex in PR and US, 2011–2015
Incidence Rates by Age-Groups and Sex in PR and US, 2011-2015

Fig. 2 Age-Adjusted Incidence Rates of PTC by Age-Groups and Sex in PR and US, 2011–2015
Incidence Rates by Age-Groups, Sex and Race/Ethnicity in PR and US, 2011-2015

Adjusted Incidence Rates of PTC by Sex and Race/Ethnicity in PR and US, 2011-2015. Women (a), Men (b)
Reasons that explain the increase in TC incidence and population differences.

- Multifactorial
- Overdiagnosis of small lesions
  - Increase use of new diagnostic modalities¹
  - Increase medical surveillance
  - Increase access to healthcare services²
- Radiation exposure from CT scans
- Nutritional, Obesity, Insulin Resistance³
- Physical Inactivity⁴
- High Socioeconomic Status⁵

Since the vast majority of these subclinical thyroid cancer foci progress either slowly or not at all, it is critical to reevaluate the traditional management approach.
Risk Stratification in Thyroid Cancer
A dynamic, iterative, active process

From Detection to Final Follow-Up
Differentiating “Detectable Findings” from “Actionable Findings”

Risk Stratification Decision-Making Framework

- **Detectable Findings**
  - Non-Actionable Findings
  - Actionable Findings

- **Key Factors**
  - Tumor size (Volume)
  - Tumor location
  - Tumor Growth Rate (doubling time)
  - Symptoms
  - Patient Preference

TUTTLE, M AND ALZAHRA, AS. J CLIN ENDOCRINOL METAB 104: 4087–4100, 2019
Peri-Diagnostic Risk Stratification
Selecting Candidates for Minimalistic Initial Management Options

**Ideal**

**Appropriate**

**Inappropriate**

**Medical Team Characteristics**
- High-quality neck US
- Multidisciplinary team
- Experience with minimalistic management

**Peri-Diagnostic Imaging/Clinical Findings**
- Tumor size, location, growth rate
- Extrathyroidal extension
- Metastases
- Additional nodules or abnormalities on US

**Patient Characteristics**
- Age
- Patient preference
- Co-morbid conditions
- Supportive family/medical team
**Ideal Candidate for Active Surveillance**

<table>
<thead>
<tr>
<th>Tumor/Neck US Characteristics</th>
<th>Patient Characteristics</th>
<th>Medical Team Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Solitary thyroid nodule</td>
<td>• Older patients (&gt;60 y/o)</td>
<td>• Experienced multidisciplinary management team</td>
</tr>
<tr>
<td>• Well-defined margins</td>
<td>• Willing to accept active surveillance</td>
<td>• High-quality neck US</td>
</tr>
<tr>
<td>• Surrounded by ≥2 mm normal thyroid parenchyma</td>
<td>• Understands that sx intervention may be necessary in the future</td>
<td>• Prospective data collection</td>
</tr>
<tr>
<td>• Previous US w/ stability</td>
<td>• Expected to be compliant with follow-up plans</td>
<td>• Tracking/reminder program to ensure proper follow-up</td>
</tr>
<tr>
<td>• cN0</td>
<td>• Supportive significant others</td>
<td></td>
</tr>
<tr>
<td>• cM0</td>
<td>• Life-threatening comorbidities</td>
<td></td>
</tr>
</tbody>
</table>
American Association of Endocrine Surgeons

Estimation of the lifetime probability of disease progression of papillary microcarcinoma of the thyroid during active surveillance

Akira Miyauchi, MD, PhD a,*, Takumi Kudo, MD, PhD b, Yasuhiro Ito, MD, PhD a, Hitomi Oda, MD a, Hisanori Sasai, MD, PhD c, Takuya Higashiyama, MD, PhD a, Mitsuhiro Fukushima, MD, PhD a, Hiroo Masuoka, MD, PhD a, Minoru Kihara, MD, PhD a, and Akihiro Miya, MD, PhD a

a Department of Surgery, Kuma Hospital, Kobe, Japan
b Department of Internal Medicine, Kuma Hospital, Kobe, Japan
c Department Head and Neck Surgery, Kuma Hospital, Kobe, Japan
• From 1993–2013 at Kuma Hospital
• 1,211 low-risk papillary microcarcinoma patients aged 20–79 years underwent active surveillance
• No increase in disease-specific mortality in patients with disease progression
Appropriate Candidate for Active Surveillance

**Tumor/Neck US Characteristics**
- MPMC
- Subcapsular location (not RLN, w/o evidence of ETE)
- Ill-defined margins
- Background US findings that will make follow-up difficult (thyroiditis, nonspecific lymphadenopathy, multiple other benign-appearing thyroid nodules)
- FDG-avid PMC

**Patient Characteristics**
- Middle-aged patients (18-59 years)
- Strong family hx of PTC
- Child-bearing potential

**Medical Team Characteristics**
- Experienced endocrinologist or thyroid surgeon
- Neck US routinely available
Incidences of Unfavorable Events in the Management of Low-Risk Papillary Microcarcinoma of the Thyroid by Active Surveillance Versus Immediate Surgery

Hitomi Oda,1 Akira Miyauchi,1 Yasuhiro Ito,1,2 Kana Yoshioka,3 Ayako Nakayama,3 Hisanori Sasai,3 Hiroo Masuoka,1 Tomonori Yabuta,1 Mitsuhiro Fukushima,1 Takuya Higashiyama,1 Minoru Kihara,1 Kaoru Kobayashi,1 and Akihiro Miya1

1Department of Endocrinology, 2Department of Radiology, 3Department of Pathology, National Hospital Organization Tokyo Medical Center, Japan

Keywords: papillary microcarcinoma, active surveillance, immediate surgery, incidence, unfavorable events

Abstract:...
FIG. 1. Flow of the management and oncological outcomes of 2153 patients with low-risk papillary microcarcinoma (PMC). Of the observation group, 94 patients underwent surgery for various reasons. Rec: recurrence; DOO, died of other causes unrelated to thyroid cancer.

- 2005-2013 at Kuma Hospital
- Low risk Papillary Microcarcinoma
- Similar characteristics as the ideal and appropriate candidate
### Table 2. Unfavorable Events Following Active Surveillance and Immediate Surgery

<table>
<thead>
<tr>
<th>Unfavorable events</th>
<th>Active surveillance, 1179 pts</th>
<th>Immediate surgery, 974 pts</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Later surgery (pts)</td>
<td>94</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Temporary VCP (%)</td>
<td>7 (0.6%)</td>
<td>40 (4.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Permanent VCP (%)</td>
<td>0 (0%)</td>
<td>2 (0.2%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Temporary Hypo-PT (%)</td>
<td>33 (2.8%)</td>
<td>163 (16.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Permanent Hypo-PT (%)</td>
<td>1 (0.08%)</td>
<td>16 (1.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>On L-thyroxine (%)</td>
<td>244 (20.7%)</td>
<td>644 (66.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Postsurgical hematoma (%)</td>
<td>0 (0%)</td>
<td>5 (0.5%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Postsurgical abscess (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Surgical scar (%)</td>
<td>94 (8.0%)</td>
<td>974 (100%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Recurrence in neck (pts)</td>
<td>1</td>
<td>5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Death (%)</td>
<td>3 (0.3%)</td>
<td>5 (0.5%)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

VCP and Hypo-PT in the active surveillance group occurred in patients who converted to surgery later for various reasons, except for one patient who developed idiopathic Hypo-PT and another who developed transient idiopathic VCP contralateral to the microcarcinoma. All deaths in the present series were due to causes unrelated to thyroid cancer.

VCP, vocal cord paralysis; Hypo-PT, hypoparathyroidism.
Inappropriate Candidate for Active Surveillance

### Tumor/Neck US Characteristics
- Evidence of aggressive cytology on FNA
- Subcapsular location adjacent to RLN
- Evidence of ETE
- Clinical evidence of invasion to RLN or trachea
- N1 disease (initial or follow-up)
- M1 disease
- Increase in size ≥3mm in a confirmed PTC

### Patient Characteristics
- Young patients (<18 years)
- Unlikely to be compliant with follow-up plans
- Not willing to accept an observation approach

### Medical Team Characteristics
- Reliable neck US not available
- Little experience with thyroid cancer management
Indications and Strategy for Active Surveillance of Adult Low-Risk Papillary Thyroid Microcarcinoma: Consensus Statements from the Japan Association of Endocrine Surgery Task Force on Management for Papillary Thyroid Microcarcinoma

Iwao Sugitani,1 Yasuhiro Ito,2 Dai Takeuchi,3 Hirotaka Nakayama,4 Chie Masaki,5 Hisakazu Shindo,6 Masanori Teshima,7 Kazuhiko Horiguchi,8 Yusaku Yoshida,9 Toshiharu Kanai,10 Mitsuyoshi Hirokawa,11 Kiyomi Y. Hames,5 Isao Tabei,12 and Akira Miyauchi2
Assessing Mortality Risk
# Predictive Models for Disease Specific Mortality

## TABLE 1
Comparing Different Factors Used in Ten Different Stage Classifications

<table>
<thead>
<tr>
<th>Classification</th>
<th>EORTC</th>
<th>UICC/AJCC</th>
<th>AGES</th>
<th>AMES</th>
<th>MACIS</th>
<th>Clinical Class</th>
<th>Ohio</th>
<th>SAG</th>
<th>Noguchi</th>
<th>MSK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologies</td>
<td>All</td>
<td>All</td>
<td>Papillary</td>
<td>Differentiated</td>
<td>Papillary</td>
<td>Differentiated</td>
<td>Papillary</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Grade Age (yrs)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Continuous</td>
<td>&lt;45</td>
<td>&lt;45</td>
<td>Continuous</td>
<td>&lt;41 male</td>
<td>Continuous</td>
<td>&lt;45</td>
<td>No</td>
<td>&lt;70</td>
<td>Variable</td>
<td>&lt;45</td>
</tr>
<tr>
<td>Gender (better prognosis)</td>
<td>Yes</td>
<td>No (female)</td>
<td>No</td>
<td>Yes</td>
<td>No (female)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Size (in cm)</td>
<td>No</td>
<td>&lt;1</td>
<td>Continuous</td>
<td>&lt;5</td>
<td>Continuous</td>
<td>&lt;1.5</td>
<td>No</td>
<td>&lt;3 cm</td>
<td>≤1</td>
<td>1–4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1–4</td>
<td>≥5</td>
<td>1–4</td>
<td>1.5–4.4</td>
<td>≥4.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Extrathyroid invasion</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Residual disease</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Multifocal</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Metastases</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Validation</td>
<td>Yes</td>
<td>Unknown</td>
<td>Yes</td>
<td>Unknown</td>
<td>Yes</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

EORTC: European Organization for Research and Treatment of Cancer; UICC: International Union Against Cancer; AJCC: American Joint Committee on Cancer; AGES: Age, Grade, Extrathyroid extent and Size; AMES: Age, Metastases, Extrathyroid extension, and Size; MACIS: Metastases, Age, Completeness of resection, Invasion, and Size; SAG: Sex, Age, and Grade; MSK: Memorial Sloan-Kettering Cancer Center.
Differentiated Thyroid Cancer
Eighth Edition AJCC Staging

Age at Diagnosis

< 55 years

Distant Metastasis

No

Stage I

Yes

Stage II

≥ 55 years

Distant Metastasis

No

Gross Extrathyroidal Extension

Yes

Stage IVb

≤ 4 cm

N0/Nx

Stage I

> 4 cm or

N1a/N1b

Stage II

Strap Muscles

Only (T3b)

Stage II

Subcutaneous,

larynx, trachea,

esophagus,

recurrent

laryngeal nerve

(T4a)

Stage III

Prevertebral

fascia, encasing

major vessels

(T4b)

Stage IVA

Stage IVb
Major Changes in the AJCC/TNM 8th Edition

Age point cut-off 55 years of age

- 8th edition -- 10-year DSS rates for stage I-IV 99.5%, 94.7%, 94.1%, and 67.6%
- 7th edition – 10-year DSS rates for stage I-IV 99.7%, 97.3%, 96.6% and 76.3%
- >55 y/o had 103 differently expressed genes related to pathways associated to aggressive TC.

mETE

- Eliminated from 8th edition
- Does not influence disease-free survival, locoregional failure, and distant metastases failure.
- No longer assignment of stage III to older patients with mETE or LN mets.

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

SEER
64,342 patients
Major Changes in the AJCC/TNM 8th Edition

Mediastinal lymph nodes mets
• 7th edition – level VII considered N1b
• 8th edition – level VII considered N1a
• Reclassifies patients from stage IVa to stage II

N1 disease
• No longer upstages older patients to stage III or IV
• <55 years – stage I
• >55 years stage II

Transition from the 7th Edition to the 8th edition

MD Anderson Cancer Center
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
Biochemical Incomplete
Structural Incomplete
Indeterminate

Determining Risk of Recurrence
### Initial Static Risk Stratification of Recurrence + 2015 ATA Updates

<table>
<thead>
<tr>
<th>Low (all of these)</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any size and intrathyroidal; Complete resection</td>
<td>Microscopic invasion into perithyroidal soft tissues</td>
<td>Gross ETE; incomplete tumor resection</td>
</tr>
<tr>
<td><strong>N0 or ≤5 LN &lt;0.2cm; M0</strong></td>
<td>Clinical N1 or &gt;5 LN (all &lt;3cm)</td>
<td><strong>N1 (any LN ≥3cm); M1</strong></td>
</tr>
<tr>
<td>No aggressive histology or Intrathyroidal PTC, FV Intrathyroidal FTC (no-min vascular invasion &lt; 4 foci) Intrathyroidal PTC BRAF&lt;sup&gt;V600E&lt;/sup&gt;</td>
<td>Aggressive histology or Multifocal, microPTC with ETE &amp; BRAF&lt;sup&gt;V600E&lt;/sup&gt;</td>
<td><strong>FTC with extensive vascular invasion (&gt; 4 foci)</strong></td>
</tr>
<tr>
<td>No vascular invasion</td>
<td>Vascular invasion</td>
<td>Inappropriate postop Tg suggestive of M1</td>
</tr>
<tr>
<td>No uptake outside thyroid bed, if RAI given</td>
<td>Uptake outside thyroid bed, if RAI given</td>
<td></td>
</tr>
</tbody>
</table>
Risk of Structural Disease Recurrence
(In patients without structurally identifiable disease after initial therapy)

Guides early treatment and follow-up recommendations

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%)

High Risk

Aggressive, incomplete tumor extension, vascular invasion, or > 5 involved lymph nodes (0.2-3 cm)

Low Risk

Intrathyroidal DTC
≤ 5 LN micrometastases (< 0.2 cm)

pT3 minor ETE (∼3-8%)
pN1, all LN < 0.2 cm (∼5%)
pN1, ≤ 5 LN involved (∼5%)
Intrathyroidal PTC, 2-4 cm (∼5%)
Multifocal PTMC (∼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 PTMC, BRAF mutated*, (∼1-2%)
Intrathyroidal, encapsulated, FV-PTC (∼1-2%)
Unifocal PTMC (∼1-2%)
## Retrospective Studies Validate ATA Initial Risk Stratification System

<table>
<thead>
<tr>
<th>ATA risk</th>
<th>Study</th>
<th>NED, %</th>
<th>Biochemical incomplete, %&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Structural incomplete, %&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Tuttle et al. (538)</td>
<td>86</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Castagna et al. (542)</td>
<td>91</td>
<td>ND&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ND&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Vaisman et al. (539)</td>
<td>88</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Pitoia et al. (543)</td>
<td>78</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Intermediate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Tuttle et al. (538)</td>
<td>57</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Vaisman et al. (539)</td>
<td>63</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Pitoia et al. (543)</td>
<td>52</td>
<td>14</td>
<td>34</td>
</tr>
<tr>
<td>High</td>
<td>Tuttle et al. (538)</td>
<td>14</td>
<td>14</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Vaisman et al. (539)</td>
<td>16</td>
<td>12</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Pitoia et al. (543)</td>
<td>31</td>
<td>13</td>
<td>56</td>
</tr>
</tbody>
</table>

- **NED**: stimulated Tg < 1ng/mL with no disease radiologically or clinically
- **Biochemical incomplete**: suppressed Tg>1ng/mL, stimulated Tg>10ng/mL, or rising Tg antibody in absence of structural disease
- **Structural incomplete**: structural disease that is bx-proven or highly suspicious for disease +/- abnormal Tg
Effect of Age on Response to Therapy and Mortality in Patients With Thyroid Cancer at High Risk of Recurrence

Sona Shah and Laura Boucai

1Department of Medicine, Division of Endocrinology, Memorial Sloan-Kettering Cancer Center, New York, New York 10065

- Retrospective cohort study of 320 patients
- Median age 49.3 years
- Follicular cell-derived thyroid carcinoma classified at ATA high risk
- Followed for a median of 7 years

Table 2. Response to Therapy at Final Follow-Up Stratified by Age

<table>
<thead>
<tr>
<th></th>
<th>Age &lt;55</th>
<th>Age ≥55</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>79 (40.3%)</td>
<td>34 (27.5%)</td>
<td>113 (35.3%)</td>
</tr>
<tr>
<td>Biochemical incomplete</td>
<td>10 (5%)</td>
<td>8 (6.5%)</td>
<td>18 (5.6%)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>43 (22%)</td>
<td>16 (13%)</td>
<td>59 (18.5%)</td>
</tr>
<tr>
<td>Structural incomplete</td>
<td>64 (32.7%)</td>
<td>66 (53%)</td>
<td>130 (40.6%)</td>
</tr>
<tr>
<td>Total</td>
<td>196</td>
<td>124</td>
<td>320</td>
</tr>
</tbody>
</table>

$\chi^2 P = 0.002$. 
Risk Stratification in Thyroid Cancer

A dynamic, iterative, active process

Peri-Diagnostic Risk Assessment
Candidates for Minimalistic Management

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
Biochemical Incomplete
Structural Incomplete
Indeterminate

Dynamic Risk Assessment
Results that modify risk

- Results of RAI scanning post-treatment
- Change in serum thyroglobulin (Tg) over time
- Change in serum Tg antibodies over time
- Physical exam or symptoms
- Findings on ultrasound at follow-up visits
- Stimulated Tg levels
- Other cross-sectional imaging findings
- FDG-PET imaging results
Response to Therapy Definitions

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

**Biochemical Incomplete Response**
- Persistent abnormal thyroglobulin values in the absence of localizable disease

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

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

### Response to Therapy Definitions

**Tg cut points based on initial therapy**

<table>
<thead>
<tr>
<th></th>
<th>Total Thyroidectomy &amp; RAI ablation</th>
<th>Total Thyroidectomy</th>
<th>Lobectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Excellent</strong></td>
<td>Tg &lt;0.2</td>
<td>Tg &lt;0.2</td>
<td>Tg &lt;30</td>
</tr>
<tr>
<td><strong>Indeterminate</strong></td>
<td>Tg 0.2-1.0</td>
<td>Tg 0.2-5.0</td>
<td>-</td>
</tr>
<tr>
<td><strong>Biochemical Incomplete</strong></td>
<td>Tg &gt;1.0</td>
<td>Tg &gt;5.0</td>
<td>Tg &gt;30</td>
</tr>
</tbody>
</table>
Summary of studies analyzing dynamic risk assessment in patients with differentiated thyroid cancer treated with total thyroidectomy and radioiodine remnant ablation.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Patients included</th>
<th>Median follow-up (months)</th>
<th>Persistent/recurrent disease based on each response-to-therapy category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuttle et al. 2010</td>
<td>588</td>
<td>All-risk patients</td>
<td>84</td>
<td>Exc 4% IR 0% BIR/SIR 57%</td>
</tr>
<tr>
<td>Castagna et al. 2011</td>
<td>512</td>
<td>All-risk patients</td>
<td>81.6</td>
<td>Exc 3.4% BIR/SIR 66%</td>
</tr>
<tr>
<td>Hong et al. 2014</td>
<td>398</td>
<td>All-risk patients</td>
<td>128</td>
<td>Exc 1.3% SIR 75.9%</td>
</tr>
<tr>
<td>Pitoia et al. 2015</td>
<td>149</td>
<td>Low- and intermediate-risk patients</td>
<td>72</td>
<td>Exc 1.6% BIR/SIR 31.8%</td>
</tr>
<tr>
<td>Kowalska et al. 2016</td>
<td>916</td>
<td>All-risk patients</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Trimboli et al. 2017</td>
<td>201</td>
<td>Low- and intermediate-risk patients</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Jeon et al. 2018</td>
<td>1359</td>
<td>Patients with excellent response</td>
<td>104.4</td>
<td></td>
</tr>
<tr>
<td>Lee et al. 2018</td>
<td>667</td>
<td>PTC 1-4 cm</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Schlumberger et al. 2018$^a$</td>
<td>726</td>
<td>Low-risk patients</td>
<td>64.8</td>
<td></td>
</tr>
<tr>
<td>Dehbi et al. 2019$^b$</td>
<td>434</td>
<td>T1-T3</td>
<td>78.4</td>
<td></td>
</tr>
<tr>
<td>N0/N1/Nx M0 (TNM 6th ed.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Velsen et al. 2019</td>
<td>236</td>
<td>High-risk patients</td>
<td>72</td>
<td>Exc 14%</td>
</tr>
<tr>
<td>Tian et al. 2019</td>
<td>767</td>
<td>High-risk patients</td>
<td>67.2</td>
<td>Pre-ablation s-Tg &lt;1 ng/mL and negative anti-Tg: 2.9%</td>
</tr>
</tbody>
</table>
Summary of studies analyzing dynamic risk assessment in differentiated thyroid cancer patients treated without radioiodine ablation

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Patients included</th>
<th>Median follow-up (months)</th>
<th>Persistent/recurrent disease based on each response-to-therapy category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Momesso et al. 2016</td>
<td>TT: 320, L: 187</td>
<td>Low risk: 433, Intermediate risk: 74</td>
<td>100.5</td>
<td>Exc 0% IR 1.3% BIR 31.6% SIR 100%</td>
</tr>
<tr>
<td>Park et al. 2017</td>
<td>TT: 64, L: 293</td>
<td>Low risk: 187, Intermediate risk: 170</td>
<td>103.2</td>
<td>Exc 0.78 IR 1.5% BIR 16.7% SIR 100%</td>
</tr>
<tr>
<td>Abelleira et al. 2017</td>
<td>TT: 88</td>
<td>Low risk: 78, Intermediate risk: 10</td>
<td>28</td>
<td>Exc 0% IR 5.6%</td>
</tr>
<tr>
<td>Lee et al. 2018</td>
<td>TT: 26, L: 69</td>
<td>Low and intermediate risk</td>
<td>124</td>
<td>Exc 7.4% IR 0% BIR 0% SIR 100%</td>
</tr>
<tr>
<td>Cho et al. 2018</td>
<td>L: 619</td>
<td>Low risk: 340, Intermediate risk: 279</td>
<td>103</td>
<td>Exc 1.6% IR 3.8% BIR 2.9% SIR 100%</td>
</tr>
</tbody>
</table>
Risk of structural disease at the end of follow-up and management recommendations for each response-to-therapy category

- **Excellent response**
  - 1-4%*
  - Non-stimulated Tg every 1-2 years
  - Little role for neck US*
  - TSH goal: 0.5-2 mU/L

- **Indeterminate response**
  - 15-20%
  - Monitor non-specific findings and Tg and TgAb level
  - TSH goal: 0.5-1 mU/L

- **Biochemical incomplete response**
  - 20%
  - Declining Tg or TgAb
  - Observation
  - Neck US every 2-3 years
  - CT scan
  - 18FDG-PET/CT, etc
  - TSH goal: 0.5-1 mU/L

- **Structural incomplete response**
  - 50-85%
  - Location of the disease
  - Rate of progression
  - Radioiodine avidity
  - Surgery
  - External beam radiation
  - MKI
  - Active surveillance
  - TSH goal: <0.1 mU/L
Overall survival improved with TSH suppression – Stages III & IV DTC

Prospective, multi-institutional registry

Outcome measures – overall survival, DSS and DFS

TH suppression therapy (TSH <0.1) improved survival in high risk (Stage III and IV)

Moderate TH suppression therapy (TSH 0.1-0.5) improved survival in Stage II
No benefit with TSH <0.03
No benefit in Stage I
Retrospective Study of 2 cohorts
524 patients with DTC
1,572 sex- and age-matched controls
Mean age 49 years
Median follow-up was 8.5 years

Primary aim – CV mortality
Secondary aim – Relation between TSH level and CV mortality/All-cause mortality
Fig 3. Kaplan-Meier survival curves for (A) cardiovascular mortality and (B) all-cause mortality for patients with differentiated thyroid carcinoma, by thyroid-stimulating hormone (TSH; also known as thyrotropin) category. TSH category 1, geometric mean TSH < 0.02 mU/L; category 2, geometric mean TSH 0.02 to 0.2 mU/L; and category 3, geometric mean TSH > 0.2 mU/L.
ATA Guidelines 2015 Recommendation 59

(Weak recommendation, Low-quality evidence)

(E) For low-risk patients who have undergone lobectomy, TSH may be maintained in the mid to lower reference range (0.5–2 mU/L) while surveillance for recurrence is continued. Thyroid hormone therapy may not be needed if patients can maintain their serum TSH in this target range.

(Weak recommendation, Low-quality evidence)
Fig. 1. Kaplan-Meier curves of recurrence-free survival (RFS). (A) Tumor size. (B) Mean thyroid-stimulating hormone levels for 5 years after surgery (TSH$_{syn}$) values. (C) Dominant TSH$_{syn}$ values. (D) Levothyroxine use.
Contributions of the molecular markers to the dynamic risk assessment
What about BRAF?

A significant association of BRAF V600E mutation with decreased survival, ...but the molecular ‘risk’ already identified through histopathology

- Retrospective
- 16 centers in 8 countries
- 2099 patients
- 48% PTC BRAF V600E
Identifying multiple genomic alterations more powerful than one

…but mostly for very advanced cancer

**BRAF, TERT & RAS** - Recurrence Free Survival

Incremental & synergistic effects of the coexisting *three* mutations.
# Three Prognostic Categories

**Braf-like vs. Ras-like vs. NBNR**

Tang et al:
- RNA expression / Histopathologic correlation from two databases (TCGA)
- Analysis of 571 (from 676) thyroid cancer cases into BRAF-like, RAS-like, Non-BRAF/Non-RAS-like. *(about 15% into another category)*

<table>
<thead>
<tr>
<th>Pathologic Feature</th>
<th>BRAF-like</th>
<th>RAS-like</th>
<th>NBNR-like</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node mets</td>
<td>49%</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td>Gross ETE</td>
<td>7%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>N1b or T4 disease</td>
<td>22%</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Distant mets</td>
<td>3%</td>
<td>4%</td>
<td>0%</td>
</tr>
</tbody>
</table>

RNA Expression patterns predict pathologic findings (risk)
Three Prognostic Categories

Braf-like vs. Ras-like vs. NBNR

Tang et al:
- RNA expression / Histopathologic correlation from two databases (TCGA)
- Analysis of 571 (from 676) thyroid cancer cases into BRAF-like, RAS-like, Non-BRAF/Non-RAS-like. (?about 15% into another category)

Association of specific genomic alterations with RNA expression classes:

<table>
<thead>
<tr>
<th>BRAF V600-like</th>
<th>BRAF V600-like/RAS-like overlap</th>
<th>RAS-like</th>
<th>Non-BRAF-Non-RAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher</td>
<td>Lower</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF V600E</td>
<td>NTRK1-3 fusions</td>
<td>H/K/NRAS</td>
<td>DICER1</td>
</tr>
<tr>
<td>BRAF fusions</td>
<td>ALK fusions</td>
<td>Braf K601E</td>
<td>EIF1AX</td>
</tr>
<tr>
<td>RET fusions</td>
<td>FGFR2 fusions</td>
<td>TSHR</td>
<td>E2H1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SOS1</td>
</tr>
</tbody>
</table>

RNA Expression groupings (more so than DNA mutations) inform us which genomic findings are independently predictive
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
Biochemical
Incomplete
Structural
Incomplete
Indeterminate