Adjuvant Therapy of Thyroid Cancer:
rhTSH, RAI, EBRT and Targeted Therapeutics

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BC Cancer Surgeon Network Fall Update

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Disclosure(s)

- Varian Medical Systems – Research Grants, Consultant
- Genzyme/Sanofi – Advisory Board, Research Grant
- Astra Zeneca – Advisory Board
Outline

Scope of the Problem
Staging and Risk Assessment
Radioiodine Remnant Ablation and Therapy
External Beam Radiotherapy
Targeted Therapies
Scope of the Problem

• Canada:
  – Incidence: Approximately 6,300 in 2015
  – Deaths: 185 deaths in 2010

• BC (2007):
  – New cases: 68 men, 211 women
  – Deaths: 5 men and 9 women
  – Most deaths in patients over 60 yrs
Scope of the Problem

90% Well differentiated tumours
4% Medullary
5% Anaplastic

5 Year Survival:
- Papillary ca 98%
- Follicular ca 94%
- Medullary ca 80%
- Anaplastic ca < 5%
Management

Surgery – Primary Treatment

Adjuvant Radiation
- Radioiodine (131-Iodine)
- External Beam Radiation

Thyroxine

Systemic Therapy

** No Prospective Randomized Trials **

Cooper et al, Thyroid. 2006 Feb;16(2):109-42.

(Strong recommendation, Moderate-quality evidence)
Adjuvant Therapy

(How)

- Radioiodine (131-I) $\rightarrow$ microscopic disease
  - Therapy: 150-200 mCi
  - Remnant Ablation: 30 mCi
- External beam RT $\rightarrow$ macroscopic disease
- Thyroxine
Who should we treat?

- **Risk of Recurrence**
  - ATA Risk Stratification

- **Risk of Death**
  - TNM, AJCC
  - AMES, AGES
  - MACIS
### Table 11. ATA 2009 Risk Stratification System with Proposed Modifications

<table>
<thead>
<tr>
<th>ATA low risk</th>
<th>Papillary thyroid cancer (with all of the following):</th>
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<td>• No vascular invasion</td>
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<td><strong>Clinical N0 or ≤5 pathologic N1 micrometastases (&lt;0.2 cm in largest dimension)</strong></td>
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<tr>
<td></td>
<td>Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer</td>
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<tr>
<td></td>
<td>Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (&lt;4 foci) vascular invasion</td>
</tr>
<tr>
<td></td>
<td>Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including $\textit{BRAF}^{V600E}$ mutated (if known)</td>
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<td><strong>Clinical N1 or &gt;5 pathologic N1 with all involved lymph nodes &lt;3 cm in largest dimension</strong></td>
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<td>Multifocal papillary microcarcinoma with ETE and $\textit{BRAF}^{V600E}$ mutated (if known)</td>
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<td>Follicular thyroid cancer with extensive vascular invasion (&gt; 4 foci of vascular invasion)</td>
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Table 12. American Thyroid Association Risk Stratification System: Clinical Outcomes Following Total Thyroidectomy and Radioiodine Remnant Ablation or Adjuvant Therapy

<table>
<thead>
<tr>
<th>ATA risk</th>
<th>Study</th>
<th>NED, %</th>
<th>Biochemical incomplete, %(^b)</th>
<th>Structural incomplete, %(^c)</th>
</tr>
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<tbody>
<tr>
<td>Low</td>
<td>Tuttle et al. (538)</td>
<td>86</td>
<td>11</td>
<td>3</td>
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<tr>
<td></td>
<td>Castagna et al. (542)</td>
<td>91</td>
<td>ND(^a)</td>
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<td></td>
<td>Vaisman et al. (539)</td>
<td>88</td>
<td>10</td>
<td>2</td>
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<td></td>
<td>Pitoia et al. (543)</td>
<td>78</td>
<td>15</td>
<td>7</td>
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<td>Intermediate(^a)</td>
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<td>Intra- or extrathyroidal lymph node involvement</td>
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<td>Clinical N1 or N2 micrometastases with centrally located node</td>
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2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

Bryan R. Haugen,\(^{1,4}\) Erik K. Alexander,\(^{2}\) Keith C. Bible,\(^{3}\) Gerald M. Doherty,\(^{4}\) Susan J. Mandel,\(^{5}\) Yuri E. Nikiforov,\(^{6}\) Furio Pacini,\(^{7}\) Gregory W. Randolph,\(^{8}\) Anna M. Sawa,\(^{9}\) Martin Schlumberger,\(^{10}\) Kathryn G. Schuff,\(^{11}\) Steven I. Sherman,\(^{12}\) Julia Ann Sosa,\(^{13}\) David L. Steward,\(^{14}\) R. Michael Tuttle,\(^{15}\) and Leonard Warshsky\(^{16}\)
**Risk of Death – AJCC/TNM**

**Table 10. AJCC 7TH EDITION/TNM CLASSIFICATION SYSTEM FOR DIFFERENTIATED THYROID CARCINOMA**

<table>
<thead>
<tr>
<th>Definition</th>
<th>I</th>
<th>Any T</th>
<th>Any N</th>
<th>M0</th>
</tr>
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<tbody>
<tr>
<td><strong>T0</strong> No evidence of primary tumor</td>
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<tr>
<td><strong>T1a</strong> Tumor ≤1 cm, without extrathyroidal extension</td>
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<tr>
<td><strong>T1b</strong> Tumor &gt;1 cm but ≤2 cm in greatest dimension, without extrathyroidal extension</td>
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<tr>
<td><strong>T2</strong> Tumor &gt;2 cm but ≤4 cm in greatest dimension, without extrathyroidal extension</td>
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</tr>
<tr>
<td><strong>T3</strong> Tumor &gt;4 cm in greatest dimension limited to the thyroid or Any size tumor with minimal extrathyroidal extension (e.g., extension into sternohyoid muscle or perithyroidal soft tissues)</td>
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<td><strong>T4a</strong> Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve.</td>
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<td><strong>T4b</strong> Tumor of any size invading prevertebral fascia or encasing carotid artery or mediastinal vessels</td>
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<tr>
<td><strong>N0</strong> No metastatic nodes</td>
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<tr>
<td><strong>N1a</strong> Metastases to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes).</td>
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<tr>
<td><strong>N1b</strong> Metastases to unilateral, bilateral, or contralateral cervical (levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (level VII)</td>
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<tr>
<td><strong>M0</strong> No distant metastases</td>
<td></td>
<td></td>
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<tr>
<td><strong>M1</strong> Distant metastases</td>
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**Patient age <45 years old at diagnosis**

<table>
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**Patient age ≥45 years old at diagnosis**

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</tr>
<tr>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>M0</td>
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<tr>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
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**Papillary carcinoma**

![Graph showing relative survival rate over months after diagnosis for papillary carcinoma]

**Follicular carcinoma**

![Graph showing relative survival rate over months after diagnosis for follicular carcinoma]

SEER 1988-2001
Risk of Death – AGES, AMES

**AGES**
- Age: >45 years of age
- Grade: problematic
- Extrathyroidal (soft tissue) extension
- Size: 2cm (6%) vs 7cm (50%) mortality

**AMES**
- Age
- Metastasis
- Extrathyroidal extension
- Size

*Baudin and Schlumberger, Lancet Oncology, 2007*


< 40 yrs
- Metastases <1cm

< 40 yrs
- Metastases >1cm

> 40 yrs
- Metastases <1cm

> 40 yrs
- Metastases >1cm

*Fig. 2 Cumulative incidence of cause-specific survival and local-regional relapse-free rate by age.*

*Brierley et al Clin Endocrinology 2005*
Risk of Death - MACIS

What we use at BCCA:

• MACIS
  – 3.1 (<40yo) or 0.08 x age (if 40 or more years old)
  – 0.3 x tumor size (in cm)
  – +1 if incompletely resected
  – +1 if locally invasive
  – +3 if distant metastases

• MACIS – 20yr Disease Specific Mortality
  <6.0 = 1%
  6.0 – 6.99 = 11%
  7.0 – 7.99 = 44%
  >8 = 76%

Radioiodine 131-I – Who should we treat?

- No randomized trials
- Does RAI 131-I reduce risk of recurrence? **Maybe**
- Evidence of survival benefit? **Maybe**

**Two schools of thought**
- Treat more! (Mazzaferri et al)
- Treat less! (Hay et al)

**BCCA – Weekly Provincial Thyroid Conference**
- MACIS score > 6.0 or ATA high risk = treatment dose
- MACIS score 5.0 to 6.0 or ATA intermediate = Provincial Thyroid Conference
- Treating fewer patients (therapeutic dose)
- Lower doses for Ablation: 30 mCi
- More outpatient therapy
Adjuvant Therapy

Radioiodine (131-I) – how do we do it?

- TSH stimulation (> 30)
- Two methods:
  - Endogenous TSH ie. Thyroxine withdrawal
  - Exogenous TSH ie. Thyrotropin alpha (rhTSH)
- rhTSH (thyrotropin alpha)
  - Two retrospective studies: rhTSH = withdrawal
  - Improved quality of life
  - Expensive
  - Side effects
    - Common: Nausea 10%, Headache: 7%
    - Rare (<3%): fatigue, insomnia, vomiting, diarrhea, weakness

- Low Iodine Diet

Barbaro, J Clin Endocrinol Metab 2003 Sep;88(9):4110-5
Schroeder, J Clin Endocrinol Metab. 2006 Mar;91(3):878-84. Epub 2006 Jan 4
Adjuvant Therapy

Radioiodine (131-I) Protocol

• Protocol
  Monday: 0.9mg IM (thyrotropin alpha)
  Tuesday: 0.9mg IM (thyrotropin alpha)
  Wednesday: 123-I scan + 131-I therapy
    – “radioactive” Wednesday, Thursday, Friday
    – Inpatient versus Outpatient

  Monday:
    – Whole body scan
    – Blood tests: TSH, Tg

• RAI is Diagnostic and Therapeutic

RECOMMENDATION 58
A posttherapy WBS (with or without SPECT/CT) is recommended after RAI remnant ablation or treatment, to inform disease staging and document the RAI avidity of any structural disease.
(Strong recommendation, Low-quality evidence)
Hi-Lo Trials

• Increasing incidence of low risk disease
• Conflicting data for RAI and low risk disease
  – ATA: no clear recommendations
  – European Thyroid Cancer Task Force: mildly yes

• **Remnant Ablation – not therapy**

• 2 trials (Mallick, Schlumberger):
  – 2 x 2
  – 30 vs 100 mCi
  – rhTSH vs withdrawal

• Results:
  – 30 mCi and rhTSH
  – No long term FU for recurrences
  – Do they even need treatment?
Radioiodine (131-I) Side Effects

- Fatigue
- Xerostomia
- Dysgeusia
- Sialoadenitis (Dr. Irvine)
- Transient hypogonadism (spermatopenia)
- Myelosuppression (transient versus permanent)
- Hypothetical risk of aplastic anaemia and leukaemia
  - Doses >1000Ci (usual dose 80-150mCi)
Adjuvant Therapy

- Radioiodine (131-I) $\rightarrow$ microscopic disease
  - Ablation of remnant
  - Therapy of disease
- External beam RT $\rightarrow$ macroscopic disease
  - Thyroxine
  - Chemotherapy, targeted agents
External Beam Radiotherapy

- Gross (macroscopic) disease
- Unresectable gross disease
- Gross disease not responding to 131-I
- 5 to 7 weeks, daily treatment

Sequelae:

- Xerostomia, altered taste, esophagitis, pharyngitis, laryngitis, fatigue, dry/moist desquamation

RECOMMENDATION 60
There is no role for routine adjuvant EBRT to the neck in patients with DTC after initial complete surgical removal of the tumor.
(Strong recommendation, Low-quality evidence)
Adjuvant Therapy

Thyroxine - Rationale:
1. Replacement Therapy → FT4
2. Suppressive Therapy → TSH

Other Notes:
- 4 - 6 weeks to equilibrate
- Measure FT4 and TSH
  - FT4: Upper limits of normal
  - TSH: <0.1 to 2.0 mU/L
- TSH Suppression: How low do you go?

Brabant G 2008 Thyrotropin suppressive therapy in thyroid carcinoma: what are the targets? J Clin Endocrinol Metab 93:1167–1169.
Adjuvant Therapy

TSH Suppression: How low do you go?

- Low Risk: 0.5 to 2.0 mU/L
- Intermediate Risk: 0.1 to 0.5 mU/L
- High Risk: < 0.1 mU/L

- BCCA: Generally < 1.0 mU/L, depending on risk category
  - Evidence strongest for High Risk

Why not < 0.1 mU/L for everyone?

- Low TSH = High FT4
- Prolonged hyperthyroidism
  - atrial fibrillation
  - cardiac hypertrophy and dysfunction
  - accelerated osteoporosis
- Balance risk of recurrence vs hyperthyroidism

Pujol P, Daures JP, Nuakala N, Baldet L, Bringer J, Jaffiol C 1996 Degree of thyrotropin suppression as a prognostic determinant in differentiated thyroid cancer. J Clin Endocrinol Metab 81:4318–4323.
Recurrence

Gross disease:
- If resectable: Surgery
- Not resectable: 131-I + EBRT
- If non-iodine-avid: EBRT

Rising Tg – No gross disease?
- Empiric dose (100-200 mCi) 131-I **NOT a 5 mCi SCAN**
- TSH-stimulated PET scan

RAI resistant disease:
- Chemotherapy: doxorubicin
- Multi Kinase Inhibitors: vandetanib, sorafenib, lenvatinib
  - Sequelae: diarrhea, fatigue, HPT, hepatotoxicity, skin changes, nausea, dysgeusia, anorexia, thrombosis, heart failure,
Summary

Risk Stratification: Recurrence vs Survival

Does Adjuvant Therapy Change Outcomes?

Microscopic Disease: RAI, 150-200 mCi
  - Remnant Ablation: 30 mCi, rhTSH

Macroscopic Disease: EBRT

Recurrent Disease: Surgery, RAI, EBRT

RAI-Resistant Disease: Tyrosine-Kinase Inhibitors