I-131 ABLATION AND ADJUVANT THERAPY OF THYROID CANCER – 2015

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OBJECTIVES

To Describe:

- Rationale for 131-I ablation
- Distinguish between ablation & adjuvant therapy
- Selection of patients for ablation
- Methods of preparation of patients for ablation
DISCLOSURES

- Consultant
  - Asuragen; Interpace Diagnostics
  - IBSA
  - Eisei, Inc.
- Sanofi: speaker honoraria
WHO TO ABLATE OR TREAT?
ATA GUIDELINES: 2015

- AJCC/UICC staging
- ATA risk of recurrence stratification system post thyroidectomy
- Base decision for ablation on:
  - ATA Risk of Recurrence
  - Post-thyroidectomy serum Tg levels
- Adjuvant dosage for suspected residual disease
THYROID CANCER
131-I Ablation & Adjunctive Therapy

● ATA Cancer Guidelines
  - Who to Ablate? Who not to ablate?
  - 30 mCi or 100 mCi ?

● rhTSH for Ablation
  - Efficacy
  - Safety
  - Cost effectiveness
RECOMMENDATION 48: RISK STRATIFICATION

- The 2009 ATA Initial Risk Stratification System is recommended for DTC patients post-thyroidectomy.
  (Strong recommendation, Moderate-quality evidence)

- Additional prognostic variables (i.e., extent of LN mets., mutational status, and/or degree of vascular invasion in FTC not included in the 2009 ATA Risk Stratification system, may be used to refine DTC risk stratification.
  (Weak recommendation, Low-quality evidence)
ATA RISK STRATIFICATION

- **LOW RISK**
  - No local or distant metastases
  - All microscopic tumor resected
  - No locoregional tumor invasion
  - No aggressive histology or vascular invasion
  - If 131-I given, no uptake outside of thyroid bed on post-Rx scan
ATA RISK STRATIFICATION

● INTERMEDIATE RISK
  – (+) microscopic perithyroidal invasiveness
  – (+) lymph nodes or uptake outside thyroid bed
  – (+) aggressive histology or vascular invasion

● HIGH RISK
  – Macroscopic invasion of tumor
  – Incomplete tumor resection
  – Distant mets or Tg suggestive of distant mets
Post-surgical ablation

- **Definition:**
  - destruction of remnant thyroid tissue post thyroidectomy

- **Potential Benefits**
  - Decrease recurrence rate
  - Reduce cause-specific mortalities
  - Permit serum Tg measurement as follow up
  - Facilitate I-131 scans to detect recurrence
  - ? Avoid de-differentiation
  - Achieve greater certainty and peace of mind
Thyroid Cancer
Initial Treatment Strategy

Diagnosis of Thyroid Cancer

Low Risk
- Lobectomy
- Isthmusectomy
- Physical Exam
- Ultrasound

Intermediate and High Risk
- Total Thyroidectomy
- RAI Ablation

Kinder BK. *Curr Opin Oncol.* 2003;15):71-77.
ATA CANCER GUIDELINES 2015
WHO TO ABLATE?
BASIS FOR RAI ABLATION

● ATA Risk of Recurrence
● Historical outcome data
● Post thyroidectomy Status:
  ● Diagnostic Scan
  ● Serum Tg levels
  ● Neck Ultrasound
WHO TO ABLATE?

- All pts with known distant metastases, extrathyroidal extension regardless of tumor size or primary tumor >4 cms
- Tumors 1-4 cms with other risk features
WHO NOT TO ABLATE?

- Pts with **unifocal** tumor < 1 cm lacking other risk features
- Pts with **mutifocal** tumors with all foci < 1 cm lacking higher risk features
WHO TO ABLATE? RECOMMENDATION 51:
Decision based on ATA risk of recurrence stratification system post thyroidectomy

- Do not give RAI for “low risk” DTC*
  *Weak Recommendation; Low Quality evidence*

- Do not give RAI for unifocal Micro PTC*
  *Strong Recommendation; Moderate Quality evidence*

- Do not give RAI for multifocal Micro PTC *
  *Weak Recommendation; Low Quality evidence*

*absent any other higher risk features
WHO TO ABLATE? ATA GUIDELINES: 2015
Decision based on ATA risk of recurrence stratification system post thyroidectomy

- Yes, RAI ablation for **Intermediate risk**
  - selected patients with 1–4 cm tumors confined to thyroid and LN metastases
  - Other high risk features (when combination of age, tumor size, LN status, and histology predicts an intermediate/high risk of recurrence or death)

*Weak Recommendation; Low Quality evidence*
WHO TO ABLATE? ATA GUIDELINES: 2015
Decision based on ATA risk of recurrence stratification system post thyroidectomy

- Yes, RAI ablation for **High risk**
  - known distant metastases
  - Extrathyroidal extension regardless of tumor size
  - tumor size >4 cm even absent other high risk features.

*Strong Recommendation; Moderate Quality evidence*

*
ON WHAT ISSUES IS THE DECISION FOR RADIOIODINE ABLATION BASED?
RECOMMENDATION 50: SHOULD POST-OP STATUS INFLUENCE DECISION ON RAI Rx?

- Post-op disease status (i.e., presence or absence of persistent disease) should be considered to decide if additional Rx (e.g., RAI, surgery, or other Rx) is needed.

  **Strong recommendation, Low-quality evidence**

- Use post-op serum Tg to assess persistence of disease or thyroid remnant and predict future recurrence.

  **Strong recommendation, Moderate-quality evidence**
CLINICAL UTILITY OF POST-OPERATIVE THYROGLOBULIN

• Predicts likelihood of successful ablation
• Post-op THW-TSH stimulated Tg >6 ng/mL associated with higher rate of failed ablation
  • After 30 mCi (Tamilia, Nucl Med Comm 2011)
  • After 100 mCi (Bernier, Eur J Nuc Med 2005)
• TSH-stimulated Tg >6 ng/mL associated with 5-fold risk of failed ablation after THW and 30 mCi dose (Tamilia, Nucl Med Comm 2011)
HOW SHOULD PATIENTS BE PREPARED FOR RADIOIODINE ABLATION?
A low-iodine diet for 1 to 2 weeks should be considered for patients undergoing RAI remnant ablation or treatment.

Weak recommendation, Low-quality evidence
HOW SHOULD PATIENTS BE PREPARED FOR RADIOIODINE ABLATION?

Thyroxine Withdrawal or Recombinant human TSH?
HOW COST EFFECTIVE IS ABLATION BY rhTSH vs. THYROXINE WITHDRAWAL?
## THYROGEN ABLATION vs. WITHDRAWAL COST EFFECTIVENESS
Borget et al., Eur J Endocrinol 2007;156:531-8

292 patients completed a questionnaire

<table>
<thead>
<tr>
<th>Withdrawal</th>
<th>rhTSH</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 98</td>
<td>n=194</td>
<td></td>
</tr>
</tbody>
</table>

| Sick Leave | 33%   | 11%   | <0.001 |
| Duration of Sick Leave (days) | 11.2 | 3.1 | 0.002 |
| Mean indirect costs from absenteeism | 1537 | 454 | <0.0003 |
COMPARISON OF QUALITY OF LIFE
THYROGEN ABLATION vs. WITHDRAWAL
Schroeder et al., JCEM 2006;91:878-84
HOW EFFECTIVE IS rhTSH FOR RAI ABLATION OF THYROID REMNANTS?
Ablation Results: No Visible Activity or <0.1% Uptake

Ablation Results\textsuperscript{1}: Thyrogen Stimulated Tg<2ng/mL

\textsuperscript{1} Pacini, et al. J Clin Endocrinol Metab 2006; 91(2):926-32
Follow-Up Data
Elisei et al., JCEM 2009; 94:4171-9

- 51/61 patients from the earlier study
- Median follow-up = 3.7 yrs
- 48 pts had rhTSH-stimulated Tg & neck/whole body imaging
- All scans confirmed successful ablation (no visible uptake or <0.1% uptake)
- No patient had cancer recurrence in 3.7 yrs of follow-up
Strategies of Radioiodine Ablation in Patients with Low-Risk Thyroid Cancer

Martin Schlumberger, M.D., Bogdan Catargi, M.D., Ph.D., Isabelle Borget, Pharm.D., Ph.D., Désirée Deandreis, M.D., Slimane Zerdoud, M.D., Boumédiène Bridji, M.D., Ph.D., Stéphane Bardet, M.D., Laurence Leenhardt, M.D., Ph.D., Delphine Bastie, M.D., Claire Schwartz, M.D., Pierre Vera, M.D., Ph.D., Olivier Morel, M.D., Danielle Benisvy, M.D., Claire Bournaud, M.D., Françoise Bonichon, M.D., Catherine Dejax, M.D., Marie-Elisabeth Toubert, M.D., Sophie Leboulleux, M.D., Marcel Ricard, Ph.D., and Ellen Benhamou, M.D., for the Tumeurs de la Thyroïde Refractaires Network for the Essai Stimulation Ablation Equivalence Trial*

Ablation with Low-Dose Radioiodine and Thyrotropin Alfa in Thyroid Cancer

### Summary of HiLo and ESTIMABL

**Mallick, et al., NEJM, 2012; Schlumberger, et al., NEJM, 2012**

<table>
<thead>
<tr>
<th></th>
<th>HiLo</th>
<th>ESTIMABL</th>
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<tbody>
<tr>
<td>30 mCi</td>
<td>85%</td>
<td>91%</td>
</tr>
<tr>
<td>100 mCi</td>
<td>89%</td>
<td>94%</td>
</tr>
<tr>
<td>rTSH</td>
<td>87%</td>
<td>92%</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>87%</td>
<td>93%</td>
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</table>

- Equivalence criteria met in all 4 cohorts in both trials
- Higher complete ablation in ESTIMABL
- DFS and recurrence rates not determined
RECOMMENDATION 54: IS rhTSH AN ALTERNATIVE TO THWD FOR ABLATION? - 1

- If RAI ablation planned for ATA low/intermediate risk DTC without extensive LN’s (i.e., T1-T3, N0/Nx/N1a, M0), rhTSH is acceptable alternative to THWD, given superior short-term QOL, non-inferiority of ablation efficacy, and no difference in long-term outcomes.

  (Strong recommendation, Moderate-quality evidence)

- In patients with ATA intermediate risk DTC with extensive LN’s but M0, rhTSH may be considered an alternative to THWD, prior to adjuvant RAI Rx.

  (Weak recommendation, Low-quality evidence)
In ATA high risk DTC with risks of disease-related mortality and morbidity, more long-term outcome studies are needed before rhTSH preparation for RAI adjuvant Rx can be recommended. (No recommendation, Insufficient evidence)

rhTSH should be considered in DTC of any risk level with co-morbidity precluding THWD such as:
- significant medical/psychiatric condition that hypothyroidism could worsen causing a serious adverse event
- inability to raise endogenous TSH after THWD. (Strong recommendation, Low-quality evidence)
HOW MUCH RADIOIODINE IS NECESSARY FOR ADEQUATE ABLATION?
Should employ the minimum activity (30-100 mCi) necessary to achieve successful remnant ablation, particularly for low risk patients.

Recommendation: B
Strategies of Radioiodine Ablation in Patients with Low-Risk Thyroid Cancer

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Ablation with Low-Dose Radioiodine and Thyrotropin Alfa in Thyroid Cancer

HiLo Trial: Results

RECOMMENDATION 55:
DOSE ACTIVITY OF 30 mCi SUPPORTED BY RECENT META-ANALYSES

- Ma C, et al., 2013 Nucl Med Commun 34:1150-1156
- Cheng W, et al., 2013 JCEM 98:1353-1360
Radioiodine Ablation - 2015

- Do we give it?

- So, how much do we give now?

- How do we prepare patients for therapy?
RECOMMENDATION 55:
WHAT DOSE ACTIVITY OF 131-I FOR ABLATION?

● If post-op RAI remnant ablation is performed for ATA low or intermediate risk DTC (with low volume central neck LN metastases and no other gross residual disease or other adverse features), a low administered dose activity of \( \sim 30 \text{ mCi} \) \( (1.11 \text{ GBq}) \) is favored over higher administered dose activities.

Strong recommendation, High-quality evidence
PREPARATION FOR RADIOIODINE ABLATION; WHICH IS SAFER?

Thyroxine Withdrawal
or
Recombinant human TSH?
Use of rhTSH for Ablation

IN REGARD TO RELATIVE SAFETY:

- rhTSH causes less radiation exposure to bone marrow than did hypothyroidism:
  - Hypothyroid group: 0.167 ± 0.061 mGy/MBq
  - rhTSH group: 0.109 ± 0.028 mGy/MBq (p<0.0001)

Pacini et al. J Clin Endocrinol Metab 2006; 91:926-32
WHOLE BODY RADIATION FROM REMNANT ABLATION IS LESS AFTER rhTSH

- Prospective study of patients with DTC
- Measured:
  - whole body counts (retention)
  - urine counts
  - whole body scans
  - effective $t_{1/2}$
- Confirms prior studies indicating less radiation dose after rhTSH
Figure 2. This depicts the residence times of \(^{131}\text{I}\) within a cell from various tissues. THW denotes thyroid hormone withdrawal, and rhTSH recombinant human TSH. *P = 0.0006; †P = 0.04; ‡P = 0.01; §P = 0.07; γP = 0.0006. All comparisons are between rhTSH and THW. Data for this graph are derived from Table 3 in Remy et al.

131I-Related Adverse Effects with rhTSH (Group A) and Hypothyroidism (Group B)

- Low Platelets or Neutopenia:
  - Group A: 7%
  - Group B: 21%

- Mean Decrease in Neutrophils:
  - Group A: 20%
  - Group B: 45%

- Mean Decrease in Platelets:
  - Group A: 25%
  - Group B: 52%

- Increased 8-epi-PGF 2α:
  - Group A: 56
  - Group B: 100†

- Mean increase 8-epi-PGF 2α:
  - Group A: 60
  - Group B: 125†

Clinical Thyroidology Volume 21 Issue 1 2009

131I-Related Adverse Effects with rhTSH (Group A) and Hypothyroidism (Group B)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Group A</th>
<th>Group B</th>
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<tbody>
<tr>
<td>Elevated FSH Men</td>
<td>105</td>
<td>236*</td>
</tr>
<tr>
<td>Elevated FSH Women</td>
<td>65</td>
<td>125*</td>
</tr>
<tr>
<td>Elevated Amylase</td>
<td>37</td>
<td>80*</td>
</tr>
<tr>
<td>Acute Sialoadenitis</td>
<td>30</td>
<td>58†</td>
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</table>
WHAT IS ADJUVANT THERAPY?

- **NCI**
  Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy.
WHAT IS ADJUVANT THERAPY?

Wikipedia

Treatment given in addition to the primary or initial treatment; e.g., the additional treatment usually given after surgery where all detectable disease has been removed, but where there remains a statistical risk of relapse due to occult disease. If known disease is left behind following surgery, then further treatment is not technically adjuvant.
Administered activities higher than 30 mCi may need to be considered for patients receiving less than a total or near-total thyroidectomy where a larger remnant is suspected or where adjuvant therapy is intended.

(Weak recommendation, Low-quality evidence)
RECOMMENDATION 56: WHAT DOSE ACTIVITY OF 131-I FOR ADJUVANT Rx FOR RESIDUAL DISEASE?

- When RAI is used for initial adjuvant Rx for suspected microscopic residual disease in intermediate/high risk patients, activities of 30-150 mCi are generally recommended (in absence of known distant metastases). Use of higher activities in this setting does not appear to reduce structural disease recurrence for T3 and N1 disease.

(Weak recommendation, Low quality evidence)
WHO TO ABLATE? CONCLUSIONS
ATA GUIDELINES: 2015

- Use ATA risk of recurrence stratification system post thyroidectomy
- No RAI for “low risk” DTC, unifocal PMC, or multifocal PMC
- RAI ablation for intermediate & High risk
- For thyroid remnant ablation, rhTSH:
  - is as effective as withdrawal
  - avoids Sx of hypothyroidism
  - provides 33% lower radiation exposure
CONCLUSIONS

- Use Post-op Tg for decision making on RAI ablation
- Favored Approach: Low doses (30 mCi) with rhTSH
- Longer term outcome studies will be required to confirm the wisdom of low dose ablation
- Higher activities for adjuvant Rx (? 75-150 mCi)
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