DISCUSSION

OVERVIEW OF I-131 THERAPY
IN PATIENTS WITH DIFFERENTIATED THYROID CANCER

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I-131 THERAPY encompasses:

- Remnant ablation
- Adjuvant therapy
- Therapy
• Remnant ablation:
  • Destroy normal residual functioning thyroid tissue:
    ✓ Facilitate the interpretation of thyroglobulin,
    ✓ Increase the diagnostic sensitivity of subsequent I-131 scans,
    ✓ Maximize the therapeutic effect of subsequent I-131 treatments
    ✓ Perform a post ablation scan: additional sites & final staging
• Remnant ablation:
  • Warranted in all cases except micro[carcinoma]
    ✓ T < 1 cm
    ✓ No multifocality
    ✓ No local, regional or vascular invasion
    ✓ No aggressive histology

  ▪ If surgical extent is *adequate low-risk tumors can be treated with 30 mCi of I-131 to facilitate follow-up.

*Surgery should have been total or near total thyroidectomy; the remnant volume should be < 2 g; there should not be residual tumor in regional lymph nodes.
ATA GUIDELINES 2009

Three-level stratification for assessment of risk of recurrence:

- Low-risk patients have the following characteristics: 1) no local or distant metastases; 2) all macroscopic tumor has been resected; 3) there is no tumor invasion of locoregional tissues or structures; 4) the tumor does not have aggressive histology (e.g., tall cell, insular, columnar cell carcinoma) or vascular invasion; 5) and, if $^{131}$I is given, there is no $^{131}$I uptake outside the thyroid bed on the first posttreatment whole-body RAI scan (RxWBS).

Other aggressive subtypes: diffusely sclerosing, trabecular, clear-cell.
Since initial staging is based on clinico-pathologic factors that are available shortly after diagnosis and initial therapy, the AJCC stage of the patient does not change over time.

However, 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.
• **Adjuvant therapy:**
  
  • Destroy unknown microscopic thyroid cancer and/or suspected but unproven residual thyroid cancer:
    
    ✓ to potentially decrease recurrence and mortality from thyroid cancer.
  
  • **Adequate surgery is the most important treatment variable influencing prognosis.**
  
  • Well operated intermediate-risk tumors can be treated with 100-150 mCi of I-131.
Intermediate-risk patients have any of the following: 1) microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery; 2) cervical lymph node metastases or $^{131}$I uptake outside the thyroid bed on the RxWBS done after thyroid remnant ablation (200,201); or 3) tumor with aggressive histology or vascular invasion
This study is the first to show that the risk for persistent disease (22%) is a critical point, being much higher than the risk for recurrent disease (8%).

Significant risk factors for persistent disease included the numbers of LN metastases (>10) and LN metastases with extracapsular extension (>3), tumor size (>4 cm), and LN metastases location (central).
• **Frequency of persistent disease**

  ✓ Tumor $<$ 4 cm + metastatic LN $\leq$ 10 / ECE LN $\leq$ 3: 10-13%
  ✓ Tumor $<$ 4 cm + metastatic LN $>$ 10 / ECE LN $>$ 3
    OR Tumor $\geq$ 4 cm + LN(-): 20-45%

  ✓ Tumor $\geq$ 4 cm + metastatic LN $>$ 10 / ECE LN $>$ 3: 75%
  ✓ 26 pts without involvement of central compartment: 0%
  ✓ 122 pts with involvement of central compartment: 27%

Results were not related to the age of the patients, suggesting that the same treatment and follow-up protocols should be applied to all age groups.
• **Remnant ablation/Adjuvant therapy:**
  • When is it successful?

  ✓ At [6? 12? 18?] months: no residual uptake in thyroid bed
  ✓ No measurable antithyroid antibodies
  ✓ Stimulated thyroglobulin is undetectable (<0.2 ng/ml)
  ✓ Neck ultrasound is unremarkable
Untreated group = 28 patients
Follow-up = 11.9±4.4 yr
At the end of the study stimulated Tg:
  • Undetectable in 19 cases (67.9%),
  • Significantly reduced in 6 cases (21.4%),
  • Unchanged or increased in 3 cases (10.7%)
Lung macrometastases were discovered in 1 of these patients by CT scan, 14 yr after diagnosis. Diagnostic WBS remained negative in all patients.
• Therapy:
  • Destroy known loco-regional and/or distant metastasis:

✓ To potentially cure, reduce recurrence and mortality or palliate thyroid cancer.
High-risk patients have 1) macroscopic tumor invasion, 2) incomplete tumor resection, 3) distant metastases, and possibly 4) thyroglobulinemia out of proportion to what is seen on the posttreatment scan.
• Therapy:
  • Discovered at onset or during follow-up
  • Stable disease or progressive disease?
  • Discuss surgical feasibility to reduce tumor burden
  • Are the lesions I-131 avid?
  • Are the lesions only visible with I-131 (at scanning doses, at therapeutic doses) ?
  • Is there objective evidence of response to previous I-131 therapy doses ?
  • What is the accumulated activity?
• Therapy:

• Internal dosimetry (< 2 Gy to bone marrow; < 120 mCi WB activity retention at 48 h or 80 mCi if pulmonary metastases) for:
  - elderly
  - children
  - pulmonary metastases

• Discuss the utility of adjunctive or stand-alone radiotherapy

• Research protocols (off-label use of thyrosin kinase inhibitors, chemotherapy, etc)
<table>
<thead>
<tr>
<th>Factors</th>
<th>Description</th>
<th>Decrease risk of death</th>
<th>Decrease risk of recurrence</th>
<th>May facilitate initial staging and follow-up</th>
<th>RAI ablation usually recommended</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>1 cm or less, intrathyroidal</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>1-2 cm, intrathyroidal</td>
<td>No</td>
<td>Conflicting data</td>
<td>Yes</td>
<td>Selective use</td>
<td>I</td>
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<td>T2</td>
<td>&gt;2-4 cm, intrathyroidal</td>
<td>No</td>
<td>Conflicting data</td>
<td>Yes</td>
<td>Yes</td>
<td>C</td>
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<tr>
<td>T3</td>
<td>&gt;4 cm</td>
<td>No</td>
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<tr>
<td></td>
<td>&lt;45 years old</td>
<td>No</td>
<td>Inadequate data</td>
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<td>B</td>
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<tr>
<td></td>
<td>≥45 years old</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td></td>
<td>Any size, any age, minimal</td>
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<td>Yes</td>
<td>Yes</td>
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<tr>
<td>T4</td>
<td>Any size with gross</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>B</td>
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<tr>
<td></td>
<td>extrathyroidal extension</td>
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<td></td>
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<tr>
<td>Nx, N0</td>
<td>No metastatic nodes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>I</td>
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<td>documented</td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>N1</td>
<td>&lt;45 years old</td>
<td>Conflicting data</td>
<td>Conflicting data</td>
<td>Yes</td>
<td>Selective use</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>&gt;45 years old</td>
<td>Conflicting data</td>
<td>Conflicting data</td>
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<td>Selective use</td>
<td>C</td>
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<tr>
<td>M1</td>
<td>Distant metastasis present</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>A</td>
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</tbody>
</table>

**Evidence of benefit is graded based on the following scale:**

- **A,** strongly recommends based on good evidence;
- **B,** recommends based on fair evidence;
- **C,** recommends based on expert opinion;
- **D,** recommends against based on expert opinion;
- **E,** recommends against on fair evidence;
- **F,** recommends against based on good evidence;
- **I,** recommends neither for nor against.

**Because of either conflicting or inadequate data, we cannot recommend either for or against RAI ablation for this entire subgroup. However, selected patients within this subgroup with higher risk features may benefit from RAI ablation (See original guidelines (4)).**

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RAI, radioactive iodine.
The Long-Term Management of Differentiated Thyroid Cancer

Thyroglobulin

AS EVIDENCE OF DISEASE

- TSH normal: 1 g of thyroid tissue produces 1 ng/ml of Tg.
- TSH suppressed: 0.5 ng/ml of Tg.
- TSH suppressed = undetectable Tg: only if previous total/subtotal thyroidectomy + I-131.

Facts:

- Suppressed TSH ≤ 0.1 mUI/mL (on levothyroxine)
- Stimulated TSH > 30 mUI/mL (off levothyroxine) or rhTSH
- If TSH is stable, changes in Tg will reflect changes in tumor mass IF MEASUREMENTS ARE MADE IN THE SAME LAB.
- Functional sensitivity of assay: at least 1 ng/ml
- Thyroglobulin measurement invalidated by autoantibodies
- Thyroglobulin: NOT A TUMOR MARKER. Ablate thyroid remnant.
- Thyroglobulin: biologically is only produced in thyroid cells, but what do we test for in clinical practice?
Thyroglobulin
AS EVIDENCE OF DISEASE

• Scenarios:

✓ Preablation
✓ Postablation
✓ “Shot in the dark”
The objective was to investigate the **prognostic values of serum Tg for disease-free remission and death**, measured at fixed time-points after initial therapy using receiver operator characteristic (ROC) curve analyses.
Patients & Methods

• Single-centre observational study.
• 366 consecutive patients with DTC, all treated with the same protocol for initial therapy and follow-up.
• Tg concentrations were measured at five fixed time-points after surgery.
• Tg cut-off values with highest accuracy were calculated with ROC analyses.

Serum thyroglobulin concentrations predict disease-free remission and death in differentiated thyroid carcinoma

Preablation –Results–

<table>
<thead>
<tr>
<th>Tg cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>27.5 ng/ml</td>
<td>87.9%</td>
<td>90.3%</td>
<td>61.7%</td>
<td>97.7%</td>
</tr>
</tbody>
</table>

Serum thyroglobulin concentrations predict disease-free remission and death in differentiated thyroid carcinoma

Postablation –Results–

<table>
<thead>
<tr>
<th>Thyrogblobulin</th>
<th>Cut off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mo Stimulated</td>
<td>10 ng/ml</td>
<td>100%</td>
<td>93,1%</td>
<td>76,7%</td>
<td>100%</td>
</tr>
<tr>
<td>6 mo Suppressed</td>
<td>2,5 ng/ml</td>
<td>89,2%</td>
<td>93,5%</td>
<td>75%</td>
<td>97,5%</td>
</tr>
<tr>
<td>2 y suppressed</td>
<td>2,0 ng/ml</td>
<td>85%</td>
<td>85,7%</td>
<td>60,6%</td>
<td>95,7%</td>
</tr>
<tr>
<td>5 y suppressed</td>
<td>2,5 ng/ml</td>
<td>82,9%</td>
<td>96,7%</td>
<td>87,9%</td>
<td>95,1%</td>
</tr>
</tbody>
</table>

Thyroglobulin

AS EVIDENCE OF DISEASE

Decision making: what to expect

- **Preablation**
  - TSH-stimulated Thyroglobulin $\leq 27.5$ ng/ml

- **6-12 months Postablation**
  - TSH-stimulated Thyroglobulin $\leq 10$ ng/ml

- **2-5 years Postablation**
  - TSH-suppressed Thyroglobulin $\leq 2.0$ ng/ml

- **>5 years Postablation**
  - TSH-suppressed Thyroglobulin $\leq 2.5$ ng/ml
Decision making: what to do (if expectations not met)

- Further studies/ I-131 dose adjustment
- Tg Undetectable
- Detectable 2-10 ng/ml
- Detectable > 10 ng/ml

- Preablation
- 6-12 months Postablation
- L T4 suppression therapy
- Screen for lesions
- Shot in the dark
- Posttherapy scan
- PET CT
Thyroglobulin
AS EVIDENCE OF DISEASE

Decision making: what to do (if expectations not met)

2-5 years
- ✓ Tg Undetectable

➢ Detectable ≤ 2.0 or 2.5 ng/ml
- ✓ Detectable > 2.0 or 2.5 ng/ml

➢ Tg > 10 ng/ml

➢ Tg ≤ 10 ng/ml

➢ TSH-stimulated Thyroglobulin

➢ Screen for lesions

PET CT ➔ Posttherapy scan ➔ Shot in the dark ➔ Tg > 10 ng/ml

➢ L T4 suppression therapy

➢ Screen for lesions