Advances in the Management of Thyroid Cancer

Leonie Gordon
Division of Nuclear Medicine
Medical University of South Carolina, Charleston SC
Nuclear Medicine and Thyroid Cancer: Outline

- The basics
- What’s new (.. or at least sort of …)
  - FDG PET for thyroid cancer
  - $^{131}$I therapy with thyrogen
Differentiated Thyroid Cancer

- **Papillary**
  - Orderly progression of spread
  - Nodes --> Lungs ---> Bone and Brain
  - Troublesome histology - tall cell variant

- **Follicular**
  - Hematogenous spread
  - Early spread to lung and bones, brain
  - Troublesome histology - insular, Hurthle cell
Thyroid Cancer: Rationale for \( ^{131}I \) Rx

**All Recurrences**

**Distant Recurrences**

(Mazzaferri, JCEM 86: 1447, 2001)
Differentiated Thyroid Cancer
Risk Factors for Recurrence and Death

- Tumor size (<> 1.5 cm)
- Age (<> 50)
- Capsular penetration
- Distant Metastases
- Multi-focality
- LN metastases
Goals of Thyroid Cancer
Radioiodine Ablation

- Ablate thyroid remnant
  - Decrease change of recurrence
  - Improve ease of follow-up

- Thyroid cancer Rx
  - Adjuvant Rx of small-volume disease
  - Primary Rx of distant metastases

- Goal and dose depend upon expected disease burden
Treating Thyroid Cancer: The Ideal

- Near-total thyroidectomy + removal of macroscopic nodal disease
- Post-surgical I-131 Rx with dose titrated to surgical, path, and scan findings
- F/u using TG plus I-131 scans (possibly with rTSH)
- Re-rx with I-131 as necessary
- Unfortunately, it’s not always that simple!
Radioiodine for Thyroid Cancer Diagnosis and Treatment

- Diagnostic scans
  - Thyroid cancer metastatic survey
  - I-131 or I-123
  - Requires preparation - withdrawal versus rTSH

- Radioiodine therapy
  - I-131 only
  - Post-operative remnant ablation
  - Post-operative systemic adjuvant therapy
  - Systemic therapy of metastatic disease
Radiopharmaceuticals Used for Nuclear Thyroid Studies

<table>
<thead>
<tr>
<th>Tracer</th>
<th>T1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-131</td>
<td>8 days</td>
</tr>
<tr>
<td>1-123</td>
<td>12 hours</td>
</tr>
<tr>
<td>Tc</td>
<td>6 hours</td>
</tr>
<tr>
<td>F-18 FDG</td>
<td>110 minutes</td>
</tr>
</tbody>
</table>
$^{131}\text{I}$ Scanning & Therapy
Hormone w/d- old way

- Start Prep
- Stop T4, Start T3
- Stop T3
- Low Iodine Diet
- $1-3 \text{ mCi}^{131}\text{I}$ Therapeutic Dose
- $^{131}\text{I} \text{ Dx Scan}$
- $\text{Post-Rx Scan}$

Timeline:
- 6 wks
- 2-3 wks
- 1-2 wks
- 72 hrs
- 7-10 d
A Multi-Disciplinary Approach to Endocrine Neoplasia

- Surgery
  - Surg Onc, Oto

- Systemic Therapy
  - Endocrine, Med Onc

- Endocrine Neoplasia Clinic
- Endocrine Neoplasia Tumor Board

- Radiation
  - Nucl Med, Rad Onc
I -131 therapy without initial scan

- **I131 therapy ordered**
  - Stop synthroid 6wks
  - Start Cytomel for 4 weeks
  - Low iodine diet
  - Treat with I-131 dose depends on pathology
  - 10 day post therapy scan
Low Iodine Diet

The purpose of a low-iodine diet is to deplete the body of its stores of iodine, to help increase the effectiveness of the radioactive iodine scan or treatment.

The premise is that when the radioactive iodine is administered, the thyroid cells will “suck” up the iodine, because the body has been so depleted.
Foods That Are Fine to Eat on the Low-Iodine Diet

- Fresh fruits and fruit juices.
- Vegetables, preferably raw and fresh-cooked or frozen without salt.
- Unsalted nuts and unsalted nut butters.
- Grain/cereal products in moderate amounts.
- Fresh chicken, beef, and other meats in moderate amounts.
- Sugar, jelly, honey, maple syrup.
- Black pepper and fresh or dried herbs.
- All vegetable oils. Salad dressings provided they contain only allowed ingredients.
- Cola, diet cola, lemonade, sodas (except those with Red Dye #3), non-instant coffee and tea, beer, wine, other alcohol.
What can't you eat on this diet?

- Iodized salt and sea salt and any foods containing iodized salt or sea salt. Non-iodized salt may be used. For example, Kosher salt is okay.

- Seafood and sea products (fish, shellfish, seaweed, seaweed tablets, kelp). These are all very high in iodine and should be avoided.

- Dairy products (milk, cheese, cream, yogurt, butter, ice cream, powdered dairy creamers, whey, casein, other dairy products). Egg yolks or whole eggs or foods containing whole eggs.

- Red Dye #3.

- Most Chocolate (for its milk content). Cocoa powder and some dark chocolates are permitted.

- Check the label for other ingredients not allowed on the low-iodine diet.

- Some Molasses.

- Soybeans and most soy products (soy sauce, soy milk, tofu).

- Some beans besides soybeans. The National Institutes of Health diet says to avoid these beans: red kidney beans, lima beans, navy beans, pinto beans, and cowpeas. Other diets do not limit beans.

- Iodine-Containing Vitamins, and Food Supplements. Also products containing iodate or iodide.
Preparation for Iodine Cancer
Survey and/or Therapy

1. TSH > 30
   5-6 wks off T4; 2-3 wks off T3
2. Low iodine diet >= 1 week
3. Discuss radiation safety prior to scheduling
4. Cessation of breast feeding ~ 2 months
5. Day of diagnostic dose
   - Pregnancy test for fertile females
   - Measure TSH, thyroglobulin (TG)
6. ? r TSH
I-123 versus I-131 for Iodine Metastatic Survey

**I-123**
- Recent resurgence in interest with increased availability and decreased price
- Better imaging agent
- No stunning
- $T_{1/2}$ (12 hrs) too short for complete background clearance

**I-131**
- May cause stunning in higher doses (> 3 mCi)
- Poorer imaging agent
- $T_{1/2}$ (8 days) allows for background clearance
- Need long $T_{1/2}$ for dosimetry approaches
How Much I-131?
Risk Factors for Recurrence/Progression

1. Tumor size (> 2-3 cm)
2. Age (> 50)
3. Capsular penetration on path
4. Distant metastases
5. Multi-focality
6. LN metastases on path or scan
I-131 Adult Dosing Guidelines
(Approximate!)

Factors:
- Age, tumor size, multi-focality, capsular penetration, LNs, other mets - scan and path

Low risk (1 or fewer factors): 50 - 100 mCi
Medium risk (2-3 factors, LNs): 150 mCi
High risk (capsular penetration, extensive LNs, distant mets found on Dx scan): 200 mCi
Very high risk: (Distant mets, locally aggressive Dz)
Dosimetry (> 200 mCi)

Dose reduction for large thyroid remnant
10 days after 200 mCi I-131
Post-Therapy I-131 Scan

1. Should be done in all patients
2. Should be obtained 7-10 days post-Rx
3. **Not** to evaluate response
4. May show other sites of disease
   - e.g., Small-volume pulmonary metastases
Approach to Suspected Thyroid Recurrence with Negative I-131 Scan

MRI Brain if lung mets

Surgery

? I-131 Rx or XRT

I-131 Rx or XRT, chemoRx

'n'd TG, neg I-131

Non-contrast chest CT Neck U/S or MRI FDG PET

resectable dz

non-resectable dz

negative scans

No Rx

Serial f/u
Residual Thyroid Cancer: FDG PET Scan

- L Cervical Lymph Nodes
- ? Central Lymph Nodes
FDG PET and Thyroid Cancer: Summary of Literature and Some Observations

- Approximately inverse relationship between I-131 and FDG uptake
  - Iodine negative - FDG positive
  - Iodine avid - FDG uptake low or absent
- Can miss small-volume disease, especially in the lungs
- Presence or absence of FDG uptake is prognostically significant
FDG PET for Iodine Non-Avid Thyroid Cancer

- FDG finds sites of disease in ~ 70% of patients (Wang, JCEM 84:2291, 1998)
- Sensitivity = 85% (Grunwald, EJNM 26: 1547, 1999)
- FDG PET has PPV= 92% if TG is elevated (Wang, JCEM 84:2291, 1998)
- Meta-analysis (Hooft, JCEM, 2001):
  - Sensitivity 70% - 90%
  - Specificity 77% - 100%
  - FDG PET found disease in 82% of TG elevated, I-131 negative patients
PET Images

FUSED PET/CT Images
Approach to Suspected Thyroid Recurrence with Negative I-131 Scan

- 'd TG, neg I-131
- FDG PET
  - Non-contrast chest CT Neck U/S or MRI
  - negative scans
- resectable dz
  - Surgery
    - ? I-131 Rx or XRT
  - non-resectable dz
    - I-131 Rx or XRT, chemoRx
    - ? I-131 Rx or XRT
- No Rx
  - Serial f/u
Caution! - Iodine-Avid Tumors May Not Be Well-Visualized on FDG PET

-both patients had iodine-avid tumors, but persistent nodes

-FDG underestimated the extent of disease in both cases

Patient 1

Patient 2

(arrow indicates lymph node seen on MRI or U/S)
PET/CT to Direct Surgery
Persistent R Para-Pharyngeal Tumor Despite I-131 Rx

FDG PET

PET/CT Fusion
FDG Uptake in Thyroid Cancer: A Prognostic Indicator?

- Wang, JCEM 85:1107, 2000
- 125 patients s/p thyroidectomy
- Predictors of survival - FDG+, SUV, volume of FDG-avid disease
- 3 year survival by volume of FDG-avid Disease
  - < 125 mL - 0.96
  - > 125 mL - 0.18
- Only 1 death in 60 FDG-negative patients
  - Includes no deaths in 10 patients with FDG-negative metastases
Residual Thyroid Cancer: FDG PET Scan

CT Chest = negative
MRI = no enlarged nodes

L Cervical Lymph Node
I-131 Rx of Pulmonary Metastases
Complete Remission Using Dosimetry-Guided $^{131}$I Rx

150 mCi → 2/11/00
Widespread Metastases

400 mCi → 10/5/00
Small Residual Dz by $^{131}$I and CT

450 mCi → 12/10/01
$^{131}$I-131, CT, TG negative

Slides are not to be reproduced without permission of author.
Advances in Thyroid Cancer Treatment

Recombinant TSH (rTSH, Thyrogen)
Recombinant TSH (thyrogen)

- FDA Approved
  - Diagnostic scanning with I-131 or I-123
  - Thyroid remnant ablation post-op
- Off-label use
  - Treatment of metastatic disease
  - FDG PET
- Well-tolerated (IM dosing)
- Expensive - close to $1k/dose
  - Well-covered by most insurers
- Altered iodine kinetics versus w/d
  - Faster clearance - better GFR
  - Less tumor uptake/mCi
rTSH-Stimulated Iodine Scanning
Manufacturer’s Recommendations

- Low Iodine Diet
- 0.9 mg rTSH IM
- TSH, TG
- 5 mCi $^{131}$I
- 48 hours
- Scan TSH, TG
Evolving indications
- Patients who cannot tolerate hormone w/d
- Post-surgical remnant ablation
- Tumors over-stimulated by hormone w/d?

Differences versus hormone w/d
- Better patient tolerance!
- Faster iodine clearance
- Less tumor uptake - probably
rhTSH - Thyrogen

- Recombinant thyrotropin A
- Given as IM injection
  - 0.9 mg standard dose
- Approved indication
  - Dx iodine scanning
  - Stimulation of Tg for diagnosis
  - “Routine” thyroid remnant ablation
### rhTSH: Side Effects

#### Table 8. Summary of Adverse Events During Clinical Studies (≥1%)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Percent (Number) of Patients With Adverse Events (N=381)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body As a Whole</strong></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>7% (28)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>3% (13)</td>
</tr>
<tr>
<td>Chills</td>
<td>1% (4)</td>
</tr>
<tr>
<td>Fever</td>
<td>1% (4)</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>1% (4)</td>
</tr>
<tr>
<td><strong>Digestive System</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>11% (40)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2% (8)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>1% (5)</td>
</tr>
<tr>
<td><strong>Nervous System</strong></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>2% (6)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>2% (6)</td>
</tr>
</tbody>
</table>
Side Effects: rhTSH vs w/d

Figure 10. Assessment of Hypothyroid Symptoms at Time of Thyrogen WBS vs at Time of Withdrawal WBS

Percentage of Patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>On THT with Thyrogen</th>
<th>Off THT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periorbital puffiness</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>Slow movements</td>
<td>50%</td>
<td>30%</td>
</tr>
<tr>
<td>Cold intolerance</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>Cold skin</td>
<td>30%</td>
<td>10%</td>
</tr>
<tr>
<td>Weight increase</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>Slowing of ankle jerk</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Decrease in pulse rate</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Constipation</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Dry Skin</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Diminished sweating</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Coarse skin</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Deafness</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Side Effects: rhTSH vs w/d - QOL

Figure 11. Comparison of QOL Assessments During Thyrogen Period and During the THT-Withdrawal Period

- Physical Function
- Physical Role
- Body Pain
- General Health
- Vitality
- Social Functioning
- Emotional Role
- Mental Health
- Mental Composite Score
- Physical Composite Score

Mean change in SF-36 score from baseline

On THT with Thyrogen
Off THT

Slides are not to be reproduced without permission of author.
Expected TSH Levels
Ladenson, NEJM 837:888, 1997

Hormone w/d:
> 30 mU

rhTSH:
24 hrs: 132 +/- 89 mU
72 hrs: 16 +/- 12 mU
Iodine Clearance Faster, Uptake Lower for rhTSH vs w/d Remnant Uptake After Rx Dose

(Ladenson, NEJM 837:888, 1997)
rhTSH Clinical Pharmacology - Summary

- Recommended dosing 0.9 mg IM qd x 2
- rhTSH better tolerated than w/d
- Peak TSH values high, but average lower than hormone w/d
- Faster clearance for rhTSH vs w/d
  - Remnant uptake decreased by ~ 50%
Does rhTSH Help FDG PET for Thyroid Cancer?

Suppression rhTSH

(Chin, JCEM 89: 91, 2003)
Should patient’s be on a low iodine diet if they are receiving therapy with rTSH?

Preferable because you are trying to optimize uptake of I-131
rTSH-Directed I-131 Therapy of Metastatic Thyroid Cancer - When?

- "Routine" post-op ablation
- Patient cannot tolerate hormone w/d
  - Medical conditions - e.g., CHF
  - Psychiatric conditions - e.g., depression
- Tumors grows too quickly when patient off T4
  - ? Pediatric tumors
  - ? Safer for tricky locations - CNS
rTSH-Stimulated Iodine Therapy Recommendations

Low Iodine Diet

0.9 mg rTSH IM

Therapy dose mCi $^{131}$I

7-10 days

Scan
Advances in Thyroid Cancer Treatment

Dosimetry and enhancing iodine effectiveness
Iodine Dosimetry for Thyroid Cancer

Approach: give I-131 up to the toxicity limit
- Marrow
- Lungs

Indications
- Life-threatening disease - need more I-131!
  - Distant metastases
  - Locally aggressive disease
- Altered iodine clearance
  - Large disease burden
  - Poor renal function
Can We Improve Iodine Uptake in Tumors? Iodine “Boosters”

- Lithium
  - Slow iodine release
- Retinoic Acid
  - “Re-differentiate” the cancer
- Other approaches to “selective” enhancement of gene expression
  - De-methylation agents
  - PPAR antagonists
Iodine Retention is Highly Variable
Examples from an I-131 Dosimetry Study

- Multiple lesions in the same patient
- Variable iodine retention

48 hrs | 72 hrs | 96 hrs
--- | --- | ---
Anterior

Posterior
Iodine-Refractory Thyroid Cancer
Options other Than I-131

- Chemotherapy
  - Low response rate (< 25%)
  - High toxicity
  - Some less toxic “maintenance” regimens (capecitabine (Xeloda))

- Targeted agents
  - Targeted to particular oncogenes - e.g. Gleevec for GIST
  - Clinical trials just starting
    - Anti-angiogenesis, anti-EGFR, etc.
    - Anti - B-raf
    - Anti-RET tyrosine kinase inhibitor (Martins, SCCA)
May we grow in Wisdom!