Radioactive Iodine (RAI) Treatment: Preparation for and Complications in Patients with Differentiated Thyroid Cancer (DTC)

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No Conflict of Interests to Declare
Learning Objectives

• Preparation for the RAI diagnostic work-up and treatment (Rx) – You've Gotta Have a System!
  a. Know the referral pattern and construct your clinical workflow
  b. How do you proceed with hormone withdrawal
  c. Indication for rhTSH use vs thyroid hormone withdrawal (THW)
  d. Preparing the patient for hormone withdrawal
  e. Determining if you are aiming at ablation vs adjuvant treatment

• Minimizing side effects of and preparation for RAI treatment (RAIT) – “Evidence-based” is superfluous when the answer is “evident”
  a. Controlling hypothyroid side effects
  b. The pros and cons of "drink tons of fluids"
  c. Preventing nausea and vomiting
  d. Preventing or reducing incidence of sialadenitis
DTC Patients’ Management at Penn State University (PSU) Nuclear Medicine – Know Your Referrals Pattern

Internal PSU Endocrinology Patients
Consultation in Endocrinology Clinic

Patient presented at PSU Thyroid Unit Conference - scheduled for the best testing/treatment strategy

Other Imaging Strategies
Surgery

External and Non-Endo PSU Referrals
Consultation with a Nuclear Medicine Physician

Appropriate for I-131 Rx?

No Yes

Nuclear Medicine
Consultation: Key Considerations for I-131 Scan and Treatment

1. Review path, screen for gross metastatic disease
2. Determine appropriate thyroid tissue stimulation method:
   I. Endogenous TSH – Thyroid hormone withdrawal (THW)
      a. Review hypothyroid manifestations
   II. Exogenous hrTSH (Thyrogen®) stimulation
3. Educate about radiation hygiene/precautions
4. Screen for iodine-containing medications, check for CT contrast exposure (past 3 mo.)
5. Instruct re: low-iodine diet (LID)
6. Screen for complicating factors (incontinence, abnormal renal function, diabetes, etc.)
Consultation: Iodine Depletion (No More Than 50 µg of I-127 / day)

- Screen for **iodinated contrast** in the past 3 months
- Screen for dietary iodine (kelp, health foods, etc.)
- Medications to pay special attention to:
  - **Multivitamins** typically include 150 µg of iodine
  - Calcium supplements
    - avoid oyster shell derived calcium (Os-Cal)
    - Tums and **elemental calcium** (carbonate) are safe.
  - Calcitriol (Rocaltrol®)
    - 0.5 µg size contains FD&C red die #3 (iodinated)
    - 0.25 µg size does not
  - **Amiodarone** (3.5 mg Iodide/100 mg)
Preparation: Starve Thyroid Tissue for Iodine

- Excess iodide/iodine block I-131 uptake through Na/I symporter (NIS) mechanism – this fact is indisputable
- Make sure that no radiographic contrast was given to the patient for the past 3 months and advise patients to avoid it
- Place the patient on the low iodine diet for 2 weeks prior to start of I-131 evaluation
- Excellent booklet is available from thyca.org website, free download
- No exceptions for Thyrogen® stimulated patients – they need stricter restriction
THYROID CANCER STAGING CALCULATOR

American Thyroid Association » Thyroid Cancer Staging Calculator

Please note: Due to HIPAA regulations, the information entered into the calculator is not retained by the ATA system. Once you exit the calculator page, any calculated data and results will no longer be available. However, you may enter a non-HIPAA patient identifier and print the calculator results to maintain for your record-keeping purposes.

The calculator below is provided as a tool for staging differentiated papillary thyroid cancer and follicular thyroid cancer. The TNM definitions included are based on AJCC/UICC 2010 Seventh Edition criteria. Click here to access the ATA Fellows Card which provides more information on the TNM System of the American Joint Committee on Cancer (AJCC). The predictive value of MACIS scoring is limited to the assessment of papillary thyroid cancer only.

 Age at diagnosis (years)
 Gender
 Size of primary tumor (maximal dimension in cm)
 Invasion

 Invasion (Any)
 Invasion (RLN, Larynx, Trachea, Esophagus)
 Invasion (Posterior cervical fascia / vessels)
 Complete surgical resection
 Nodes (Region VI – central)
 Nodes (Regions I – V, or VII – other)
 Distant metastases
 Tumor grade

 MACIS (7 high risk)
 AGES (≤4 low risk; >4 high risk)
 AMES

 pTNM
 Stage

 [Click to calculate]
### Table 14. Characteristics According to the American Thyroid Association Risk Stratification System and AJCC/TNM Staging System That May Impact Postoperative Radioiodine Decision-Making

<table>
<thead>
<tr>
<th>ATA risk staging (TNM)</th>
<th>Description</th>
<th>Body of evidence suggests RAI improves disease-specific survival?</th>
<th>Body of evidence suggests RAI improves disease-free survival?</th>
<th>Postsurgical RAI indicated?</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATA low risk T1a N0, Nx M0, Mx</td>
<td>Tumor size ≤ 1 cm (uni- or multifocal)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ATA low risk T1b, T2 N0, Nx M0, Mx</td>
<td>Tumor size &gt; 1–4 cm</td>
<td>No</td>
<td>Conflicting observational data</td>
<td>Not routine—May be considered for patients with aggressive histology or vascular invasion (ATA intermediate risk).</td>
</tr>
<tr>
<td>ATA low to intermediate risk T3 N0, Nx M0, Mx</td>
<td>Tumor size &gt; 4 cm</td>
<td>Conflicting data</td>
<td>Conflicting observational data</td>
<td>Consider—Need to consider presence of other adverse features. Advancing age may favor RAI use in some cases, but specific age and tumor size cutoffs subject to some uncertainty.</td>
</tr>
<tr>
<td>ATA low to intermediate risk T3 N0, Nx M0, Mx</td>
<td>Microscopic ETE, any tumor size</td>
<td>No</td>
<td>Conflicting observational data</td>
<td>Consider—Generally favored based on risk of recurrent disease. Smaller tumors with microscopic ETE may not require RAI.</td>
</tr>
<tr>
<td>ATA low to intermediate risk T1-3 N1a M0, Mx</td>
<td>Central compartment lymph node metastases</td>
<td>No, except possibly in subgroup of patients ≥ 45 years of age (NTCTCSG Stage III)</td>
<td>Conflicting observational data</td>
<td>Consider—Generally favored, due to somewhat higher risk of persistent or recurrent disease, especially with increasing number of large (&gt;2–3 cm) or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use. However, there is insufficient data to mandate RAI use in patients with few (&lt;5) microscopic nodal metastases in central compartment in absence of other adverse features.</td>
</tr>
<tr>
<td>ATA low to intermediate risk T1-3 N1b M0, Mx</td>
<td>Lateral neck or mediastinal lymph node metastases</td>
<td>No, except possibly in subgroup of patients ≥ 45 years of age</td>
<td>Conflicting observational data</td>
<td>Consider—Generally favored, due to higher risk of persistent or recurrent disease, especially with increasing number of macroscopic or clinically evident lymph nodes or presence of extranodal extension. Advancing age may also favor RAI use.</td>
</tr>
<tr>
<td>ATA high risk T4 Any N Any M</td>
<td>Any size, gross ETE</td>
<td>Yes, observational data</td>
<td>Yes, observational data</td>
<td>Yes</td>
</tr>
<tr>
<td>ATA high risk M1 Any T Any N</td>
<td>Distant metastases</td>
<td>Yes, observational data</td>
<td>Yes, observational data</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Recent data from the NTCTCSG (National Thyroid Cancer Treatment Cooperative Study Group) have suggested that a more appropriate prognostic age cutoff for their classification systems could be 55 years, rather than 45 years, particularly for women. In addition to standard clinicopathologic features, local factors such as the quality of preoperative and postoperative US evaluations, availability and quality of Tg measurements, experience of the operating surgeon, and clinical concerns of the local disease management team may also be considerations in postoperative RAI decision-making.*
PSU Criteria for Lower-Risk Patient Must Fulfill All 6 Requirements:

1. Age: < 55 years
2. Histopathology: Papillary common-type or follicular variant (exclude high-risk variants: tall cell, diffuse sclerosing, insular and other variants with aggressive behavior)
3. Size: < 4 cm (can be multifocal)
4. Surgical margins: NOT involved
5. Lymph nodes: NO metastases
6. Distant metastasis: NONE

Those who do not fulfill all 6 = **Higher-Risk**
Consultation: Preparation for THW and for GI Side Effects of I-131

- Switch from long half-life T4 (Synthroid®) to shorter half-life T3 (Cytomel®)
  - Stop T4 and start T3 for 4 weeks
  - Stop all TH meds for 2 weeks/start LID
- Towards end of the 2nd week check TSH, if > 35 start the diagnostic I-131 process or RAIT
- Nausea is common after the treatment I-131 dose
  a. Ondansetron, 8 mg p.o. TID for RAIT below 200 mCi
  b. Start with prophylactic oral dose 4 hours before RAIT
  c. RAIT above 200 mCi, ondansetron 8 mg p.o., start 6-4 hrs. prior to treatment, then 8 to 12 mg IV TID for 2-3 days, transition to 8 mg p.o. TID before discharge, as needed after discharge
Thyrogen versus Withdrawal

Case 1

48 hour uptake = 0.01%

72 hour uptake = 0.4%
rhTSH versus THW

- The I-131 uptake is equal in remnant normal tissue with rhTSH versus THW stimulation\(^1\)
- The I-131 uptake and dose to metastatic tissue is GREATER with THW versus rhTSH stimulation. Uptake of I-131 was on average almost twice with THW as compared to rhTSH.\(^2\)


Fig. 1: $^{124}$I PET/CT images of the MHH patient at 24 h after $^{124}$I administration: iodine uptake in a cervical metastasis is substantially lower after rhTSH stimulation (a) than after THW (b). An iodine-avid adrenal gland metastasis is not visible after rhTSH (c) but visible after THW (d).
Consultation: Control Hypothyroid Manifestations

- Forewarn the patient about upcoming hypothyroidism
- Older patients will tolerate it worse than younger
- Weakness and depression are main complaints
  - Patients prone to depression need special consideration
- Edema may be prominent
  - Remove tight rings, etc.
  - CHF may be exacerbated
  - Hyponatremia is a concern – don’t restrict NaCl
- Beware of higher sensitivity to beta-blockers and other anti-hypertensive medications, self monitoring
- *Recommend not to drive – pts are impaired!

DOI: 10.1089/thy.2014.0371
Post-Op. DTC Patient – First Encounter Workflow at PSU

Risk Assessment

Lower Risk
Treat, 30-100 mCi I-131, Under rhTSH Stimulation
Whole Body I-131 Post-treatment Scan
5-10 days after treatment

Higher Risk
Remnant Evaluation with I-131 24-hour Uptake, 10 µCi
Main Goal: Prevent “Stunning” by Identifying Larger Amounts of Residual

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Higher Risk Thyroid Cancer Patient: First Encounter vs. Re-evaluation

First Post-Operative Evaluation?

Yes

24 hour, 10 uCi, I-131 uptake

> 2%

Evidence of residual tumor?

No

10 mCi Tc-99m Thyroid Scan

< 2%

No

5 mCi I-131 Whole Body Scan

No (re-evaluation)

Any Evidence of Mets?

< 2%

Yes

Consider Formal Dosimetry

> 2%

Yes

Image, Consider Re-operating If Uptake > 15%

No
First Post-thyroidectomy Evaluation: Looking for Expected Tg Levels for the Amount of Remnant Thyroid

- DTC patients referred for ablation on hormone withdrawal stimulation protocol in the past 3 years were reviewed.

- Excluded: 1) positive regional metastatic disease at surgery, 2) positive scan or thyroglobulin at one year of follow-up, 3) suspicious ultrasound findings or any other indication for residual disease at one year follow-up evaluation, and 4) abnormal Tg antibody titer.
First Post-thyroidectomy Evaluation: Looking for Expected Tg Levels Due to the Normal Residual Thyroid

- 43 patients (30 females) were included. The patients’ data [mean ± standard deviation (range)] included:
  - age of 50.0±15.0 (21-88)
  - 24 hour iodine uptake (24HrIU) of 7.12±7.51 (0.1-32.7)
  - Tg of 5.87±8.43 (0.2-47.8)
  - TSH ranged from 6.58 to >100 (<35 in 6 pts, ≥35 to 100 in 19 pts, and >100 in 18 pts)
First Post-thyroidectomy Evaluation

We Look at TG vs. 24hr Uptake:
Suspect Residual Tumor if TG is Above Expected

Expected TG values in withdrawal stimulated DTC patients without residual tumor.

Per 1% of 24 hr uptake expect 1 ng/mL TG ± 50%

Tulchinsky M, Gent ML
Abstract presented 2014 SNMMI
Considering Tg in the First Post-Op Group of DTC Patients

- \((24\text{HrIU} \times 2) + 1\) < Tg or \((24\text{HrIU} \times 2) + 2\) < Tg were analyzed for specificity (requires only cases without disease) of detecting remnant DTC. The 2 proposed equations rendered specificities (true negative cases) of 95.3% (41) or 97.7% (42), respectively.
- Next is to test it for sensitivity – work in progress
First Post-Operative Presentation

- 57 y/o with follicular variant of papillary CA and PSU low risk.
- The post-op 24 hour uptake, obtained with 7 µCi of I-131 on a probe, was 23.5% on 9/14/2001.
- 9/13/2001 labs: TSH = 34.2; Tg = 5.6; Tg Ab <0.3
- What’s the next step?
9/13/2001 labs: TSH = 34.2; Tg = 5.6; Tg Ab < 0.3

(23.5 x 2) + 1 = 48. Tg of 5.6 is less than 48, i.e. no excess Tg, no evidence for residual tumor.

Evaluation prior to RAIT indicates Ablation is sufficient.
Post-Treatment I-131 Whole Body Scan

Case 3

9-25-01
Thyroid Cancer Patient: Re-Evaluation After I-131 Ablation

Risk Assessment - Suspected or Known Mets?

No

I-131 5 mCi Scan

Abnormal Uptake

Surgically accessible?

Yes

Surgery

No

Surgically accessible?

Yes

No

Abnormal Uptake

I-131

Dosimetry

No Abnormal Uptake

Thyroglobulin

Low

High

PET/CT

Negative

Positive

Thyroglobulin

Done, F/U in 1 Year

Treat with 150 mCi – f/u post treatment scan
Salivary gland trouble after RAI

By skygal · March 23, 2014 at 5:37 pm · 33 replies
In Papillary and follicular thyroid cancer (differentiated)

I was wondering if anyone has experienced any salivary gland problems several months after RAI treatment. I had the RAI treatment in July. I had the usual symptoms of fatigue, etc. but no drastic problems. In November I started experiencing problems with my salivary glands to the extreme that I couldn’t eat. The pain and swelling in the glands were so severe I went to my ENT. He prescribed an antibiotic thinking it was possibly an infection but when it didn’t go away he thought it may have been a virus so we gave it some time. I no longer get the swelling and the pain isn’t as extreme but it is still there. I now have dry mouth when I try to eat and find it difficult to swallow until I have water with the food.

My ENT doesn’t believe it is the result of the RAI but I have never experienced anything like this in my life and the swelling that occurred was very similar to the swelling I had during the RAI. I am still in pain when I eat and have difficulty swallowing as my mouth is so dry. So I am hoping someone may have an idea what this is that I am experiencing!! I certainly don’t hope anyone has experienced this as I wouldn’t wish it on my worst enemy (if I had one!!)

33 replies. Join the discussion
I have also posted about this issue before. Have been dealing with this for about 6 weeks now. I am happy to report it is slowly getting better. I did end up back at my ENT/TT surgeon as my Endo said to check with him. The day I saw him there were 3 others with the same complaint. One was seven years post TT. He reassured me it is most definitely related to the RAI. He told me not to worry unless I had hardness in the area, redness of the skin or fever. I have been using Biotene mouthwash and toothpaste. I ended up on an antibiotic for a sinus infection. Maybe this has helped, I don't know. He claims this will go away on its own.

I have my RAI tomorrow and am very nervous. The Oncologist's office has basically told me nothing other than flush the toilet twice and suck on sour candies. He said in his 30 years practicing, he has only seen 2 cases of problems with salivary glands. With his short responses to everything else plus the apparent late onset of problems my fears are still there.

On another note, I took it upon myself to visit my dentist who said the Biotine is not as effective as XyliMelts as the Biotine only 'works' while it is in your mouth and a short period after. The XyliMelts stick to the insides of your mouth and dissolve over 4-5 hours. Needless to say, I've got a box of em ready and am prepared to drink plenty of water.
I believe that instead of being scared to death we need to listen to the medical field that deals with this daily. Read all you can and finally the decision is individual. All medicines, radiation, etc. has side effects in my case I decided to have RAI. I have had salivary problems but like other people have said it does go away. For me it hasn't been extremely painful. I hope that everyone continues to heal.

I have had many salivary issues since RAI (August 2012). Several months afterward, I experienced symptoms ranging from jaw pain to mouth dryness to loss of taste, to pain in the glands centered in the cheek area and under my neck. I still suffer from side effects. What has helped me the most has been drinking lots of water and using hot compresses. I bought a 'bed buddy' from Walgreens (it's a rice cloth pack that can be microwaved) and this has helped ease the discomfort when it gets bad. I lie down and rest it one the bottom half of my face, over the mouth and cheek areas. It stimulates the glands and improves the moisture flow and reduces pain/discomfort. Hope this helps.

I recall going through a period where it was very painful when eating, but it did eventually improve. I also had a period where dry food like crackers would coagulate in my mouth (long after the RAI). This is not to be graphic, but to show you are not alone and these after-effects of RAI are very real and it's extremely unfortunate we are not forewarned from a medical standpoint.
Take-Home Message: If we don’t get the salivary protection right,

- pts. who need I-131 treatment will be avoiding it
- referring doctors may 1) underutilize I-131, and 2) press for inappropriately low I-131 activity that is unlikely to be effective
Anatomy of Major Salivary Glands

Glands/ducts well exposed for inspection/access:

- **Parotid** is the largest, 80% exposed to palpation, 20% retromandibular

- **Submandibular**
  - superficial lobe comprises most of the gland, with the mylohyoid muscle under it
  - The deep lobe is the smaller part

Cannot palpate or canulate:

- **Sublingual**, the smallest, between Mandible & Genioglossus
The Minor Salivary Glands

- 800 – 1,000 in total
- Located throughout the upper aerodigestive tract, but mostly in the oral and nasal cavities, as well as throughout the paranasal sinuses
- They are opening into the cavities through their ducts and have no capsule
- Produce mostly mucous saliva
Salivary Gland Functional Histology

Salivary concentration of Iodine is 20-100 times that found in serum.
Isaac F. Dingle et al. Salivary Morbidity and Quality of Life following Radioactive Iodine for Well-Differentiated Thyroid Cancer. Otolaryngology–Head and Neck Surgery 148(5); 746–752, 2013

- Cross-sectional survey, MUSC, Rx with RAI 2000-2012, 145/379 pts replied (38%)
- Salivary prophylaxis: start 2 h post, X 2 d, stimulate q 1-2 h, during waking hours only
- Main findings, sialadenitis in 29/142 (20%):
  - 12% (10/84) in ≤ 150 mCi Rx ("low dose") group
  - 34.5% (20/58) in > 150 mCi ("high dose") group
  - 0% in 43 pts with < 100 mCi and no RAI Rx
  - 26% in ? pts with 100-200 mCi
  - 43% in ? pts with >200 mCi cumulative
Post RAI Salivary Gland Damage: Starts with Ductal Obstruction

Salivary Complications: Take-Home Messages

- Salivary injury and complications are directly related to the cumulative administered activity, starting at 100 mCi
- Parotid glands are the most commonly injured, parotid/submandibular – 3/1
- Sialadenitis/xerostomia are common, variability in incidence are due to variability in prophylaxis (or lack thereof)
- Sialadenitis/xerostomia significantly worsens patients Quality of Life
Case 4. Normal SGS

30 Minutes of Dynamic Imaging (1 min per frame)
Activity dumps abruptly with stimulation, re-accumulation is slower, returning to the initial activity level in 20-30 min.
Uptake Image: 12 – 14 Minutes Composite

Salivary gland uptake: 
[(Salivary activity frame 12-14) (inj. Activity)]
Ejection Image: 18 – 20 Minutes Composite

\[ EF = \left[ \frac{(C_{12-14} - C_{18-20})}{C_{12-14}} \right] \times 100\% \]
Salivary Scintigraphy: Results

<table>
<thead>
<tr>
<th>Uptake</th>
<th>Excretion Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT. PAROTID</td>
<td>0.72%</td>
</tr>
<tr>
<td>LT. PAROTID</td>
<td>0.60%</td>
</tr>
<tr>
<td>RT. SUBMANDIBULAR</td>
<td>0.68%</td>
</tr>
<tr>
<td>LT. SUBMANDIBULAR</td>
<td>0.65%</td>
</tr>
<tr>
<td>THYROID</td>
<td>1.50%</td>
</tr>
</tbody>
</table>

- **RT. PAROTID**
  - Counts/Sec vs Minutes graph

- **LT. PAROTID**
  - Counts/Sec vs Minutes graph

- **RT. SUBMANDIBULAR**
  - Counts/Sec vs Minutes graph

- **LT. SUBMANDIBULAR**
  - Counts/Sec vs Minutes graph
Iodine Kinetics in Salivary Glands and Sialagogue Stimulation: Basics #1

- Sialagogue action of LJ is immediate
- It can dump 30% to 50% of activity out of salivary glands in 1-2 min
- Re-accumulation of radioactivity in salivary glands is slower than dumping
  - In 15-20 min one can return to nearly the same activity as before stimulation
- **Take-Home Message:** Stimulate often (Q 20-30 min), if the goal is to keep salivary radioactivity as low as possible
TABLE 2
Comparison of Incidence of Salivary Side Effects After High-Dose Radioiodine Therapy Between Group A and Group B

<table>
<thead>
<tr>
<th>Event</th>
<th>Incidence* (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A (n = 105)</td>
<td>Group B (n = 125)</td>
<td></td>
</tr>
<tr>
<td>Sialoadenitis</td>
<td>63.8 (67/105)</td>
<td>36.8 (46/125)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Taste dysfunction</td>
<td>39.0 (41/105)</td>
<td>25.6 (32/125)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>23.8 (25/105)</td>
<td>11.2 (14/125)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>14.3 (15/105)</td>
<td>5.6 (7/125)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Values in parentheses are numbers of patients.

Conclusion:

• The Authors’: “Stimulation of saliva flow by means of lemon candy in close temporal proximity to $^{131}$I administration is associated with increased side effects on subsequent salivary gland function. Lemon candy should be given after 24 h following $^{131}$I therapy.”

Hypothetical Mechanism for Detrimental Effect of Early SG Stimulation

• Stimulating salivary glands increases blood flow, which could increase salivary delivery and uptake of RAI – rebound phenomena

• Rebound phenomena may ultimately increase radiation exposure of salivary glands to RAI, as compared to no stimulation at all

• But is that true? Or may be it is SG stimulation regime they used?

Kinetics of RAI in Salivary Glands During First 48 Hours After I-131 Administration

49-y-old woman with DTC, representative salivary time–activity curves after ingestion of 100 mCi of 131I. (RP & LP = right and left parotid; RSG & LSG = right & left submandibular glands)

Iodine Kinetics in Salivary Glands and Salivary Stimulation: Basics #3

- Activity of absorbed I-131 peaks in the first 3 hours after administration.
- After 24 hours less than 90% of peak activity remains in the salivary glands.
- By 48 hours there is negligible activity left in the salivary glands.

**Take-Home Message:** Start prophylaxis in the first 3 hours or you’ll miss the train …
Iodine-123 Kinetics During the First 4 Hours after Administration: Effect of Lemon Juice Stimulation

There was 47% reduction in potential radiation absorbed dose with LJ

Kulkarni K, Van Nostrand D, et al. Does lemon juice increase radioiodine re-accumulation within the parotid glands more than if lemon juice is not administered? Nuc Med Comm 2014;35(2):210-16.
I-123 Activity in Parotid Glands: Comparison of First and Second Lemon Juice Stimulations

Table 3. Data for Combined Right and Left Parotid Gland Radioactivity: Phase 1 Versus Phase 2

<table>
<thead>
<tr>
<th></th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>p-Value for difference between phases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>84%</td>
<td>83%</td>
<td>0.6646</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>18%</td>
<td>21%</td>
<td>0.1399</td>
</tr>
<tr>
<td>Percent washout relative to baseline</td>
<td>4 min</td>
<td>4.4 min</td>
<td></td>
</tr>
<tr>
<td>Time from administration of lemon juice to nadir of washout of radiiodine</td>
<td>1.5 min</td>
<td>2.1 min</td>
<td></td>
</tr>
<tr>
<td>Time from nadir to re-accumulation of radiiodine to baseline</td>
<td>17 min</td>
<td>36 min</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time from administration of lemon juice to re-accumulation of radiiodine to baseline</td>
<td>10 min</td>
<td>14 min</td>
<td></td>
</tr>
<tr>
<td>Maximum ratio of radiiodine relative to baseline during each phase</td>
<td>2.2</td>
<td>1.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Percent reduction in radiation absorbed dose to the parotid glands</td>
<td>37%</td>
<td>47%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>14%</td>
<td>16%</td>
<td></td>
</tr>
</tbody>
</table>

Iodine Kinetics in Salivary Glands and SGS: Basics #2

- Salivary gland stimulation with lemon juice (LJ) every hour, starting 2 hours after RAI administration, can reduce radiation absorbed dose by 47%!

- There was no rebound (rising over the original peak levels) of RAI accumulation in SG after LJ … as long as you don’t stop

- **Take-Home Message:** Repeat LJ does not cause increase in radiation dose to SG … but STOPPING STIMULATION THE FIRST NIGHT DOES!?
20130419 First Post-Thyroidectomy Tc-99m Pertechnetate Scan
20130429 Post-Treatment I-131 Scan
### 20140718 Salivary Gland Scintigraphy

**Case 5**

**Pre-Syringe [Series ROI And Curve] 7/23/2014 - Image1**

<table>
<thead>
<tr>
<th>Frame Name</th>
<th>Statistic</th>
<th>Frame</th>
<th>BKG</th>
<th>RT.PAROTID</th>
<th>LT.PAROTID</th>
<th>RT.SUBMANDIB</th>
<th>LT.SUBMANDIB</th>
<th>THYROID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frame1</td>
<td>Avg</td>
<td>12.74</td>
<td>12.37</td>
<td>20.25</td>
<td>27.27</td>
<td>44.88</td>
<td>42.44</td>
<td>18.71</td>
</tr>
<tr>
<td></td>
<td>Pix</td>
<td>16384</td>
<td>86</td>
<td>309</td>
<td>223</td>
<td>222</td>
<td>197</td>
<td>234</td>
</tr>
<tr>
<td></td>
<td>Tot</td>
<td>208708.00</td>
<td>1084.00</td>
<td>6256.00</td>
<td>6081.00</td>
<td>9966.00</td>
<td>8381.00</td>
<td>4377.00</td>
</tr>
</tbody>
</table>

**Post-Syringe [Series ROI And Curve] 7/23/2014 - Image1**

<table>
<thead>
<tr>
<th>Frame Name</th>
<th>Statistic</th>
<th>Frame</th>
<th>PRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>Avg</td>
<td>98.06</td>
<td>5318.49</td>
</tr>
<tr>
<td></td>
<td>Pix</td>
<td>16384</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td>Tot</td>
<td>1800868.00</td>
<td>1435992.00</td>
</tr>
</tbody>
</table>

**ARM [Series ROI And Curve] 7/23/2014 - Image1**

<table>
<thead>
<tr>
<th>Frame Name</th>
<th>Statistic</th>
<th>Frame</th>
<th>BKG</th>
<th>ARM</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM</td>
<td>Avg</td>
<td>2.29</td>
<td>8.16</td>
<td>7.29</td>
</tr>
<tr>
<td></td>
<td>Pix</td>
<td>16384</td>
<td>70</td>
<td>222</td>
</tr>
<tr>
<td></td>
<td>Tot</td>
<td>37500.00</td>
<td>431.00</td>
<td>1618.00</td>
</tr>
</tbody>
</table>

**Pre**

11:05:27 AM

**Post**

12:09:04 PM

**ARM**

12:01:34 PM

**12 - 14 Uptake Counts**
Salivary Gland Scintigraphy

18 - 20 Excretion Counts

<table>
<thead>
<tr>
<th>Frame Name</th>
<th>Statistic</th>
<th>Frame</th>
<th>BKG</th>
<th>RT.PAROTID</th>
<th>LT.PAROTID</th>
<th>RT.SUBMANDIB</th>
<th>LT.SUBMANDIB</th>
<th>THYROID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frame1</td>
<td>Avg</td>
<td>12.63</td>
<td>11.01</td>
<td>22.07</td>
<td>30.87</td>
<td>33.80</td>
<td>33.45</td>
<td>19.72</td>
</tr>
<tr>
<td></td>
<td>Pix</td>
<td>16384</td>
<td>86</td>
<td>309</td>
<td>223</td>
<td>222</td>
<td>197</td>
<td>234</td>
</tr>
<tr>
<td></td>
<td>Tot</td>
<td>206807.00</td>
<td>947.00</td>
<td>6821.00</td>
<td>6884.00</td>
<td>7504.00</td>
<td>6590.00</td>
<td>4614.00</td>
</tr>
</tbody>
</table>
20140718 Salivary Gland Scintigraphy

<table>
<thead>
<tr>
<th>Location</th>
<th>Uptake</th>
<th>Excretion Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT. PAROTID</td>
<td>0.18%</td>
<td>(NORMAL &gt; 0.17%)</td>
</tr>
<tr>
<td>LT. PAROTID</td>
<td>0.24%</td>
<td>(NORMAL &gt; 0.17%)</td>
</tr>
<tr>
<td>RT. SUBMANDIBULAR</td>
<td>0.52%</td>
<td>(NORMAL &gt; 0.15%)</td>
</tr>
<tr>
<td>LT. SUBMANDIBULAR</td>
<td>0.43%</td>
<td>(NORMAL &gt; 0.15%)</td>
</tr>
<tr>
<td>THYROID</td>
<td>0.15%</td>
<td>(NORMAL 0.36% - 1.6%)</td>
</tr>
</tbody>
</table>

**RT. PAROTID**

**LT. PAROTID**

**RT. SUBMANDIBULAR**

**LT. SUBMANDIBULAR**
20140811 Diagnostic I-131 Scan Magnified Neck

72 Hours Post Dose

Marker View
Why Do Salivary Scintigraphy? Could Anything Be Done To Help?

- **Sialendoscopy** has shown to be a safe and effective treatment for RAI-induced sialadenitis
- Small studies are available, showing that up to 75% of so treated will improve (1)
- Another study reported 91% improved immediately, 54% sustained improvement at 2 years (2)
- But the above wouldn’t matter if you do not diagnose RAI-induced sialadenitis early, which can be done routinely with salivary scintigraphy
- If left undiagnosed, thus untreated, it could impact pt life forever, causing difficulty eating and dental decay

Sialendoscopy Example

Right submandibular sialendoscopy initial work done through microscope from head of bed; video tower for sialendoscopy to the right of patient with nurse and equipment on left.
Randomly assigned to receive sialorrheic prophylaxis with or without pilocarpine, 5 mg every 8 h orally for 1 wk

All pts received 8 mg of dexamethasone and 100 mg of the serotonin subtype 3 receptor antagonist dolasetron mesylate 2 h before their $^{131}$I therapy and every 12 h for another 5 doses after $^{131}$I ingestion

Sugar-free hard candy or gum in their mouths at all times when awake for 1 wk
All patients were awakened every 3 h for the first 3 nights, first to urinate, then to chew a piece of gum or suck candy.

Each patient also ingested at least 2,400 mL (ten 8-oz glasses) of non-dairy liquid.

Salivary scintigraphy and other quantitative measures of saliva output were not used.

Patients questioned about side effects:
- 4–10 d after therapy
- 6- to 8-mo after therapy
Results

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Pilocarpine (n = 32)</th>
<th>No pilocarpine (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sialadenitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>1 (3%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Chronic</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis or glossitis</td>
<td>5 (16%)</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>Subjective xerostomia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>2 (6%)</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

For all comparisons, $P > 0.05$.  

PSU Salivary Protection Schedule

- Start LJ or LC 2 hrs after $^{131}\text{I}$
- Take a tablespoon of LJ or squeeze a LC into your mouth, swish until it makes your mouth water and swallow, use 2-3 sips of water to swish and swallow after
- Repeat at least every 1 h, preferably every 30 min, if doesn't make the pt nauseous
- **Continue hourly through the first night!**
- Take about 6 glasses of nondairy liquid / d
- < 2% acute sialadenitis, <5% xerostomia (unpublished communication)
1. When does the activity of I-131 peaks in the salivary glands after its oral administration?
   a. It peaks 10-12 hours after administration
   b. It peaks in the first 3 hours (KEY)
   c. It peaks at about 48 hours after administration
   d. It peaks at about 24 hours after administration

   A is incorrect. By 12 hours the percent of administered I-131 in the salivary glands is already on the decline.
   B is correct. The percent uptake of I-131 in the salivary glands peaks between 1-3 hours following oral administration. It subsequently rapidly declines with negligible amounts left by 48 hours. Therefore, it is important to initial protective salivary maneuvers in the first hours after I-131 dosing.
   C is incorrect. Only negligible amount of iodine is left in the salivary glands at 48 hours.
   D is incorrect. By 24 hours less than 10% of peak I-131 activity is left in the salivary glands, thus the major radiation absorbed dose has been already deposited in the salivary glands. Hence, starting salivary stimulation at that time missed the main radiation exposure opportunity.

   Reference:

2. When does the radioactive iodine activity in the salivary glands return to pre lemon stimulation levels?
   a. It takes about 20 min (KEY)
   b. It takes at least 1 hour
   c. It takes 3-4 hours
   d. It never returns to pre lemon stimulation levels

   A is correct. In a carefully designed study (1), Dr. Van Nostrand demonstrated that it takes on average 22 min for the salivary activity to return to the level equal to pre stimulation.
   B is incorrect. The activity can be seen on routine salivary gland scintigraphy to reach the same levels as pre-stimulation by as early as 15 min. By 1 hour after stimulation the radioactive iodine activity could reach double the activity prior to the stimulation (2)
   C is incorrect. This choice is obviously incorrect, given the discussion in the preceding options.
   D is incorrect. This option is furthest from the truth, as shown in the cited studies.

   Reference:
3. What is the main pathological reason for the intermediate and late side effects associated with patients’ ability to eat and enjoy the food following radioactive iodine treatment?
   a. Vascular endothelial injury leading to salivary interstitial edema
   b. Decreased saliva production by the salivary acini damaged by the free oxygen radicals
   c. Salivary duct stricture due to damage of the ductal epithelium and mucous plugging (KEY)
   d. Intensive sialagogue stimulation during the first day and night following radioactive iodine treatment

A is incorrect. This mechanism is responsible for the acute symptoms of sialadenitis after the radioactive iodine therapy, but not central to the intermediate and late complications.
B is incorrect. This mechanism is important in external beam radiation injury of the salivary glands, but does not play key role in the intermediate and late complications of post radioactive iodine salivary gland problems.
C is correct. The ductal stricture has been demonstrated to be central to the intermediate and late complications following radioactive iodine treatment. (1)
D is incorrect. This option is the furthest from the truth, as shown in the cited study. (2)

Reference:

4. Which statement is correct in reference to rhTSH (THYROGEN ®) preparation of differentiated thyroid cancer (DTC) patients in the context of I-131 scan and/or treatment?
   a. It results in percent iodine uptake in differentiated thyroid cancer metastases (DTC) that is indistinguishable when compared with thyroid hormone withdrawal (THW) preparation.
   b. It results in percent iodine uptake in postoperative remnant thyroid tissue that is indistinguishable when compared with THW preparation. (KEY)
   c. It produces long term outcomes in DTC patients with distant metastases that are comparable with patients prepared with THW undergoing remnant tissue ablation.
   d. It produces same sensitivity for distant metastases in DTC patients as compared with similar patients prepared with THW.
A is incorrect. One study showed that uptake and dose to metastatic tissue is GREATER with THW versus rhTSH stimulation. Uptake and dosimetry of I-124 was on average almost doubled with THW, as compared to rhTSH. (1)

**B is correct.** One study showed that dosimetry in the normal thyroid tissue remaining after surgery is about the same with both stimulation methods. (2)

C is incorrect. There is no study in the literature that conclusively addressed long term outcomes in the context of the stimulation methods.

D is incorrect. The package insert for rhTSH states: The THYROGEN scan failed to detect remnant and/or cancer localized to the thyroid bed in 17% (14/83) of patients in whom it was detected by a scan after thyroid hormone withdrawal. In addition, the THYROGEN scan failed to detect metastatic disease in 29% (7/24) of patients in whom it was detected by a scan after thyroid hormone withdrawal."

Reference:
1. Freudenberg LS et al. ...Dosimetric Comparison of rhTSH versus Thyroid Hormone Withholding ... Exp Clin Endocrinol Diabetes 2010. DOI: 10.1055/s-0029-1225350

5. Which of options below represents the most durable effective therapy for the late post I-131 complication manifested as unremitting salivary gland(s) swelling?
   a. Applying a warm compress to the effected gland.
   c. Sialendoscopy. **(KEY)**
   d. Salivary stimulation with lemon juice for two weeks every hour during the waking time.

A, B, and D are incorrect. Swelling of the salivary gland late after I-131 treatment is typically secondary to scar development in the salivary ducts. While in the early stages the simple procedures, such as warm compress, massage, and lemon juice stimulation may transiently relieve swelling, it often fails in the long run.

**C is correct.** Sialendoscopy is able to remove stricture and/or obstruction of the salivary ducts. It is reported by one study that 91% improved immediately, 54% sustained improvement at 2 years. (1)

Reference: