WORLD CONGRESS ON
THYROID CANCER July 10-14
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“Meet the professor section”

RAI ablation: ablation preparation and dose selection

Daniele Barbaro
Sezione Endocrinologia
Azienda USL 6 Livorno, Italy
CASE: Veronica B., female, 31 years old

Sent to surgical intervention for microfollicular nodule (Thyr 3 with atypia and nuclear overlapping) 2.5 cm increasing in size

Analysis of BRAF mutation negative, US no lymph-nodes

Final decision for total thyroidectomy

CONCLUSIONS:

Diagnosis: Lobo destro: parenchima tiroideo nella norma (LD1-3).
Lobo sinistro: carcinoma papillare variante follicolare capsulato di 2,5 cm (LS2-3). Collaterale parenchima tiroideo nella norma (LS1-3).

Conclusioni: carcinoma papillare (2,5 cm) variante follicolare capsulato.

pT2NxMx secondo TNM 2009

Primo lettore: Dott.ssa M. Granai

Radioiodine yes or not? Which type of stimulation?
We decided to give radioiodine activity 30mCi empiric. Post-operative Tg stimulated is 1.2ng/ml*

*Rosario PW et al. Thyroid 2011
*Vaisman A et al. Head and Neck 2010
No need for ablation when Tg stimulated is < 1.0 ng/ml
Type of stimulation

- RhTSH?
- L-T4 withdrawal for 30 days?
- L-T4 withdrawal for 40 days and T3 administration till to 10 days before?
- Short L-T4 withdrawal?
- Short L-T4 withdrawal plus rhTSH 1 injection?
We decided for rhTSH stimulation

...summary of the literature:
Destroying effects of 131I

* a) 131 I uptake
  - TSH dependent
  - Depends also on iodine intake

* b) 131 I organification
  - TSH dependent
  - Depends also on intrathyroid iodine content?

* c) 131 I secretion in thyroid hormones and iodine leak by follicular cells
  - TSH dependent
  - Can be variably compromised in tumoral cells
The balance of radioiodine destructive effects

131I uptake *
131I organification*?

+ Iodine body pool***
Renal iodine clearance***

131I secretion in thyroid hormones**

Effective half time in thyroid remnants
Residence time in thyroid remnants
Body effective half time

* Probably in favour of LT4W  ** In favour of rhTSH  *** Major during rhTSH stimulation
### Iodine biokinetics and dosimetry

#### “summary”

<table>
<thead>
<tr>
<th></th>
<th>RhTSH</th>
<th>LT4W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body effective half time</td>
<td>mean 10.5 h**/10.3***</td>
<td>mean 15.7 h <strong>/12.9</strong>*</td>
</tr>
<tr>
<td>Body residence time</td>
<td>mean 15.2 h**</td>
<td>mean 23.0 h **</td>
</tr>
<tr>
<td>Blood absorbed dose</td>
<td>+</td>
<td>++ (about 30-50% more)</td>
</tr>
<tr>
<td>Body absorbed dose</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Thyroid effective half time</td>
<td>mean 67.6 h *</td>
<td>mean 48.0 h *</td>
</tr>
<tr>
<td>131I uptake</td>
<td>mean 0.51 48h*</td>
<td>0.91 48h*</td>
</tr>
<tr>
<td></td>
<td>2.29 24h****</td>
<td>3.30 24h****</td>
</tr>
<tr>
<td>Thyroid residence time</td>
<td>0.86 h *</td>
<td>mean 1.38 h *</td>
</tr>
</tbody>
</table>

Data recently reconfirmed by Taieb D JCEM. 2010
**** Barbaro D BoniG. Nucl Med Com . 2006
Effectiveness of rhTSH aided radioiodine ablation of post-surgical thyroid remnants

<table>
<thead>
<tr>
<th>Type Of Study</th>
<th>Subjects</th>
<th>Stage of disease</th>
<th>Dose of 131I</th>
<th>131I uptake</th>
<th>Urinary iodine</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective non randomized Robbins RJ., et al 2001</td>
<td>10</td>
<td>T1-T4</td>
<td>30-250 mCi</td>
<td>/</td>
<td>/</td>
<td>100% complete absence of uptake, 60% Tg &lt;1.0</td>
</tr>
<tr>
<td>Prospective randomized Pacini F., et al 2002</td>
<td>42</td>
<td>T1-T4 N0-N1</td>
<td>30</td>
<td>2.5± 4.3% 9.4 ± 9.5%</td>
<td>/</td>
<td>54% WBS negative 84% WBS negative</td>
</tr>
<tr>
<td>Prospective not randomized, c.e. Berg G. 2003</td>
<td>3</td>
<td>N.R.</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>100% Tg values</td>
</tr>
<tr>
<td>Prospective randomized, c.e. Barbaro D., Boni G., et al 2003</td>
<td>16</td>
<td>1-2</td>
<td>30</td>
<td>/</td>
<td>/</td>
<td>76.9% WBS negative 86.5% Tg &lt;1.0</td>
</tr>
<tr>
<td>Prospective randomized Multicenter Pacini F., et al 2003</td>
<td>32</td>
<td>T1-T4 N0-N1</td>
<td>100</td>
<td>0.5</td>
<td>90 ± 8</td>
<td>100%* (75%)** 100%* (86)***</td>
</tr>
<tr>
<td>Prospective randomized, c.e. Barbaro D., Boni G., et al 2006</td>
<td>52</td>
<td>1-2</td>
<td>30</td>
<td>2.29± 0.45%</td>
<td>/</td>
<td>76.9% negative WBS 78.0% Tg &lt;1.0</td>
</tr>
<tr>
<td>Prospective randomized, Pilli., et al 2007</td>
<td>72</td>
<td>/</td>
<td>50 mCi (36 subjects)</td>
<td>2.0± 1.5%</td>
<td>/</td>
<td>88.9% 78.9% Tg &lt;1.0</td>
</tr>
<tr>
<td>Prospective randomized, Chianelli M., et al 2009</td>
<td>21</td>
<td>/</td>
<td>54 mCi</td>
<td>1.38+/-.141</td>
<td>/</td>
<td>85.0% Tg&lt;1.0 90.5% no visible uptake</td>
</tr>
</tbody>
</table>

N.R.: Not reported c.e.: consecutively enrolled

° 76.3 +/- 4.0 without the short stop of LT4

* No visible uptake or <0.1% uptake
** Only no visible uptake
The summary of these data of the literature is that low activity (30 mCi), using rhTSH, is not always capable to ablate post surgical remnants, urinary intake could be the crucial points although the role of short stoppage of L-T4 is still controversial, but L-T4 is unquestionably a source of L-T4...
### Urinary iodine in studies about comparison between RhTSH and LT4W

<table>
<thead>
<tr>
<th></th>
<th>RhTSH</th>
<th>LT4W</th>
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<tbody>
<tr>
<td><strong>Median</strong></td>
<td>75 μg/L</td>
<td>50 μg/L</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Loffler M</td>
<td></td>
<td></td>
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<tr>
<td>Nuclear Medicine, 2003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>76.4 μg/L**</td>
<td>38.6 μg/L**</td>
<td></td>
</tr>
<tr>
<td>Barbaro D</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>J.Clin Endocrinol Metab, 2003</td>
<td></td>
<td></td>
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<tr>
<td>After 4 days stop LT4</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>47.2 μg/L*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p=0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>**p &lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>120 μg/L</td>
<td>90 μg/L</td>
<td>P = N.S</td>
</tr>
<tr>
<td>Pacini F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J. Clin Endocrinol Metab 2005</td>
<td></td>
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</tbody>
</table>
Ablation with Low-Dose Radioiodine and Thyrotropin Alfa in Thyroid Cancer

Mallick U et al. NEJM . May 2012

438 Patients enrolled

Two aims: to compare 30 mCi Vs 100 mCi
to compare rhTSH Vs LT4W

Patients pT1 – pT3 Nx, N1, N0 MO

Criteria of ablation

Tg < 2.0 ng/ml

Negative WBS < 0.1 % uptake

Ablation was successfull in 85% in the group receiving low –
dose radioiodine Vs 88% in the group receiving High dose.
The success rate was also similar in the groups treated with
the aid of rhTSH treated groups (87.1 %) Vs LTW (86.7%)
Strategies of Radioiodine Ablation in Patients with Low-Risk Thyroid Cancer

Schlumberger M et al. NEJM. May 2012

752 Patients enrolled

Two aims: to compare 30 mCi Vs 100 mCi

To compare rhTSH Vs LT4W

Patients

pT1a   N0   N1   Nx
pT1b   N0   N1   Nx   M0
pT2    N0

Ablation criteria

Tg < 1.0

Neck US negative

WBS in patients with antibodies anti Tg
R 34 Remnant ablation can be performed following thyroxine withdrawal or rhTSH stimulation.

Recommendation rating: A
Advantages of rhTSH aided radioiodine treatment

1. Euthyroid state
2. Minor Body irradiation

In front of a modest net cost

Mernagh P, Campbell S, Dietlein M, Luster M, Mazzaferri E, Weston AR

Eur J Endocrinol. 2006
RhTSH Costs

Thyrogen: 1.129.60 Euros

- Quality of life → absence from work reduction by 8.1 days**
- Length of hospitalization 2.4 Vs 3.5 days*(Costs 1807 Vs 2148 Euros)

** Borget I, European Journal of Endocrinology. 2007

“The use of rhTSH prior to radioiodine ablation represents good value-for-money with the benefits to patient and society obtained at modest net cost”

Long term clinical outcome

394 patients

74 L-T4W

320 RhTSH

75 – 100 mCi: intrathyroid papillary carcinoma

100 – 150 mCi: lymph – nads positive

> 150 mCi: Locally aggressive or metastatic disease

Clinical outcomes

( median 29 months)

No clinical evident disease

76% rhTSH

62% LT4W

p 0.1

Persistence of disease

16% rhTSH

24% LT4W

p 0.1

Recurrence

4% rhTSH

7% LT4W

p 0.1

CASE  Veronica B. at the RAI ablation (after two weeks low iodine diet)

TSH: 69.2 μU/ml (v.n. 0.4-4.0)

Tg: 1.2 ng/ml

Urinary iodine: <250 mUI/ml

Ab-Tg: <6UI/ml (v.n.<30)

Ab-TPC: <2.5 UI/ml (v.n. < 10)
Our kit use at the moment of radioiodine ablation can only tell us if urinary iodine is < 250 mcg/L, is it enough?
Urinary iodine assayed with another method showed 131 microg/L, was it good?
Maxon HR et al

Low iodine diet in I-131 ablation of thyroid remnants

*Clin Nucl Med 1983* at least < 25% respect of basal value → better outcome

Goslings BM

Proceedings: Effect of a low iodine diet on 131-I therapy in follicular thyroid carcinoma

*J Endocrinol 1975*

Pluijmen MJ et al

Effects of low-iodine diet on postsurgical radioiodide ablation therapy in patients with differentiated thyroid carcinoma.

*Clin Endocrinol 2003* better outcome with urinary iodine < 50 mcg/L

Morris LF

Reevaluation of the impact of a stringent low-iodine diet on ablation rates in radioiodine treatment of thyroid carcinoma

*Thyroid 2001* no difference but urinary iodine was quite high mean 173 Vs 381 and high radioiodine doses was administered (100-200 mCi)
Klein HA

Radioiodine dilution due to levothyroxine when using recombinant human thyroid-stimulating hormone: case report and discussion

Clin Nucl Med 2011
Two-week low iodine diet is necessary for adequate outpatient preparation for radioiodine rhTSH scanning in patients taking levothyroxine.

Morsch EP, Vanacor R, Furlanetto TW, Schmid H
Two-weeks of a low iodine diet are equivalent to 3 weeks for lowering urinary iodine and increasing thyroid radioactive iodine uptake.

R 38 A low-iodine diet for 1-2 weeks is recommended for patients undergoing RAI remnant ablation, particularly for those patients with high iodine intake.

Recommendation rating: B
Possible sources of Iodine interference
Multivitamins containing iodine: 7 days
Seaweed compounds, disinfectants containing iodine
Toothpaste, vaginal lavages containing iodine: 2-3 wks
Iodine tincture: 2-3 wks
Water soluble iodinated contrast agent: 3-4 wks
Oil soluble iodinated contrast agent: some months
Amiodarone: 6 months of more if obese

Guidelines SIE, AIMN, AIFM (modified)
SOME PARADIGMATIC PAPERS

Padovani RP et al
One month is sufficient for urinary iodine to return to its baseline value after the use of water – soluble iodinated contrast agents in post-thyroidectomy patients requiring radioiodine therapy
Thyroid 2012

Razavi B et al
Systemic iodine absorption associated with the use of preoperative ophthalmic antiseptics containing iodine
Cutan Ocul Toxicol 2013
10 % PVP-I 1.2 – 1.5-fold increase in urinary iodine excretion after 24 h

Nimmons GL
Urinary iodine excretion after contrast computed tomography scan: implications for radioactive iodine use
JAMA Otolaryngol Head Neck Surg 2013
Median time for urinary iodine level to normalize was 43 days, 75% of subjects returning to baseline within 60 days, and 90% of subjects within 75 days
Mekaru K et al
Thyroid function after hysterosalpingography using an oil-soluble iodinated contrast medium
Gynecol Endocrinol 2008

Toubert ME et al
Plasma exchanges overcome persistent iodine overload to enable 131I ablation of differentiated thyroid carcinoma
Thyroid 2008
A 55 year-old obese man had taken amiodarone (200 mg/d) for 3 years
A_0 WHICH CAN REDUCE m_0 TO 0.1 g FOR THREE DIFFERENT TARGET UPTAKES

... so the amount of thyroid remnant also plays a paramount role in RAI ablation
...So all the concept just quoted must be focused also considering the amount of surgical remnants...

Case Veronica B.

Tests 3 months after RAI ablation (30 mCi)

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FT4</td>
<td>1.45</td>
</tr>
<tr>
<td>Tg</td>
<td>&lt;0.20 ng/ml</td>
</tr>
</tbody>
</table>

Tests 8 months after RAI ablation

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FT4</td>
<td>1.45</td>
</tr>
<tr>
<td>Tg</td>
<td>&lt;0.36 ng/ml (repeated 0.46 after 2 months)</td>
</tr>
</tbody>
</table>
CASE V.B.: Follow up at one year

- Ultrasonography negative
- Tg stimulated after rhTSH
  Tg 3.6 ng/ml (basal 0.49)

Radioiodine again: yes? Not?
RhTSH or LT4 W?
Due to basal increase and to Tg stimulated value we decided for a second activity of 100 mCi by rhTSH:

Post-treatment WBS scanning showed an uptake in thyroid bed and a minor uptake on left L.C. lymph-nodes
SUMMARY

• **To treat or not to treat**: ATA guidelines plus consider also post-surgical basal Tg and/or stimulated Tg

• **Empiric Vs. Dosimetry**: empiric activities are good in most cases

• **Type of stimulation**: rhTSH is probably the best option we can offer the patients at a modest cost net

• **Activity**: as low as possible, 30 mCi for (low risk cancer) if a good TT as been performed; also depending on Tg stimulated value (just before 131 I administration). Higher activities for more advanced stages.

• **Low iodine diet**: for two weeks and with a great attention to avoid iodine excess, we also perform a short stoppage of L-T4 for 4 days. Perform urinary iodine before ablation.