The Management of Hyperthyroidism due to Graves’ disease in Europe 1986 - Results of an International Survey -

“In conclusion, even though hyperthyroidism due to Graves’ disease can be treated in three effective ways, none of them is ideal”

Glinoer, Hesch, Lagasse, Laurberg:
15th Annual Meeting of the European Thyroid Association
Stockholm 1986

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Differential therapy of hyperthyroidism

- **Surgical intervention**
  - Goiter > 60 ml, cold nodules and large cysts, suspected malignancy, refuse of radioiodine
  - Immediate effect
  - Possible adverse effects (e.g. vocal cord paralysis, hypoparathyroidism)

- **Antithyroid drugs (ATD)**
  - 1 to 2 years treatment
  - High relapse rate
  - Major adverse effects rare, minor adverse effects frequent

- **Radioactive iodine (I-131)**
  - Goiter < 60 ml, previous thyroid surgery, intolerance of ATD
  - Full effect after 3-6 months
  - No relevant adverse effects
Primary therapy of Graves’ hyperthyroidism

USA
Europe
Japan

I-131
Thionamides
Surgery

Ref.: Wartofsky L et al. Thyroid 1991; 1: 129-135
## Antithyroid medication

<table>
<thead>
<tr>
<th>Thionamides</th>
<th>Initial dose (mg/d)</th>
<th>Maintaining dose (mg/d)</th>
<th>Dose-interval (hours)</th>
<th>Monthly costs (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propylthiouracil*</td>
<td>300-600</td>
<td>25-150</td>
<td>6-8</td>
<td>51.96</td>
</tr>
<tr>
<td>PTU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbimazole***</td>
<td>30-60</td>
<td>2.5-15</td>
<td>12-24</td>
<td>56.76</td>
</tr>
<tr>
<td>(MMI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methimazole**</td>
<td>20-40</td>
<td>2.5-10</td>
<td>12-24</td>
<td>18.98</td>
</tr>
<tr>
<td>MMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Partial inhibition of peripheral conversion of T4 to T3  
** Once daily one tablet (best compliance)  
*** Entirely and rapidly decarboxylated to methimazole
Antithyroid drugs: adverse effects in 1,256 pts.

- **Minor**
  - Frequent (1-5 %)
    - Skin rush
    - Itching
    - Fever
    - Arthralgia
    - Mild leukopenia
  - Rare (< 0.5 %)
    - Oropharyngitis

- **Major**
  - Rare (< 0.5 %)
    - Agranulocytosis*
  - Very rare (< 0.2 %)
    - Hepatitis (PTU)
    - Cholestasis (MMI)
    - Thrombocytopenia
    - Aplastic anemia
    - Hypoglykemia

* Dose-dependent effect: more than 30 mg methimazole/day


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## Therapy of Benign Thyroid Diseases …

### Relapse rates after antithyroid drug therapy

<table>
<thead>
<tr>
<th></th>
<th>Patients (#)</th>
<th>Relapse rate after 1 year (%)</th>
<th>Relapse rate after 4 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves’ disease</td>
<td>124</td>
<td>40</td>
<td>63</td>
</tr>
<tr>
<td>Plummer’s disease</td>
<td>72</td>
<td>46</td>
<td>64</td>
</tr>
</tbody>
</table>

Risk factors for recurrence:
- **GD**: age < 21 years, volume > 50 ml, persistent negative TRH-test
- **PD**: age > 55 years, volume > 50 ml, nodular goiter, persistent negative TRH-test, urinary iodine < 50 µg/g creatinine

**Smoking and positive TSH-r ab after Tx are further risk factors for recurrent Graves’ hyperthyroidism**

Ref.: Voth E et al. Nuklearmedizin 1990; 29: 1-6

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Indications for I-131 Tx of benign thyroid diseases

- Hyperthyroidism
  - Toxic diffuse goiter  (Graves’ disease)
  - Toxic adenoma
  - Toxic multinodular goiter  (Plummer’s disease)
- Euthyroidism
  - Non-toxic goiter

PD patients may be euthyroid in iodine deficiency despite significant amounts of autonomously functioning thyroid tissue

Adapted from AACE Guidelines. Endocrine Practice 2002; 8: 458-469
Contraindications for I-131 therapy of benign...

- **Absolute**
  - Pregnancy
  - Breastfeeding/lactation
- **Relative**
  - Urinary incontinence
  - Children and adolescents (?)

Women of childbearing age should routinely be tested for pregnancy few days before I-131 administration
Patient preparation for I-131 therapy I

- No iodine exposure for an appropriate time before I-131 therapy (e.g. iodine containing medications, topical iodine, radiographic contrast agents)
- Low iodine diet 1 week before treatment
- Withdrawal of ATD’s 3 (-7) days before treatment
- Beta blockade can be continued throughout
- TSH-suppression in Plummer’s disease essential
- Withdrawal of thyroid hormones in non-toxic goiter
Patient preparation for I-131 therapy II

- Recent measurements of TSH, fT4, (f)T3
- Increased TSHr-ab or E.O.
- Thyroid/nodule volume (sonography)
- Quantitative thyroid scintigraphy
- 24 h radioiodine uptake (RAIU)
- Cortisone for 4-6 weeks in case of previous E.O.
- Patient should not eat for 4-6 h before and 1 h after oral administration of I-131
Dose determination for I-131 therapy

• “Fixed dose”
  – Small: 74-185 MBq I-131, repeated as necessary
  – Large: 370-740 MBq I-131, or a sliding scale

• Calculated dose*
  – Activity per gram thyroid tissue: 1.5 to 7.4 MBq I-131 / g

\[
\text{Activity (MBq)} = \frac{\text{MBq/g selected} \times \text{gland weight} \times 100}{24 \text{ h uptake} (\%)}
\]

  – Absorbed radiation dose: 50 to 400 Gy Marinelli-formula

\[
\text{Activity (MBq)} = \frac{\text{Gy selected} \times \text{gland weight} \times 24.8}{\text{Teff (days)} \times 24 \text{ h uptake} (\%)}
\]

* Radioiodine uptake test required
I-131 therapy in Graves’ disease: fixed versus calculated doses in different thyroid volumes*

Hypothyroidism (%) 6 months after Tx

### I-131 therapy: results* in Graves’ disease I

<table>
<thead>
<tr>
<th></th>
<th>Pts. (#)</th>
<th>Hypothyroid (%)</th>
<th>Euthyroid (%)</th>
<th>Hyperthyroid (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 Gy</td>
<td>84</td>
<td>27.4</td>
<td>45.2</td>
<td>27.4</td>
</tr>
<tr>
<td>200 Gy</td>
<td>78</td>
<td>33.3</td>
<td>43.6</td>
<td>23.1</td>
</tr>
<tr>
<td>300 Gy</td>
<td>62</td>
<td>67.7</td>
<td>24.2</td>
<td>8.1</td>
</tr>
<tr>
<td>Total</td>
<td>224</td>
<td>40.6</td>
<td>38.8</td>
<td>20.6</td>
</tr>
</tbody>
</table>

* 185-2,220 MBq I-131; median follow-up 15 months

# I-131 therapy: results in Graves’ disease II

<table>
<thead>
<tr>
<th>Patients (#)</th>
<th>Absorbed dose (Gy)*</th>
<th>Volume (ml) before Tx</th>
<th>Volume (ml) after Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroid</td>
<td>91</td>
<td>256+/-80</td>
<td>21+/-10</td>
</tr>
<tr>
<td>Euthyroid</td>
<td>87</td>
<td>215+/-84</td>
<td>38+/-23</td>
</tr>
<tr>
<td>Hyperthyroid</td>
<td>46</td>
<td>187+/-67</td>
<td>42+/-69</td>
</tr>
</tbody>
</table>

* Measured during I-131 therapy

Importance of quantitative thyroid scintigraphy for I-131 therapy of Plummer’s disease

Baseline scintigraphy

<table>
<thead>
<tr>
<th>cpm</th>
<th>qcm</th>
<th>cpm/qcm</th>
<th>cpmmax/qcm</th>
<th>Uptake Tc</th>
<th>Uptake 100qcm</th>
</tr>
</thead>
<tbody>
<tr>
<td>22478</td>
<td>63.9</td>
<td>352</td>
<td>1422</td>
<td>10.2</td>
<td>16%</td>
</tr>
<tr>
<td>5445.6</td>
<td>8</td>
<td>682</td>
<td>1422</td>
<td>2.5%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Suppression-scintigraphy

<table>
<thead>
<tr>
<th>cpm</th>
<th>qcm</th>
<th>cpm/qcm</th>
<th>cpmmax/qcm</th>
<th>Uptake Tc</th>
<th>Uptake 100qcm</th>
</tr>
</thead>
<tbody>
<tr>
<td>6774.8</td>
<td>56</td>
<td>121.1</td>
<td>841.2</td>
<td>3.7%</td>
<td>6.6%</td>
</tr>
<tr>
<td>1519.2</td>
<td>4.7</td>
<td>322</td>
<td>841.2</td>
<td>.8%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Palpable nodule of 12 ml volume in the right thyroid lobe
Total thyroid volume ~ 60 ml
I-131 therapy*: results in Plummer’s disease

<table>
<thead>
<tr>
<th>TcTUs (%) before I-131 Tx</th>
<th>Patients (#)</th>
<th>Absorbed dose (Gy)</th>
<th>Success (%)**</th>
<th>TSH &lt; 0.3 mU/L (%)</th>
<th>TSH &gt; 4.0 mU/L (%)***</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5-2.5</td>
<td>168</td>
<td>150</td>
<td>97.0</td>
<td>4.8</td>
<td>1.8</td>
</tr>
<tr>
<td>2.51-3.5</td>
<td>93</td>
<td>200</td>
<td>95.7</td>
<td>3.2</td>
<td>1.1</td>
</tr>
<tr>
<td>3.51-4.5</td>
<td>81</td>
<td>250</td>
<td>96.3</td>
<td>4.9</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 4.5</td>
<td>96</td>
<td>300</td>
<td>94.8</td>
<td>5.2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>438</td>
<td>-</td>
<td>96.1</td>
<td>4.6</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* 817+/-269 MBq I-131 (185-2,220); size 54+/-26 ml (19-140)
** Normalized TcTUs (< 1.5 %)
*** Only subclinical hypothyroidism


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Therapy of Benign Thyroid Diseases...

I-131 Tx: success vs. frequency of hypothyroidism

- **Graves' disease**
- **Plummer's disease**

Graph showing the rate of success (%) vs. frequency of hypothyroidism with different dosage ranges:
- 60-100 Gy
- 150-200 Gy
- 300 Gy
Lithium as an adjuvant in I-131 Tx of hyperthyroidism?

**Pro**
- Retrospective study
- 900 mg lithium carbonate/day for 6 days in 55 pts.
- 55 controls
- Pre-treatment with ATD
- 556+/−141 MBq (lithium) vs. 521+/−148 MBq (controls)
- Cure rate after 1 y.: 83 % vs. 72 % but 75 % vs. 40 % in pts. with > 40 ml vol.
- Conclusion: Effect of I-131 Tx is enhanced by lithium

**Contra**
- Randomized controlled trial
- 900 mg lithium carbonate/day for 3 weeks in 175 pts.
- 175 controls
- Pre-treatment with ATD
- 344+/−281 MBq (lithium) vs. 326+/−204 MBq (controls)
- Cure rate after 32+/−10 mo.: 96.7 % vs. 96.3 %
- Conclusion: Effect of lithium in I-131 Tx is insignificant

Ref.: Bogazzi F et al. JCEM 1999; 84: 499-503  
Ref.: Bal CS et al. Thyroid 2002; 12: 399-405
## I-131 therapy of benign thyroid diseases: genetic risk

<table>
<thead>
<tr>
<th>Organ*</th>
<th>370 MBq</th>
<th>740 MBq</th>
<th>1,100 MBq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovaries</td>
<td>0.015 Gy</td>
<td>0.03 Gy</td>
<td>0.045 Gy</td>
</tr>
<tr>
<td>Red marrow</td>
<td>0.045 Gy</td>
<td>0.09 Gy</td>
<td>0.13 Gy</td>
</tr>
</tbody>
</table>

* Assuming 55% thyroid uptake and a 20 g hyperthyroid gland (ICRP 53)

Increase of spontaneous birth defects in the patient’s children from 4% to 4.008%, 4.016%, and 4.024%
Basic principles to reduce radiation exposure to others

• **Distance**
  - Sleep alone for the first few days after treatment
  - Avoid prolonged physical contact particularly with babies, children, pregnant women (not more than 30 min/day; for more than 1 h contact keep 2 m distance)

• **Time**
  - Minimize the time spend in close contact with others

• **Hygiene**
  - Wash the hands with soap and plenty of water each time you go to the toilet and flush it twice/trice after each use
  - Rinse bathroom sink and tub thoroughly after using them
  - Use separate eating utensils, bedclothes, towels

Adapted from Article 31 Commission Euratom
Complications of I-131 therapy of benign thyroid diseases

• **Early**
  – Exacerbation of hyperthyroidism, thyroid storm
  – Thyroid swelling (local compression)
  – Thyroiditis

• **Late**
  – No success
  – Hypothyroidism
  – Exacerbation of endocrine ophthalmopathy (?)
Endocrine ophthalmopathy after I-131 therapy for Graves’ hyperthyroidism

“Conclusion:
As compared with other forms of antithyroid therapy: iodine-131 is more likely to be followed by the development or exacerbation of Graves’ ophthalmopathy”

**Therapy of Benign Thyroid Diseases**

## E.O. after treatment of Graves’ disease

<table>
<thead>
<tr>
<th></th>
<th>Surgery*</th>
<th>ATD</th>
<th>I-131 Tx**</th>
</tr>
</thead>
<tbody>
<tr>
<td>587 pts.</td>
<td>164</td>
<td>182</td>
<td>241</td>
</tr>
<tr>
<td>Previous E.O.</td>
<td>yes / no</td>
<td>yes / no</td>
<td>yes / no</td>
</tr>
<tr>
<td>E.O. improved</td>
<td>12.6% / -</td>
<td>14.1% / -</td>
<td>12.3% / -</td>
</tr>
<tr>
<td>E.O. unchanged</td>
<td>67.6% / -</td>
<td>66.7% / -</td>
<td>65.0 / -</td>
</tr>
<tr>
<td>E.O. exacerbated</td>
<td>19.8% / 7.1%</td>
<td>19.2% / 6.7%</td>
<td>22.7% / 4.9 %</td>
</tr>
</tbody>
</table>

* Subtotal thyroidectomy  ** 166 MBq

E.O. after treatment of Graves’ disease: effect of cortisone* as an adjunct to I-131 Tx**

<table>
<thead>
<tr>
<th></th>
<th>Cor + (26 pts.)</th>
<th>Cor – (26 pts.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous E.O.</td>
<td>21 yes / 5 no</td>
<td>16 yes / 10 no</td>
</tr>
<tr>
<td>E.O. improved</td>
<td>11 (42%)</td>
<td>-</td>
</tr>
<tr>
<td>E.O. unchanged</td>
<td>10 / 5 (58%)</td>
<td>7 / 10 (65%)</td>
</tr>
<tr>
<td>E.O. exacerbated</td>
<td>-</td>
<td>9 (35%)</td>
</tr>
</tbody>
</table>

* 20-40 mg/d for 1 month  ** 359 MBq (203-592)

E.O. after I-131 treatment* of Graves’ hyperthyroidism: effect of hormone substitution

<table>
<thead>
<tr>
<th>Thyroxine after I-131 therapy**</th>
<th>Always</th>
<th>Only when hypothyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (#)</td>
<td>244</td>
<td>248</td>
</tr>
<tr>
<td>E.O. exacerbated***</td>
<td>27 (11%)</td>
<td>45 (18%)</td>
</tr>
</tbody>
</table>

*120 Gy, follow-up 18 months
**100 µg L-T4, starting 2 weeks after Tx with 50 µg/d
***after surgery: 11-16 %; after ATD 11-15 %

Endocrine ophthalmopathy after I-131 Tx: risk factors*

- No adjunct cortisone medication
- Non-ablative dose (< 200 Gy)
- Thyroid volume > 50 ml
- T3 elevated before I-131 Tx
- No follow-up (hormone replacement)

* Excerpt from the literature
Hypothyroidism following ablative I-131 Tx in Graves’ disease at different times (0.24 - 3.12 GBq I-131)


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Follow-up plan after I-131 therapy

- **After 4 weeks**
  - Anamnesis, clinical evaluation, fT4, TSH

- **After 3 and/or 6 months**
  - Anamnesis, clinical evaluation, fT4, (T3), TSH, (TSH-<em>r ab</em>), US, (scintigraphy)

- **Then annually (lifelong)**
  - Anamnesis, clinical evaluation, TSH, (US)

In case of thyroid hormone replacement Tx, dose should be controlled after 4-6 weeks (TSH,T3) and changed accordingly.
Therapy of Benign Thyroid Diseases …

Conclusions

• I-131 therapy with a fixed dose is effective in normal sized glands with Graves’ disease.

• Using calculated doses in Graves’ disease, 250 Gy are effective in glands up to 40 ml; for larger goiters 300 Gy might be needed.

• I-131 therapy in Plummer’s disease enables selective elimination of autonomous follicles with < 5 % of subsequent hypothyroidism.