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Therapy of Benign Thyroid Diseases

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

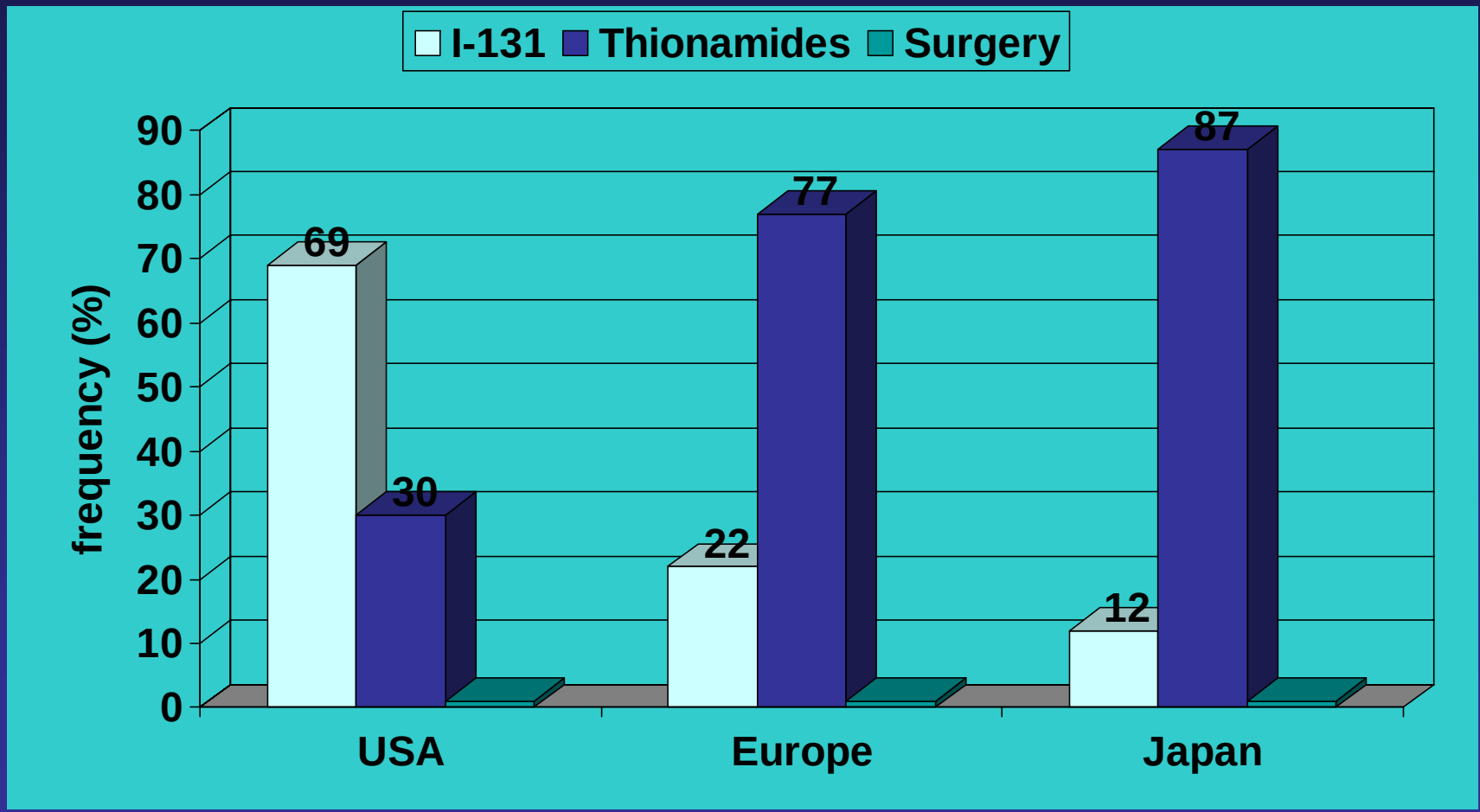
"In conclusion, even though hyperthyroidism due to Graves' disease can be treated in three effective ways, none of them is ideal"

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

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



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

Antithyroid medication

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

* 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

Ref.: Meyer-Gessner M et al. Dtsch Med Wschr 1989; 114: 166-171

Relapse rates after antithyroid drug therapy

	Patients (#)	Relapse rate after 1 year (%)	Relapse rate after 4 years (%)
Graves' disease	124	40	63
Plummer's disease	72	46	64

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

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

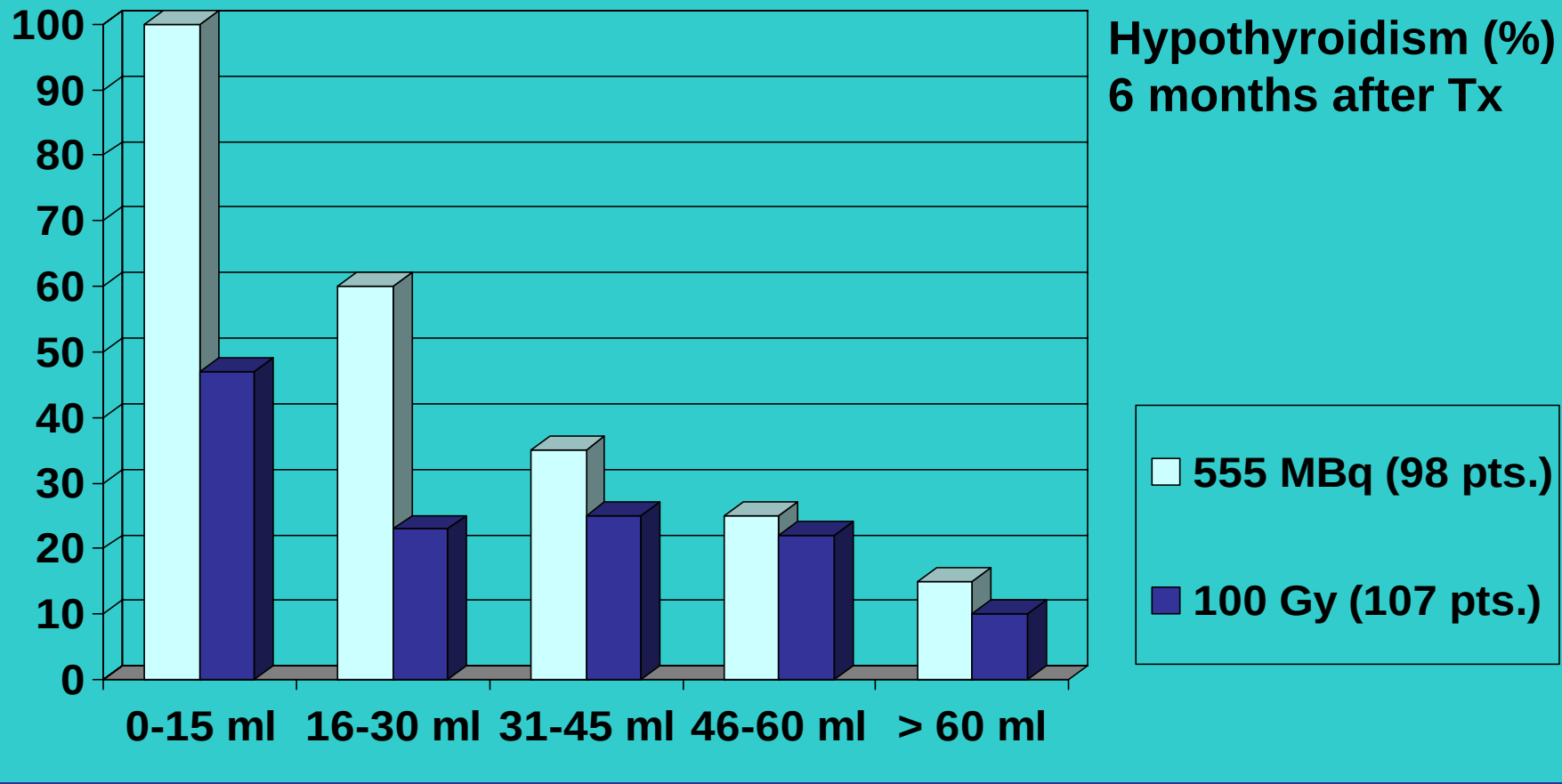
$$\text{Activity (MBq)} = \frac{\text{MBq/g selected x gland weight x 100}}{\text{24 h uptake (\%)}}$$

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

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

* Radioiodine uptake test required

I-131 therapy in Graves' disease: fixed versus calculated doses in different thyroid volumes*



Ref.: Peters H et al. Eur J Clin Invest 1995; 25: 186-93

I-131 therapy: results* in Graves' disease I

	Pts. (#)	Hypothyroid (%)	Euthyroid (%)	Hyperthyroid (%)
150 Gy	84	27.4	45.2	27.4
200 Gy	78	33.3	43.6	23.1
300 Gy	62	67.7	24.2	8.1
Total	224	40.6	38.8	20.6

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

Ref.: Reinhardt MJ et al. Eur J Nucl Med 2002; 29: 1118-1124

I-131 therapy: results in Graves' disease II

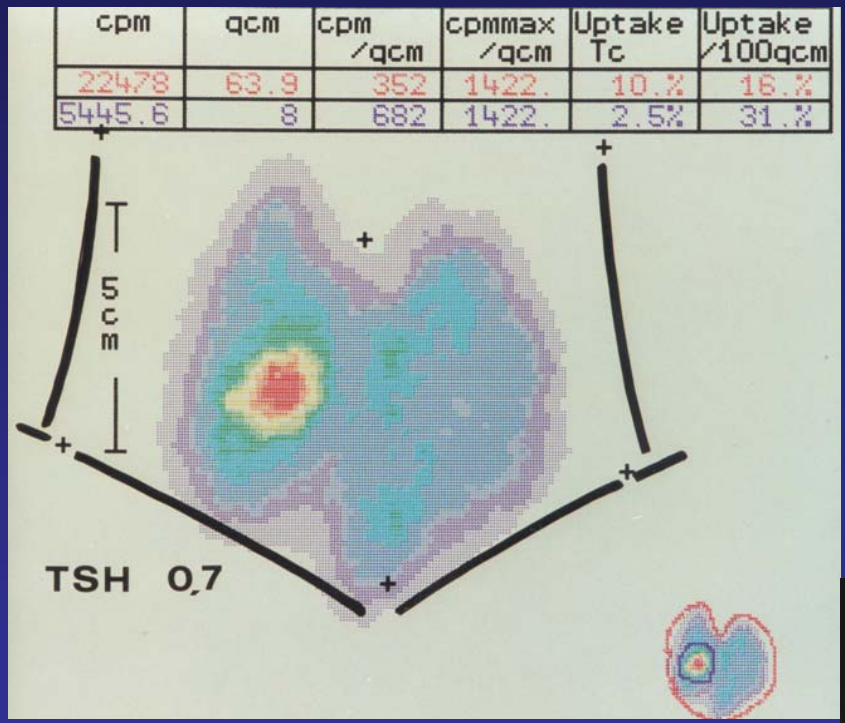
	Patients (#)	Absorbed dose (Gy)*	Volume (ml) before Tx	Volume (ml) after Tx
Hypothyroid	91	256+/-80	21+/-10	7+/-5
Euthyroid	87	215+/-84	38+/-23	17+/-13
Hyperthyroid	46	187+/-67	42+/-69	14+/-9

* Measured during I-131 therapy

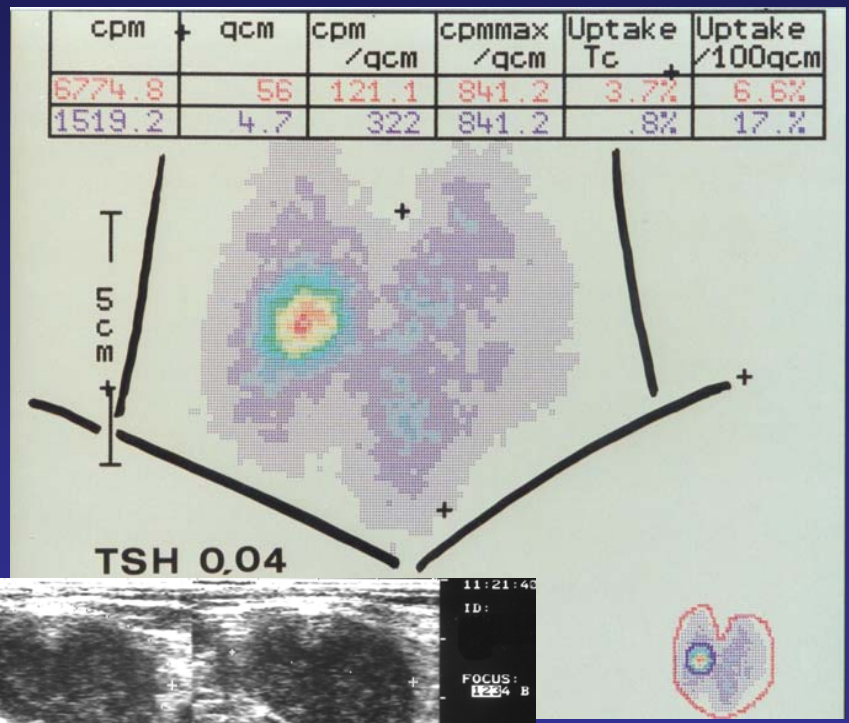
Ref.: Reinhardt MJ et al. Eur J Nucl Med 2002; 29: 1118-1124

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

Baseline scintigraphy



Suppression-scintigraphy



Palpable nodule of 12 ml volume
in the right thyroid lobe
Total thyroid volume ~ 60 ml

I-131 therapy*: results in Plummer's disease

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

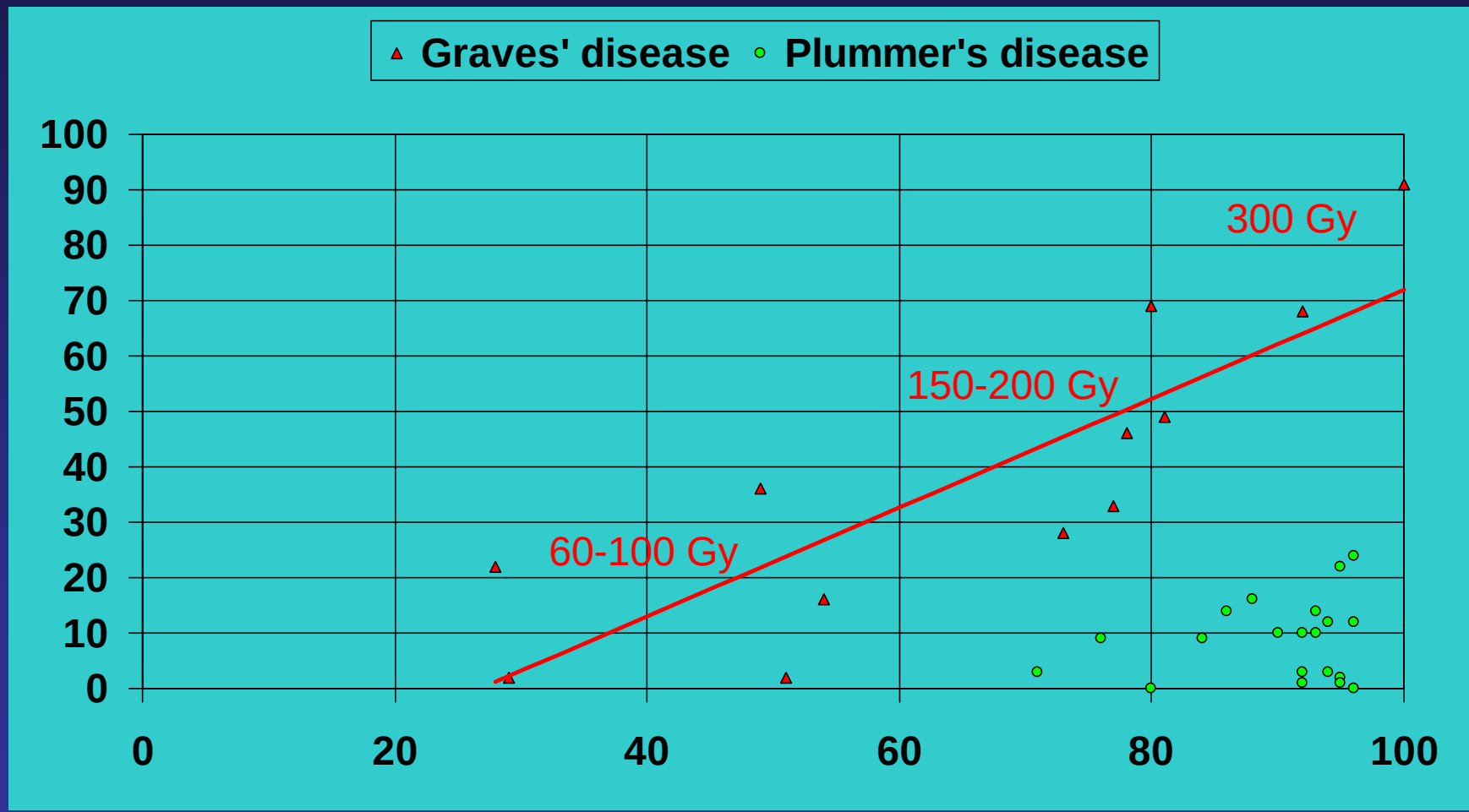
* 817+/-269 MBq I-131 (185-2,220); size 54+/-26 ml (19-140)

** Normalized TcTUs (< 1.5 %)

*** Only subclinical hypothyroidism

Ref.: Reinhardt MJ et al. Eur J Nucl Med 2002; 29: 480-485

I-131 Tx: success vs. frequency of hypothyroidism



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

Ref.: Bogazzi F et al. JCEM 1999; 84: 499-503

- Contra
- Radomized 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.: Bal CS et al. Thyroid 2002; 12: 399-405

I-131 therapy of benign thyroid diseases: genetic risk

Organ*	370 MBq	740 MBq	1,100 MBq
Ovaries	0.015 Gy	0.03 Gy	0.045 Gy
Red marrow	0.045 Gy	0.09 Gy	0.13 Gy

* 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"

Ref.: Tallstedt L et al. N Engl J Med 1992; 326: 1733-1738

E.O. after treatment of Graves' disease

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

* Subtotal thyroidectomy ** 166 MBq

Ref.: Sridama V, DeGroot LJ. Am J Med 1989; 87:70-3

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

	Cor + (26 pts.)	Cor – (26 pts.)
Previous E.O.	21 yes / 5 no	16 yes / 10 no
E.O. improved	11 (42%)	-
E.O. unchanged	10 / 5 (58%)	7 / 10 (65%)
E.O. exacerbated	-	9 (35%)

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

Ref.: Bartalena L et al. N Engl J Med 1989; 321:1349-52

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

Thyroxine after I-131 therapy**	Always	Only when hypothyroid
Patients (#)	244	248
E.O. exacerbated***	27 (11%)	45 (18%)

* 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 %

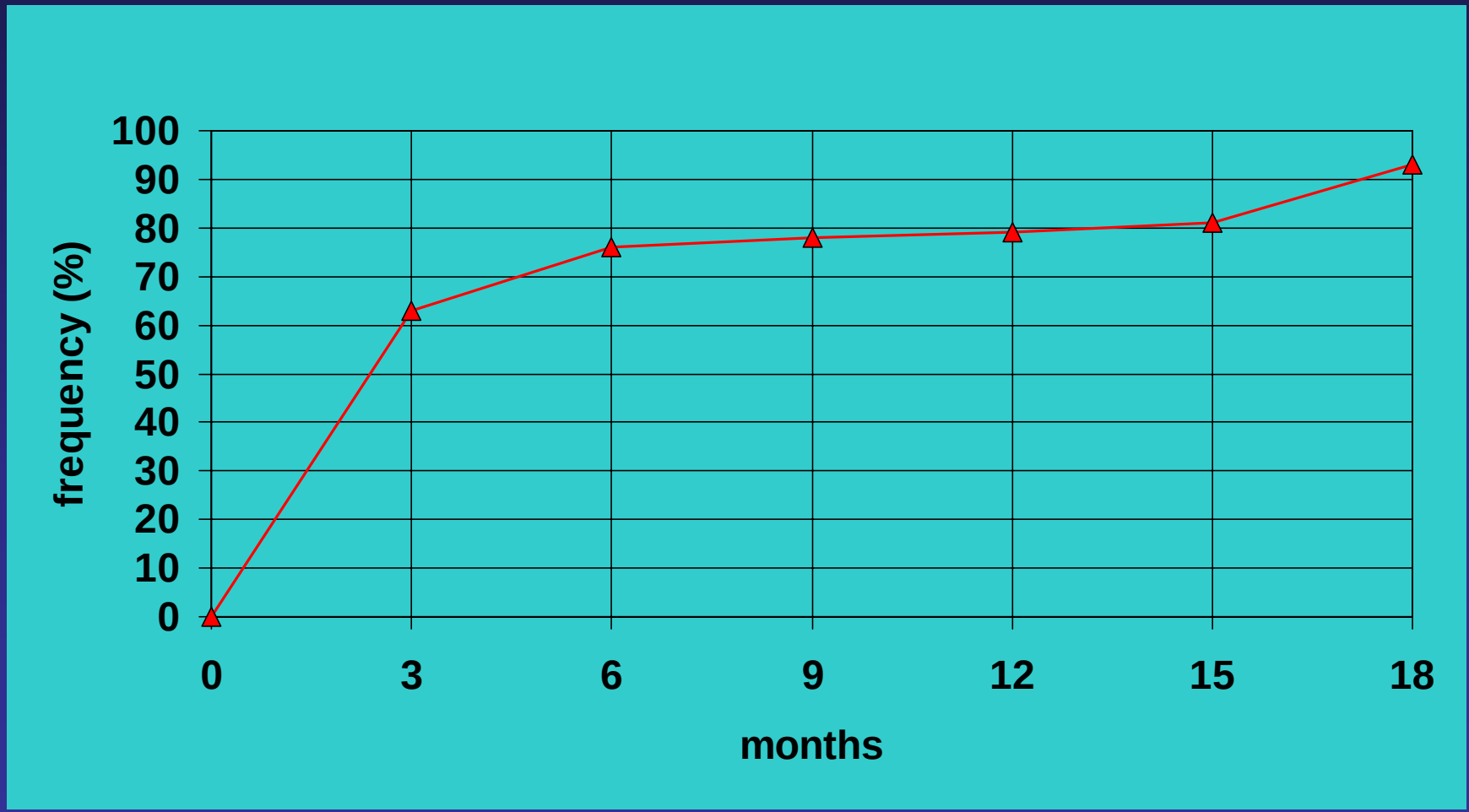
Ref.: Tallstedt L et al. Eur J Endocrinol 1994; 130:494-7

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)



Ref.: Willemsen F et al. Eur J Nucl Med 1993; 20: 1051-1055

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-r ab), 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

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