13th AME Italian Meeting
Ergife Palace Hotel
7-9 November 2014, Rome, Italy

Thyroid nodular disease: how to treat?

Nuclear Medicine

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Treatment of nodular thyroid disease

Radioiodine therapy

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Pertinent background literature

- **Bonnema SJ, Fast S, Hegedüs L.**
  The role of radioiodine therapy in benign nodular goitre.
  Best Practice & Research Clinical Endocrinology & Metabolism 2014;28(4):619.

- **Bonnema SJ, Hegedüs L.**
  Radioiodine therapy in benign thyroid diseases: effects, side effects, and factors affecting therapeutic outcome.
  Endocrine Reviews 2012;33(6):920-980.

- **Hegedüs L, Bonnema SJ, Bennedbaek FN.**
  Management of simple nodular goiter: current status and future perspectives.
  Endocrine Reviews 2003;24(1):102-132.

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Conflicts of interest: None relevant

Irrelevant conflicts of interest

Could radioiodine have been a nonsurgical alternative?

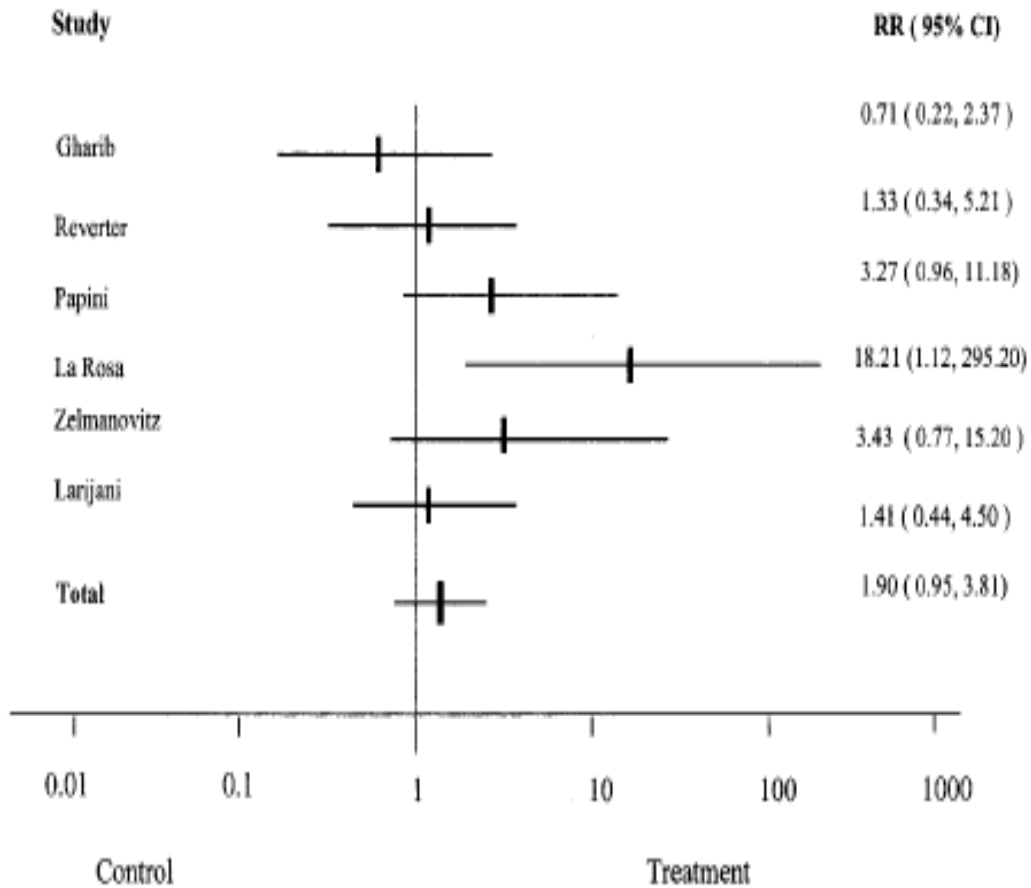
"Where do I complain?"

When given the option, 3 out of 4 Danish patients choose radioiodine

Wulff & Morgenthaler 2008

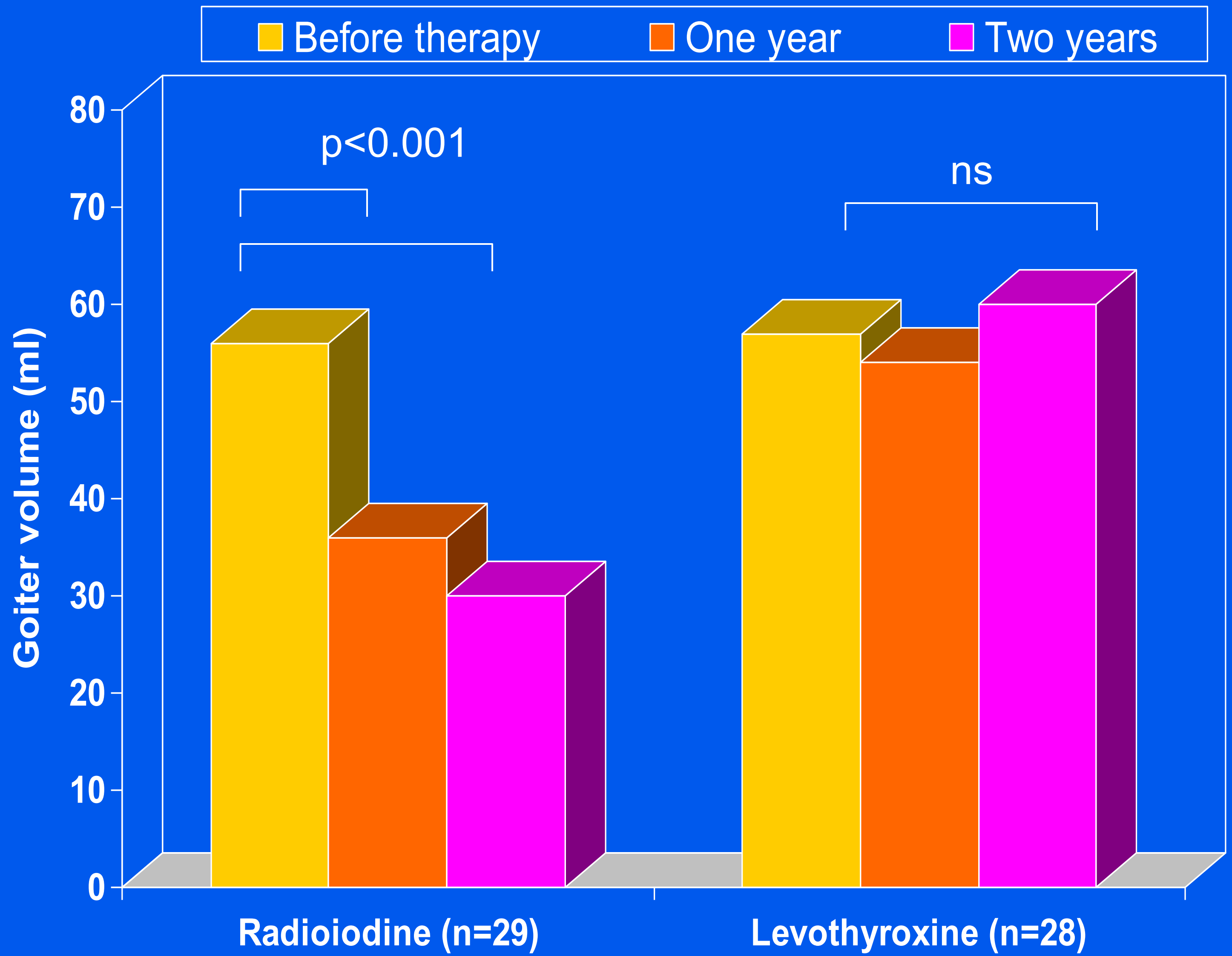
Effect of L-T4 in benign solitary nontoxic thyroid nodules

- 6 studies (n=346)
- Single benign thyroid nodule
- Follow-up ≥ 6 months
- TSH suppressed
- Volume by US



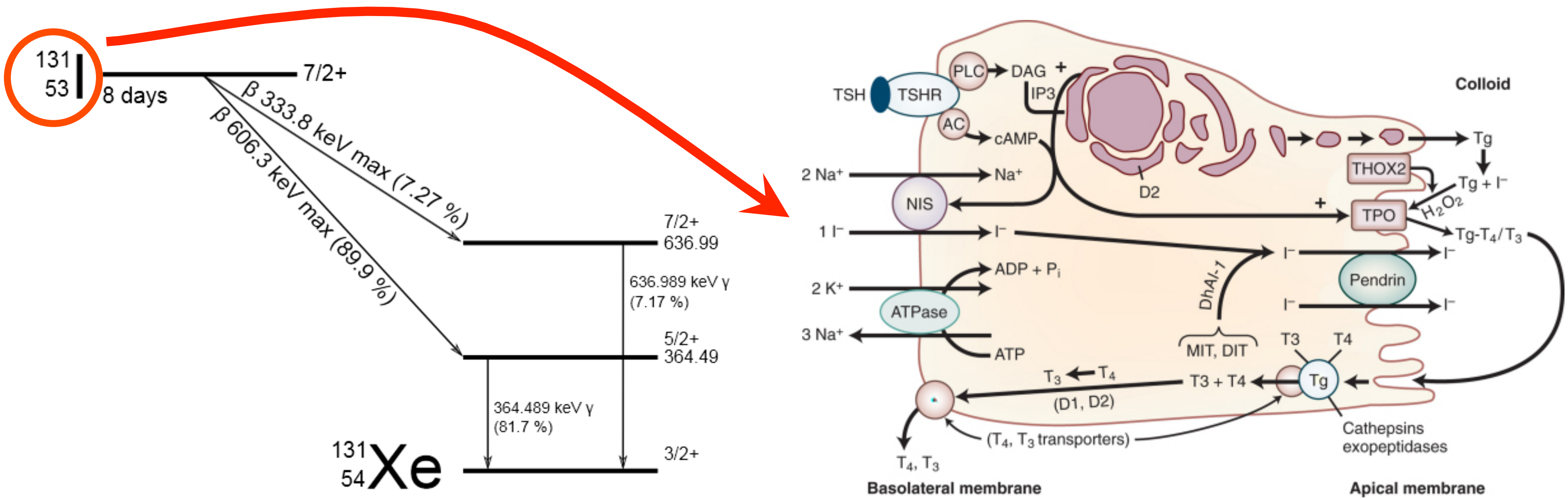
Castro et al., JCEM 2002;87:4154-59

Multinodular nontoxic goiter: radioiodine versus L-T4
Effect on goiter size



Wesche et al. JCEM 2001

Neutron bombardment of natural tellurium results in the production of ^{131}I



The thyrocyte

J. A. M. A.
May 11, 1946

RADIOACTIVE IODINE IN THE STUDY OF THYROID PHYSIOLOGY

VII. The Use of Radioactive Iodine Therapy in Hyperthyroidism

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In previously published experiments of this series [1] radioactive iodine was used as an indicator in the study of animal and human thyroid physiology and iodine metabolism. Much of this preliminary work was done with a view to the discovery of the conditions under which radioactive iodine might be administered with maximum radiational effect in the pathologic thyroid of patients ill with hyperthyroidism. The present paper is a progress report on our early experiences (1941-1946) with such "internal irradiation" in the treatment of 29 cases of hyperthyroidism. It is, indeed, a three to five year follow-up report on these cases.

PROCEDURE

Patients were selected who had had no previous iodine treatment and who were judged clinically to have hyperthyroidism. The usual clinical tests were made and the patients were presented to the Thyroid Clinic of the Massachusetts General Hospital for discussion and determination of their suitability for this type of treatment. In each instance a dose of radioactive iodine, which had been made by the cyclotron at the Massachusetts Institute of Technology or by the Harvard University cyclotron, and separated chemically as sodium iodide, was then orally administered.

The samples of radioactive iodine used were obtained by deuteron bombardment of tellurium and at the time of administration consisted of a mixture of different radioactive isotopes of iodine. Over 90 per cent of the activity at this time consisted of the 12.6 hour isotope I^{130} and most of the remainder of the 8 day isotope I^{131}. The total activity administered varied between 0.7 and 28 millicuries. In 19 cases the total dose was administered to the individual patients as one dose; in 10 cases divided dosages were employed.

From the data already obtained from tracer studies it was considered desirable to keep the total amount of iodide administered below 2 mg. of iodine in order to insure maximum collection by the thyroid.

Urinary iodine excretion was determined during the first seventy-two hours after the administration of radio-iodine. An indirect estimate of the thyroid retention of radioactive iodine was thereby obtained, since an approximate balance exists between administered iodine on the one hand and the sum of thyroid iodine retention and urinary excretion on the other.

Urinary studies were carried out on aliquot portions of carefully collected twenty-four hour specimens, which were kept iced and corked during the collection periods.

It was early found [2] that significant amounts of the original dose were to be found only in the first three days' specimens. Fecal excretion was tested and was found to be so low as to be negligible for the purpose of these experiments.

In a few cases external gamma ray counter measurements were made of the activity of the thyroid of patients following the administration of radioactive iodine. Such measurements are difficult, for obvious reasons, to evaluate quantitatively. However, day to day measurements of this type can give good data on the variation of thyroid iodine content. They were performed in order to follow the loss of iodine from the thyroid following the initial uptake and to evaluate the effect of routine iodinization following the administration of radioactive iodine.

External counter measurements were roughly calibrated against actual direct measurements on the thyroid glands at operation and after chemical separation [2] in 2 patients, previously scheduled for surgery, who received therapeutic amounts of radioactive iodine.

Following the administration of radioactive iodine, routine iodine (nonradioactive) in the usual dosage of saturated solution of potassium iodide 5 minims (0.3 cc.) twice a day was begun at periods varying from one day to several weeks after the radioactive iodine dose.

The basal metabolic rate of the patients treated was tested frequently both before and after the radioactive iodine administration. Basal metabolic levels were taken prior to treatment to establish a measure of the degree of thyrotoxicosis present. In addition to the basal metabolic rate, weights, pulse rates and physical findings were recorded and the total clinical picture was used to evaluate the effects of treatment. No adverse effects, such as fever, nausea or irradiation sickness, were noted in this series of patients. No complaints were recorded regarding the taste of the medicament (since it is tasteless), nor were any local effects, either in the oral cavity or over the thyroid, encountered at the dosage levels used. No increase in the degree of thyrotoxicosis following the radioactive iodine treatment, per se, was recorded, although several test patients were kept uniodinized for three to four weeks prior to routine iodinization.

In most cases, after a period of two to four months following the radio-iodine administration, routine iodine therapy was stopped when an essentially normal basal metabolic rate had been maintained on iodine for a few weeks or months. Such basal metabolic rate response was taken to be indicative of good control of

A report to March 15, 1946.

From the Thyroid Clinic and Metabolism Laboratory of the Massachusetts General Hospital and the Radioactivity Center, Massachusetts Institute of Technology. This material was presented in part to the American Society for Clinical Investigation in May 1942 (see abstract of proceedings, Physiol. Rev. **22**: 4, 1942). The work was aided by a grant from the John and Mary R. Markle Fund in the names of Professors J. H. Means and Robley D. Evans and was accomplished by close cooperation of the Radioactivity Center of the Massachusetts Institute of Technology, Cambridge, Mass., and the members of the medical staff of the Massachusetts General Hospital, Boston.

This work was performed at the Massachusetts General Hospital and the Massachusetts Institute of Technology under a grant from the John and Mary R. Markle Fund. Cooperation and assistance in this work were given by Professor J. H. Means, Professor J. W. Irvine, Dr. Wendell C. Peacock, Professor M. Stanley Livingston, Professor Robley D. Evans, Drs. R. W. Rawson and Jacob Lerman, the technical assistants Mrs. Phyllis Brown Shattuck, Miss Ann Gaurdo and Miss Mary Lennon as well as the nursing, surgical and medical staffs of the Massachusetts General Hospital. The speech of President Karl T. Compton of the Massachusetts Institute of Technology before a Harvard Medical School colloquium in the fall of 1936 served to inspire the senior author in the initiation of this investigative program.

1. Hertz, S.; Roberts, A., and Evans, R. D.: Radioactive Iodine as an Indicator in the Study of Thyroid Physiology, Proc. Soc. Exper. Biol. & Med. **38**: 510 (May) 1938. Hertz, S.; Roberts, A.; Means, J. H., and Evans, R. D.: Radioactive Iodine as an Indicator in Thyroid Physiology: II. Iodine Collection by Normal and Hyperplastic Thyroids in Rabbits, Am. J. Physiol. **129**: 565 (Feb.) 1940; Tr. Am. A. Study Goiter, 1939, p. 260. Hertz, S.: Radioactive Iodine as an Indicator in Thyroid Physiology: III. Observations on Rabbits and on Goiter Patients, Am. J. Roentgenol. **46**: 467 (Oct.) 1941. Hertz, S., and Roberts, A.: Radioactive Iodine as an Indicator in Thyroid Physiology: VI. Application of Radioactive Iodine in Therapy of Graves' Disease, J. Clin. Investigation **21**: 624 (Sept.) 1942. Hertz, Roberts and Salter.[2] Hertz and Roberts.[8]

2. Hertz, S.; Roberts, A., and Salter, W. T.: Radioactive Iodine as an Indicator in Thyroid Physiology: IV. The Metabolism of Iodine in Graves' Disease, J. Clin. Investigation **21**: 25 (Jan.) 1942.

profession, this form of treatment may well prove itself not only highly effective, safe and noninjurious but also cheap and of least inconvenience to the patient who may receive it while continuing at his normal pursuits. After a short period of hospitalization for the usual preliminary clinical studies and the administration of radio-iodine, the patient may be fully iodinized and released, to be followed as an ambulatory case.

SUMMARY

On the basis of a series of animal and clinical experiments using radioactive isotopes of iodine as a tracer in the study of thyroid physiology and iodine metabolism, the treatment of 29 cases of hyperthyroidism with internal irradiation by radioactive iodine was instituted. By careful excretion studies, external counter measurements over the thyroid gland and by planned operations in 2 cases, data were obtained which allow us to construct a formula for a procedure in treatment.

The addition of ordinary iodine therapy after the administration of radio-iodine offers many advantages in the clinical care of these patients and in the economy and safety of the procedure.

By an analysis, over a long period, of both the failures and successes in this series of 29 cases, it is shown that radioactive iodine when given in the dosage range of 5 to 25 millicuries to uniodized patients with hyperthyroidism possessing goiters of 60 to 75 Gm. is highly effective as a cure of the disease in about 80 per cent of cases. When appreciable activity has been administered and subtotal thyroidectomy is resorted to, myxedema or hypometabolism may be expected to develop in a large fraction of the cases (100 per cent in 5 cases in this series).

THE TREATMENT OF HYPERTHYROIDISM WITH RADIOACTIVE IODINE

EARLE M. CHAPMAN, M.D.
and
ROBLEY D. EVANS, Ph.D.
Cambridge, Mass.

Roentgen treatment has been used for hyperthyroidism for many years. In 1923 Means and Holmes [1] pointed out that in this form of treatment about one third of the patients are cured, another third improved and another third not affected. Since 1923 ordinary iodine by mouth has been used as a preoperative method of quieting the hyperactive thyroid in preparation for surgery. Under iodine alone occasionally the patient and the doctor have been agreeably surprised to find that the symptoms and signs of hyperthyroidism disappeared, and a permanent remission apparently was effected. That x-ray treatment and iodine treatment sometimes cure hyperthyroidism led to the hope that some day a more effective, nonsurgical agent would be found. Then the MacKenzies [2] and Astwood [3] discovered that several chemical compounds inhibit the function of the thyroid in hyperthyroidism as well as under other circumstances. Several of these agents have been investigated, … to be most us…

Induced ra… same year Fermi and his co-workers [4] in Italy prepared radioactive isotopes of iodine. Because the thyroid absorbs iodine selectively, it seemed likely that beta rays from iodine rendered radioactive would have a greater radiation effect than that derived from roentgen rays delivered through the skin and overlying tissues.

The use of radioactive iodine in the study of thyroid physiology was soon undertaken and reported first in 1938 by Hertz, Roberts and Evans.[5] Subsequently these and other investigators used various isotopes of radioactive iodine as tracers for the study of thyroid function [6] and it was found that in untreated hyperthyroidism the thyroid may take up as much as 80 per cent of a small dose (less than 2 mg.) of iodide within a few hours after oral administration.[7] This established the basis for therapeutic trials of radioactive iodine, and in 1942 Hertz and Roberts [8] published a preliminary report of the treatment in this manner of 10 patients. In this series the procedure was to give the radioactive iodine and follow this with ordinary iodine by mouth for a period of several months. However, our review in the clinic of these 10 cases of Hertz and Roberts, and an additional 18 so treated under the direction of Hertz, has led to the conclusion that it is difficult to decide whether those patients who improved were responding to the ordinary iodine, to the radioactive iodine or to their combination. The dosage of radioactive iodine given to these 28 patients averaged 5 millicuries in 1941, 10 millicuries in 1942 and 14.5 millicuries in 1943, the largest single dose being 21 millicuries. In April 1943 Dr. Hertz went on active duty in the Navy and asked us to continue with this study. The present report is on a series of 22 patients with hyperthyroidism treated only with radioactive iodine and with considerably higher doses. Although both Hertz and Roberts [8] and Hamilton and Lawrence [9] were encouraged by their therapeutic trials, the details of their findings have not yet been published.

METHODS AND DOSAGE

Selection and Care of Patients

The patients selected in the Thyroid Clinic of the Massachusetts General Hospital for radioactive iodine therapy were judged by several physicians to be thyrotoxic on the basis of classic disease pattern accompanied with constantly elevated basal metabolic rates. All patients had thyroids estimated to be at least two to three times normal in size. All but 3 were kept free from all forms of treatment, especially iodine, for at least four weeks prior to giving radioactive iodine. For the administration of the drug they were usually hospitalized for a time adequate to obtain levels of their basal metabolic rate, then given radioactive iodine by mouth—simply a drink of what tastes like rather stale water.

Aided in part by a grant from the John and Mary R. Markle Foundation.

From the Thyroid Clinic of the Massachusetts General Hospital (Dr. Chapman) and the Radioactivity Center of the Department of Physics of the Massachusetts Institute of Technology (Dr. Evans).

1. Means, J. H., and Holmes, G. W.: Further Observations on the Roentgen Ray Treatment of Toxic Goiter, Arch. Int. Med. **31**: 303 (March) 1923.

2. MacKenzie, C. G., and MacKenzie, J. B.: Effect of Sulfonamides and Thioureas on the Thyroid Gland and Basal Metabolism, Endocrinology **32**: 185 (Feb.) 1943.

3. Astwood, E. B.: Treatment of Hyperthyroidism with Thiourea and Thiouracil, J. A. M. A. **122**: 78 (May 8) 1943.

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5. Hertz, S.; Roberts, A., and Evans, R. D.: Radioactive Iodine as an Indicator in the Study of Thyroid Physiology, Proc. Soc. Exper. Biol. & Med. **38**: 510 (May) 1938.

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7. Hertz, S.; Roberts, A., and Salter, W. T.: Radioactive Iodine as an Indicator in Thyroid Physiology: IV. The Metabolism of Iodine in Graves' Disease, J. Clin. Investigation **21**: 25 (Jan.) 1942.

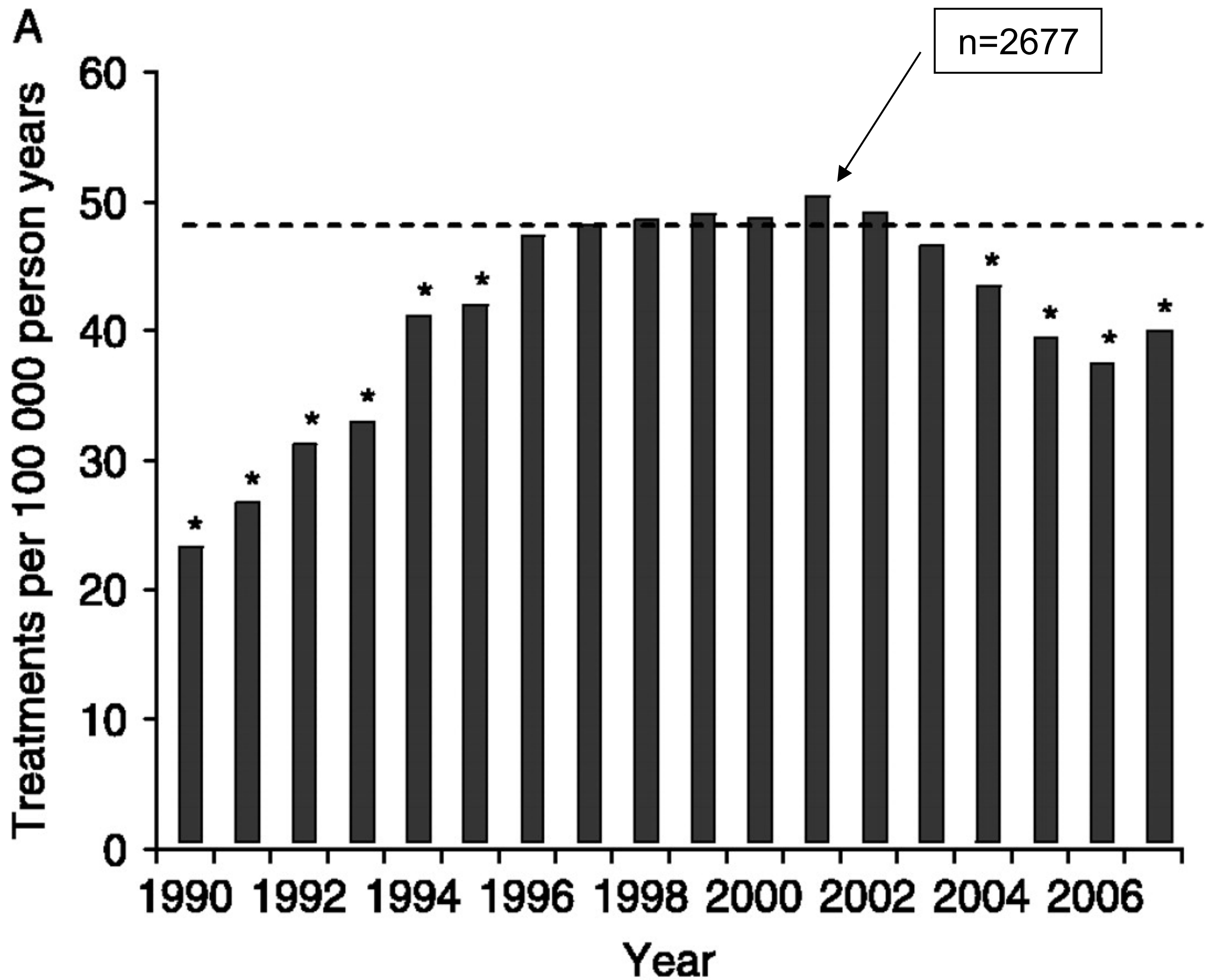
8. Hertz, S., and Roberts, A.: Application of Radioactive Iodine in Therapy of Graves' Disease, J. Clin. Investigation **21**: 624 (Sept.) 1942.

9. Hamilton, J. G., and Lawrence, J. H.: Recent Clinical Developments in the Therapeutic Application of Radio-Phosphorus and Radio-Iodine, J. Clin. Investigation **21**: 624 (Sept.) 1942.

Use of ^{131}I therapy in thyroid diseases

- Hyperthyroidism (Graves' / nodular goiter)
- Nontoxic goiter (<100 ml)
- Thyroid cancer (high dose)

Use of ^{131}I therapy in DK for benign thyroid diseases



Cerqueira et al. EJE 2010

Radioiodine - Contraindications

Absolute

- Pregnancy
- Breast-feeding

Relative

- Poor uptake in ’target tissue’
- Active/severe Graves´ orbitopathy
- Very large goiter
- Young age

Radioiodine – dose algorithms

1. Fixed dose (activity), often around 600 MBq (16mCi)
2. Semi-fixed dose (according to thyr.volume)
3. Corrected for 24h. ^{131}I-uptake and thyr.volume
4. Corrected for 24h. ^{131}I-uptake, t½, and thyr.volume

Radioiodine – dose algorithms

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4. Corrected for 24h. ^{131}I-uptake, t½, and thyr.volume

Cost increases in the same order

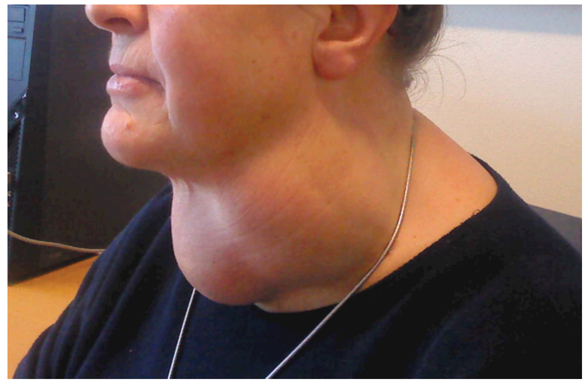
Radioiodine - Advantages

- Easy, mostly outpatient, and cheap
- ~40-50% goiter reduction within one year
- Improvement of inspiration
- Considerable patient satisfaction
- Few short-term side-effects
- Effective in case of co-existing hyperthyroidism
- May be repeated
- Does not hinder/complicate subsequent thyroid surgery
- No/insignificant risk of ^{131}I-induced cancer?

Radioiodine - Disadvantages/shortcomings

- No effect in ‘cold nodules’/low iodine uptake
- Adherence with radiation regulations (isolation)
- Risk of hypothyroidism (10-80%)
- Transient side-effects (pain, thyroid swelling, thyrotoxicosis)
- Slow effect (weeks/months)
- Decreasing efficacy with increasing thyroid size
- Pregnancy prohibited first 4 months after therapy
- Risk of *de novo* or worsening of Graves’ orbitopathy
- Life-long followup of thyroid function (TSH)
- No histological diagnosis

Radioiodine or surgery in nontoxic goiter?



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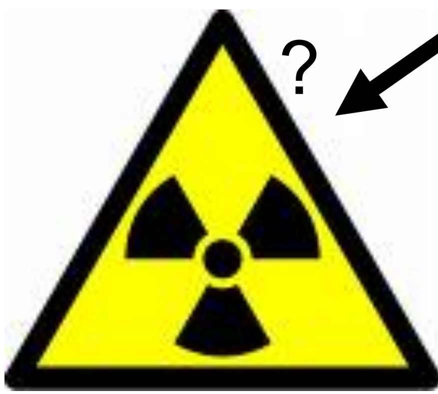

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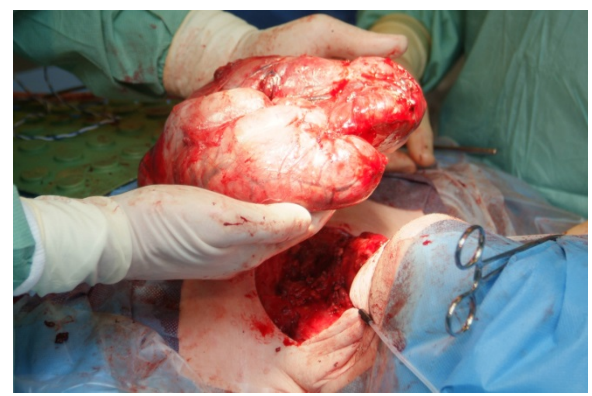
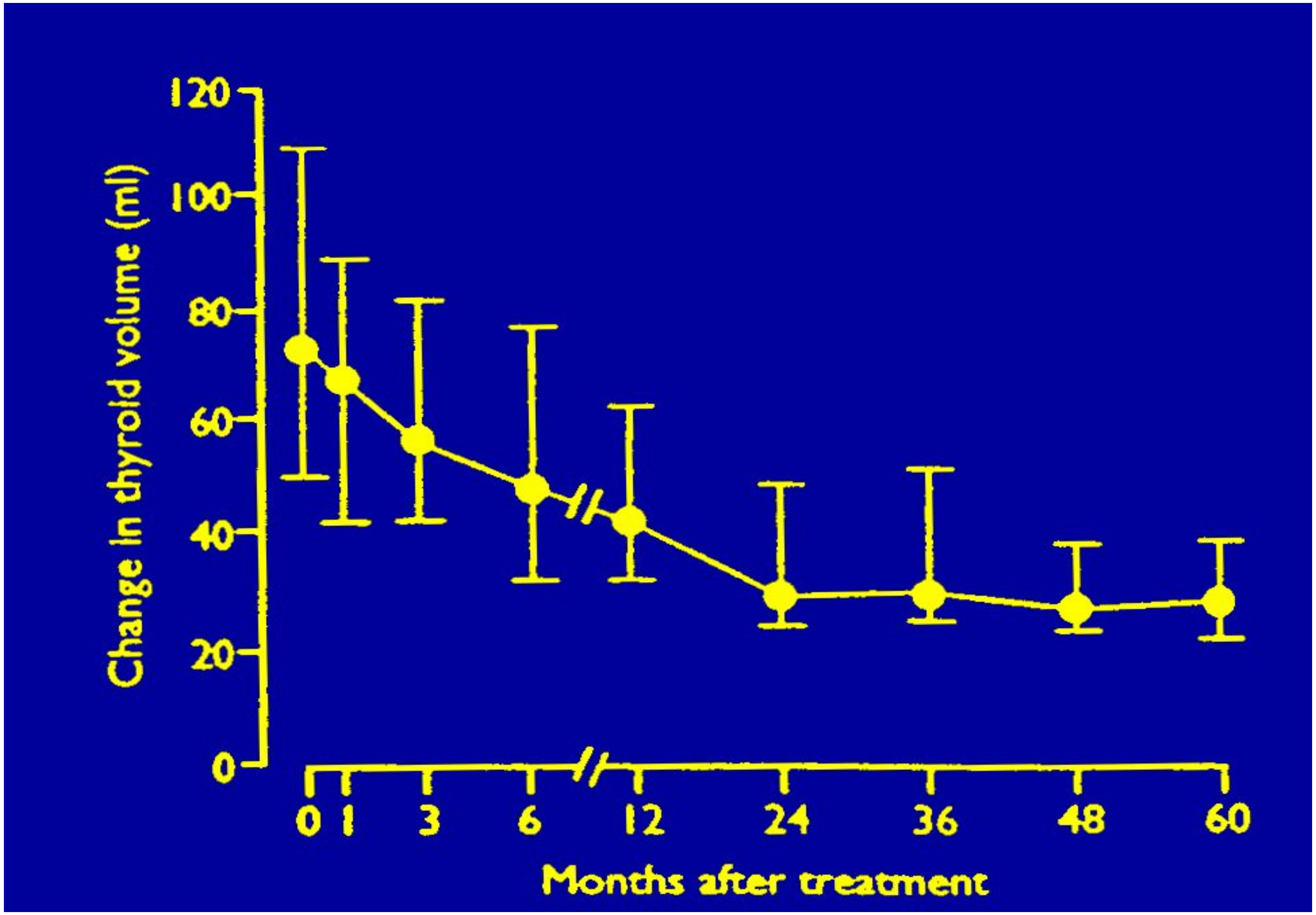


No randomized studies!

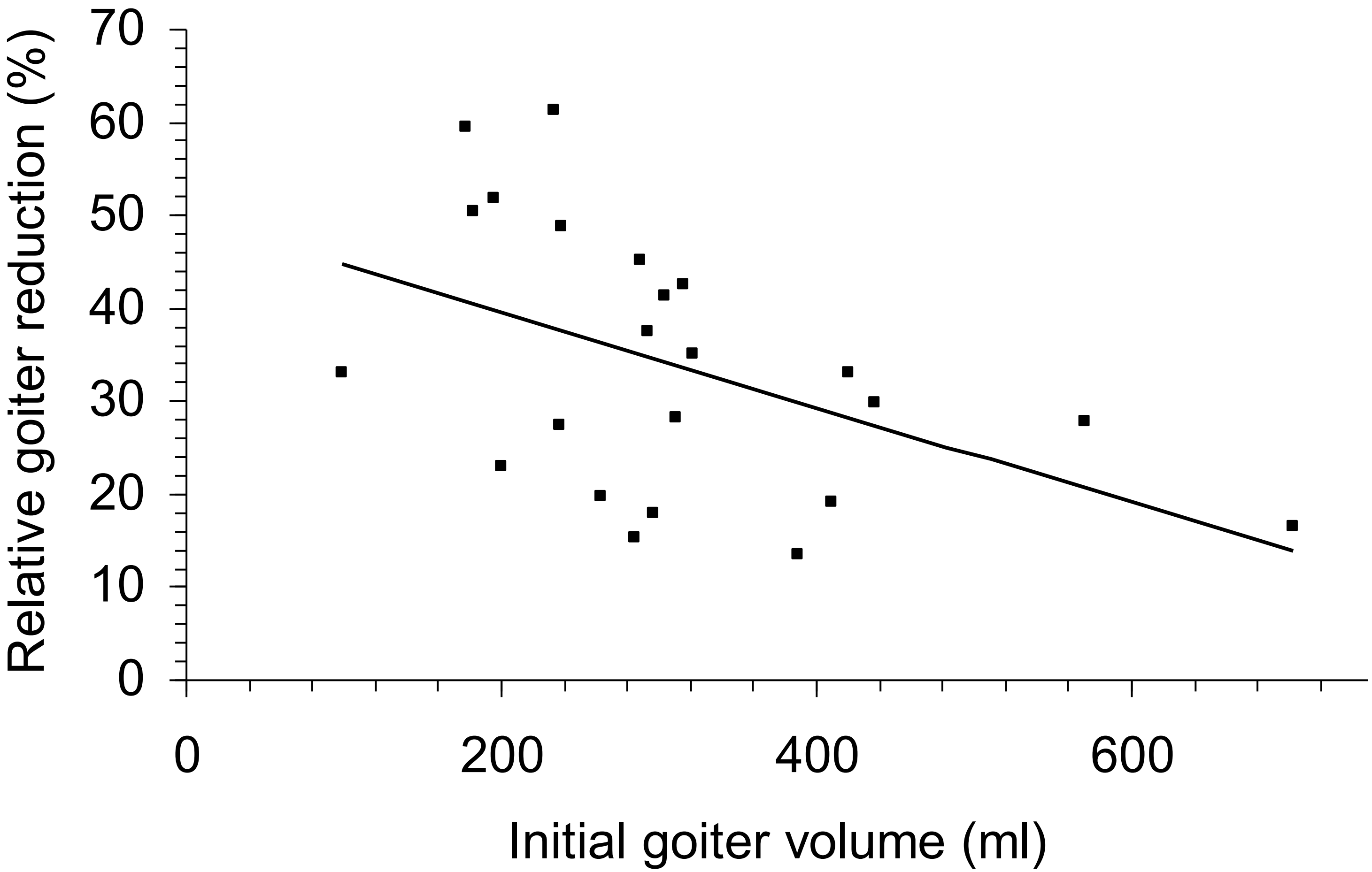
Radioiodine in nontoxic nodular goiter

Goitre volume reduction



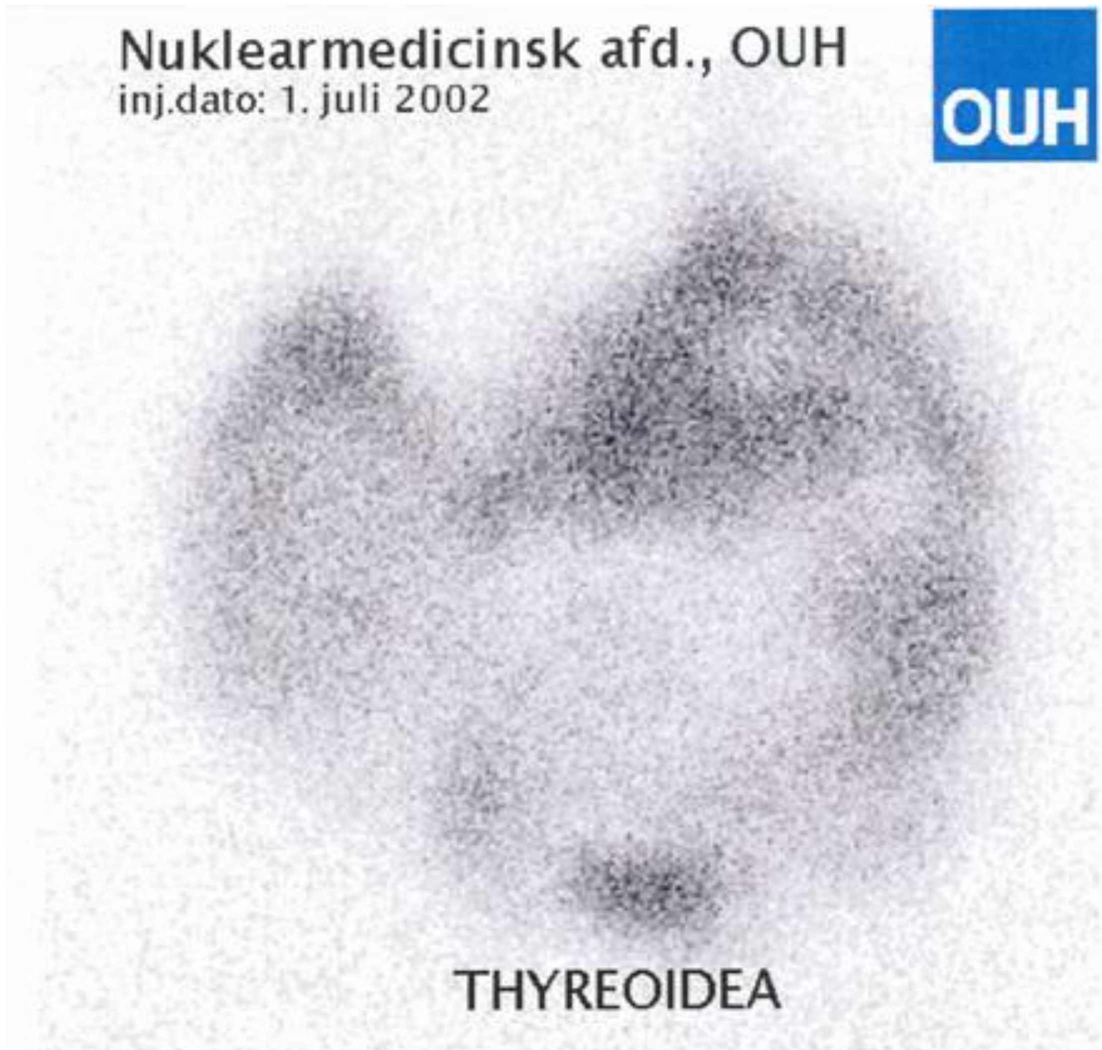
Nygaard B et al: BMJ 1993

Effect attenuates with increasing goiter size



Bonnema et al. JCEM 1999

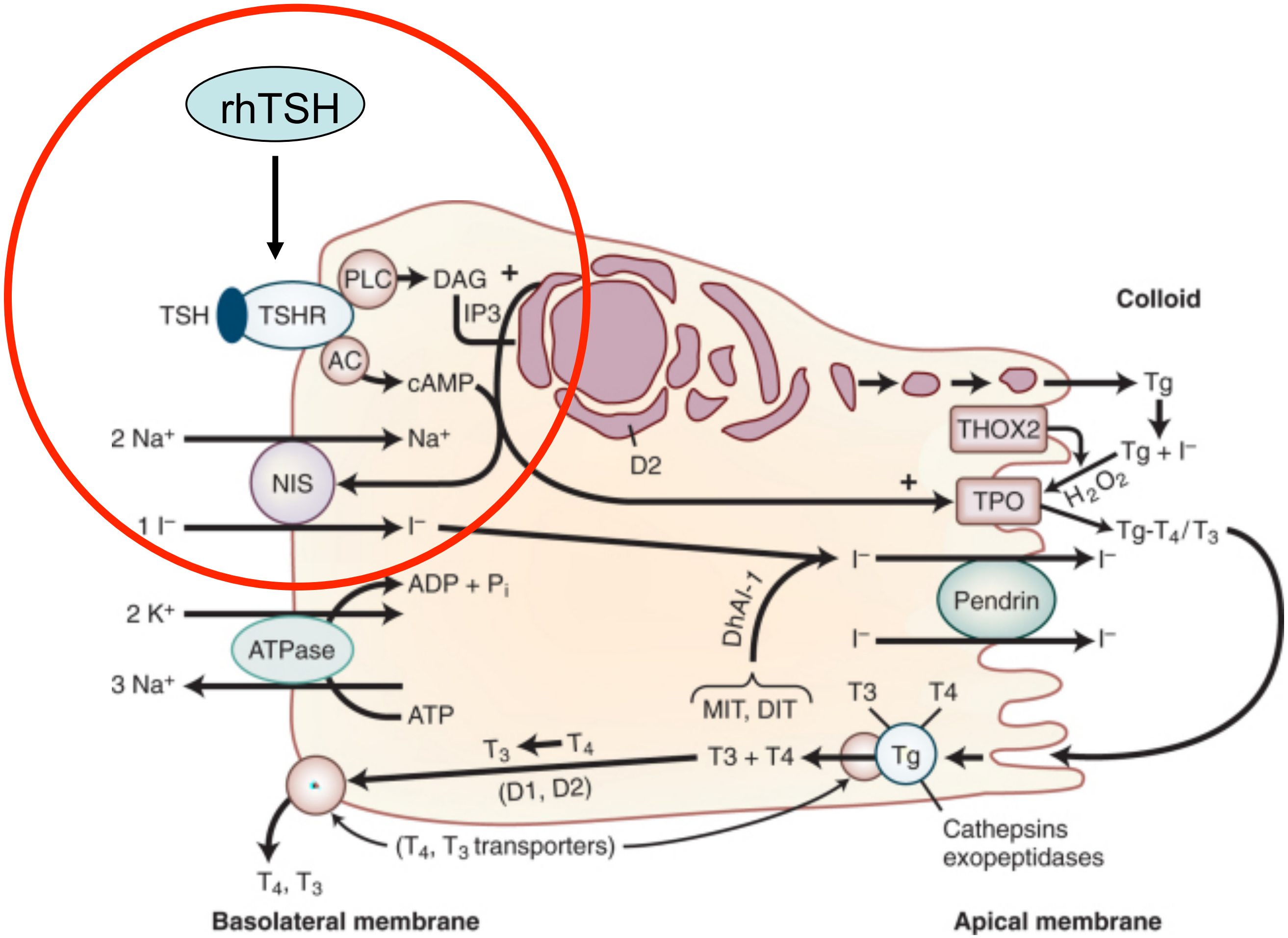
Multidodular goiter with massive low-uptake lesions



Enhancers of thyroid ^{131}I uptake

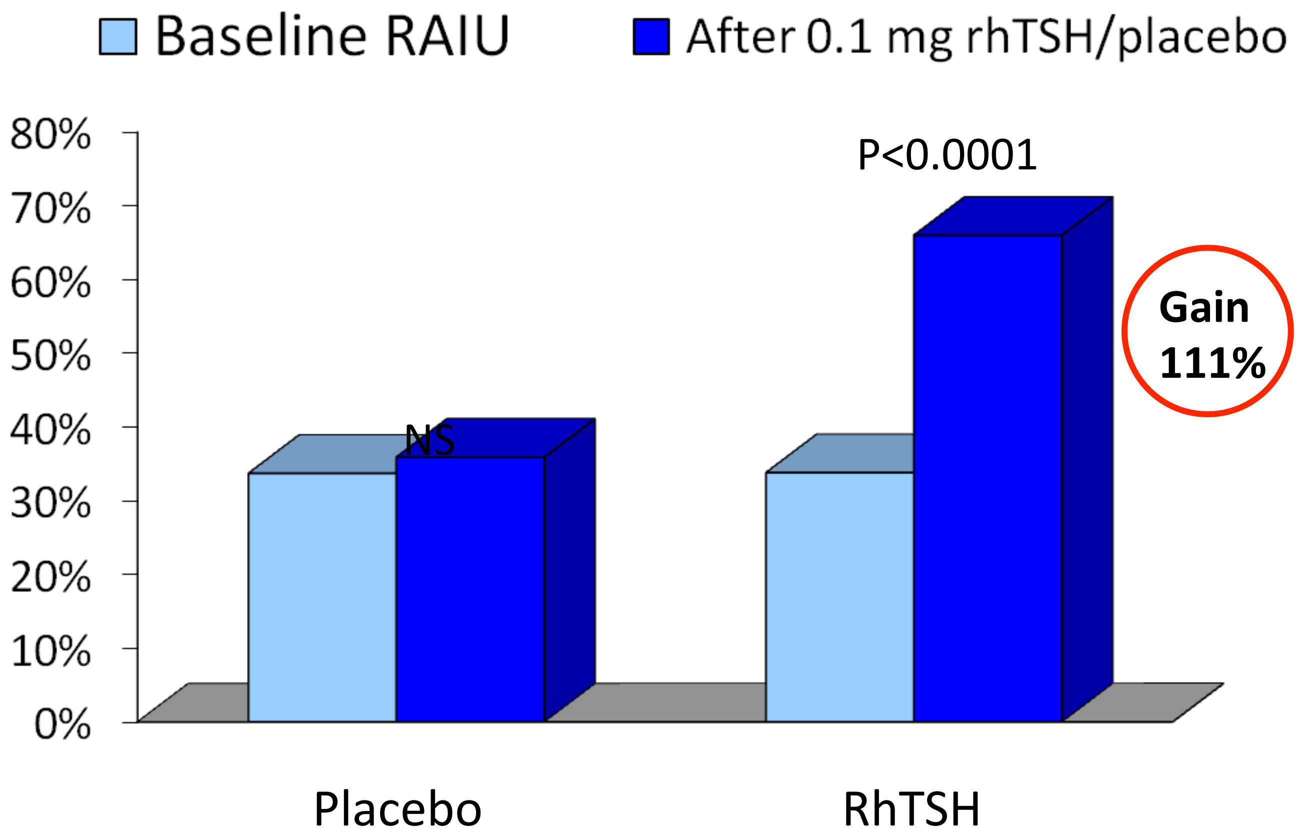
- Low-iodine diet
- Stable iodine and lithium
- Diuretics
- Recombinant human thyrotropin (rhTSH)
- Other compounds (retinoic acid, glitazones,…)

RhTSH stimulates the thyroid cell



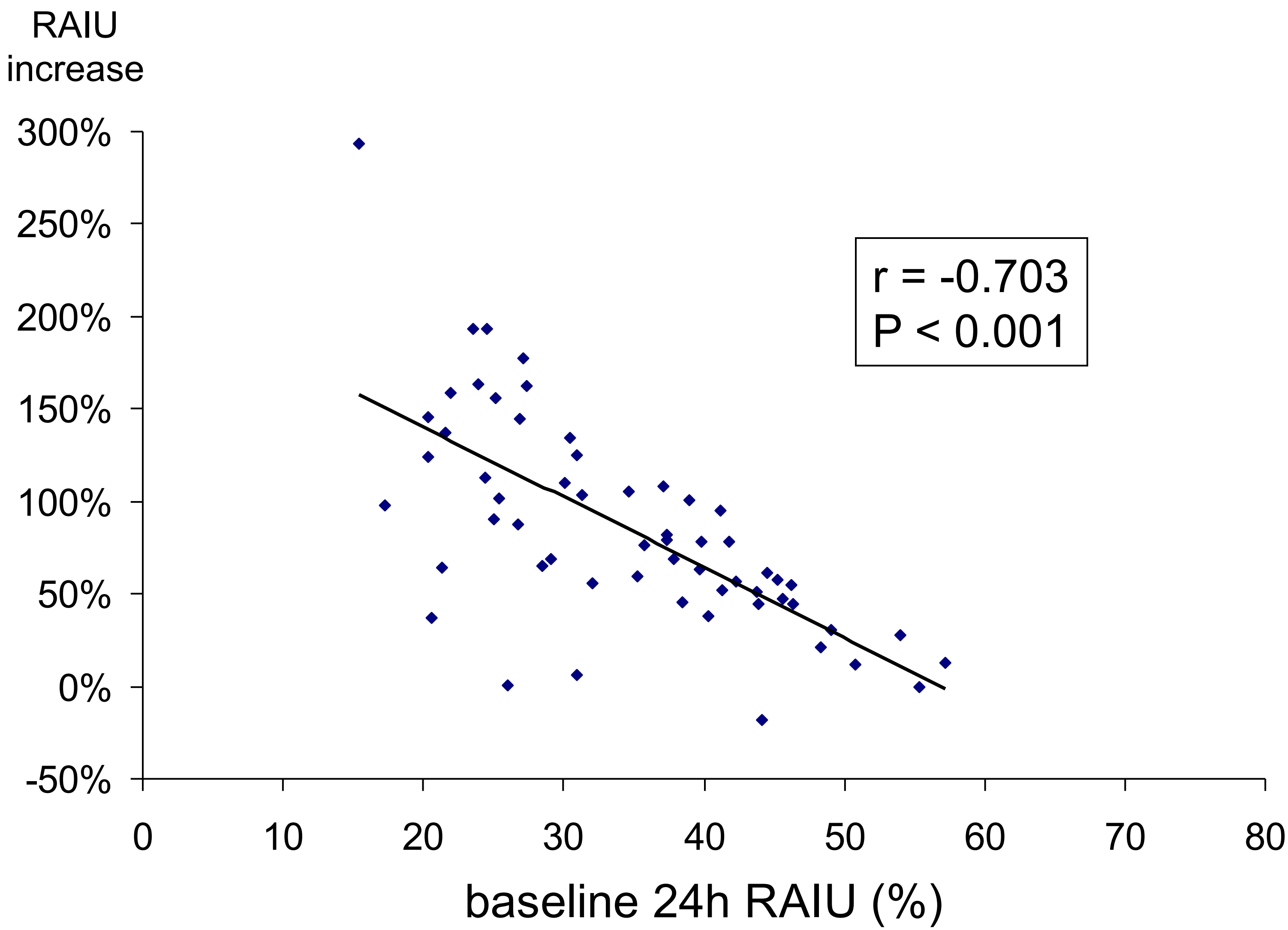
Thyroid ^{131}I uptake (RAIU) is increased by rhTSH

Impact on 24h RAIU



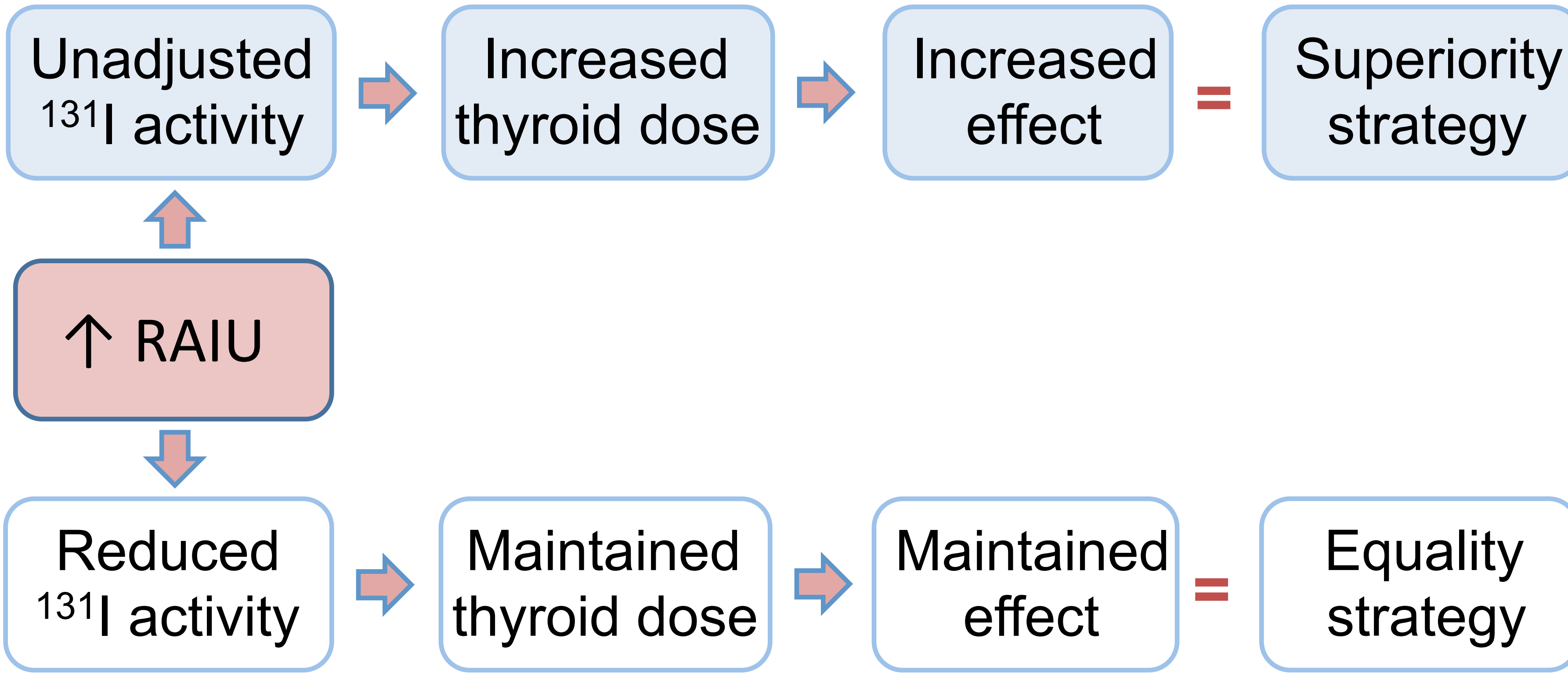
Fast et al., J Nucl Med 2009.

Effect of rhTSH: dependency on initial 24h RAIU



Fast et al., J Nucl Med 2009.

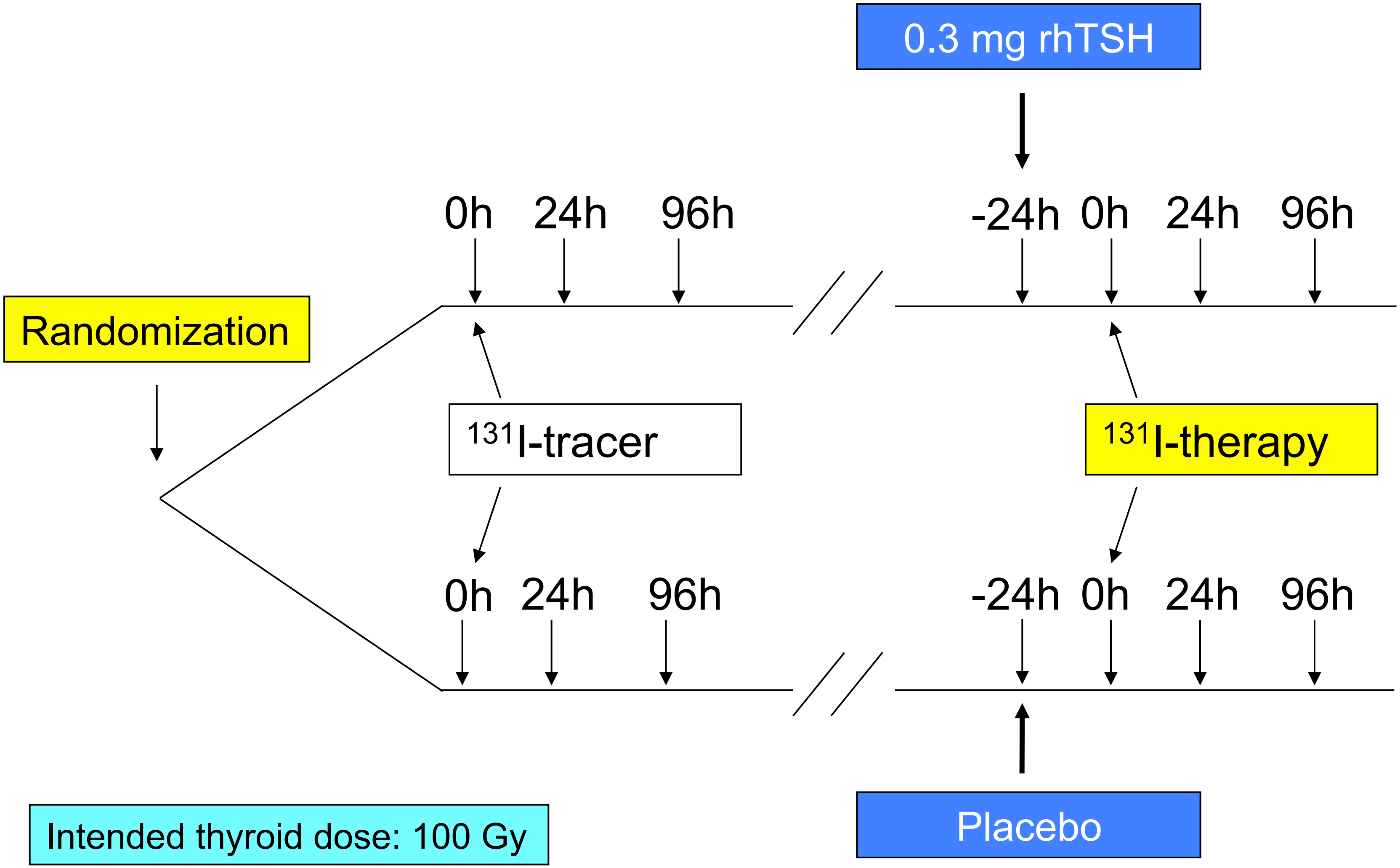
Strategies in rhTSH augmented ^{131}I therapy



Studies on rhTSH-stimulated ^{131}I-therapy of benign multinodular goiter

Author (year)	n	Dose of rhTSH (mg)	Design	Goiter size estimation	^{131}I activity or intended dose	Goiter reduction
Studies with an equality approach						
Nieuwlaat et al. (2003)	12 10	0.01 0.03	Observational non-controlled	MRI	100 Gy	35% at 1 year 41% at 1 year
Fast et al. (2010)	60 30	0.1 placebo	Randomized double-blinded	US or MRI	50 Gy 100 Gy	35% at 1 year 35% at 1 year
Ceccarelli et al. (2011)	11 7	0.03 controls	Observational matched controls	CT-scan	100 Gy	47% at 1 year 35% at 1 year
Studies with a superiority approach						
Duick et al. (2003)	6 10	0.3 0.9	Observational non-controlled	Palpation	Fixed 1110 MBq	30-40% at 7 months 30-40% at 7 months
Albino et al. (2005)	18	2 x 0.1	do	CT-scan	Fixed 1110 MBq	39% at 6 months
Cohen et al. (2006)	17	0.03	do	CT-scan	Fixed 1110 MBq	34% at 6 months
Paz-Filho et al. (2007)	17	0.1	do	CT-scan	Fixed 1110 MBq	46 & 53% at 1 & 2 years
Romão et al. (2009)	42	0.1	do	CT-scan	Fixed 1110 MBq	From 153 mL to 32mL at 3 years
Giusti et al. (2006)	12 8	2 x 0.2 controls	Observational matched controls	CT-scan	Fixed 370-555 MBq	44% at 20 months 25% at 22 months
Giusti et al. (2009)	19 21	2 x 0.1 controls	do	US-scan	Restricted to 600 MBq	60% at 3 years 44% at 3 years
Cubas et al. (2009)	9 9 10	0.1 0.005 placebo	Observational placebo-controlled	CT-scan	Fixed 1110 MBq	33 & 37% at 1 & 2 year 33 & 39% at 1 & 2 year 13 & 15% at 1 & 2 year
Silva et al. (2003)	17 17	0.45 placebo	Randomized not blinded	CT-scan	Fixed arbitrary levels	58 & 73% at 1 & 4 years 40 & 57% at 1 & 4 years
Nielsen et al. (2006)	28 29	0.3 placebo	Randomized double-blinded	US-scan	Above 100 Gy 100 Gy	62% at 1 year 46% at 1 year
Bonnema et al. (2007)	14 15	0.3 placebo	Randomized double-blinded	MRI	Above 100 Gy 100 Gy	53% at 1 year 34% at 1 year
Albino et al. (2010)	8 6 8	0.1 0.01 placebo	Randomized double-blinded	MRI	Fixed 1110 MBq	37% at 1 year 37% at 1 year 19% at 1 year

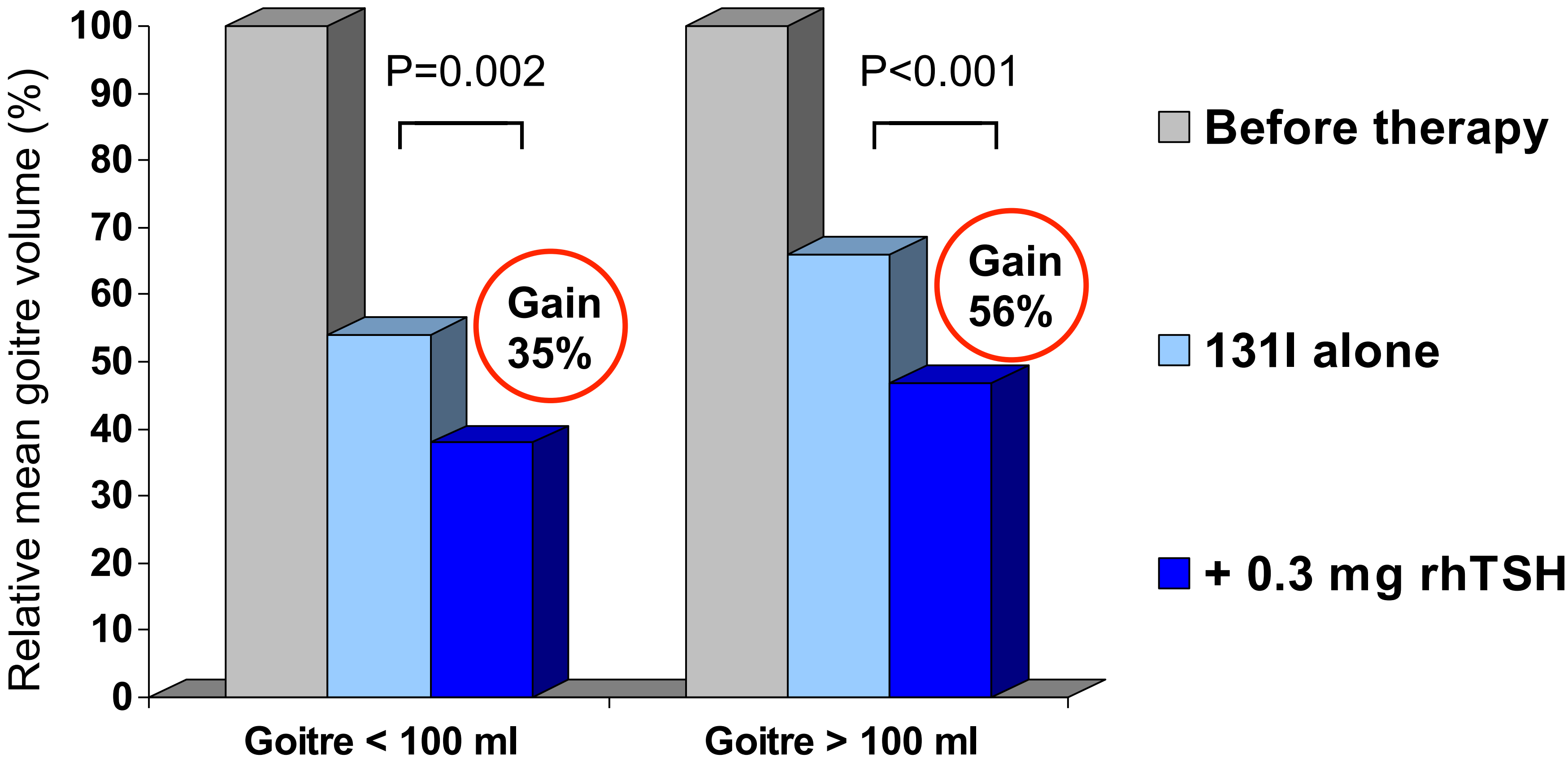
Study design – initial phase



Intended thyroid dose: 100 Gy

Bonnema et al, JCEM 2007

RCT 2002-2005: augmented goiter volume reduction at one year by rhTSH-stimulated ^{131}I therapy



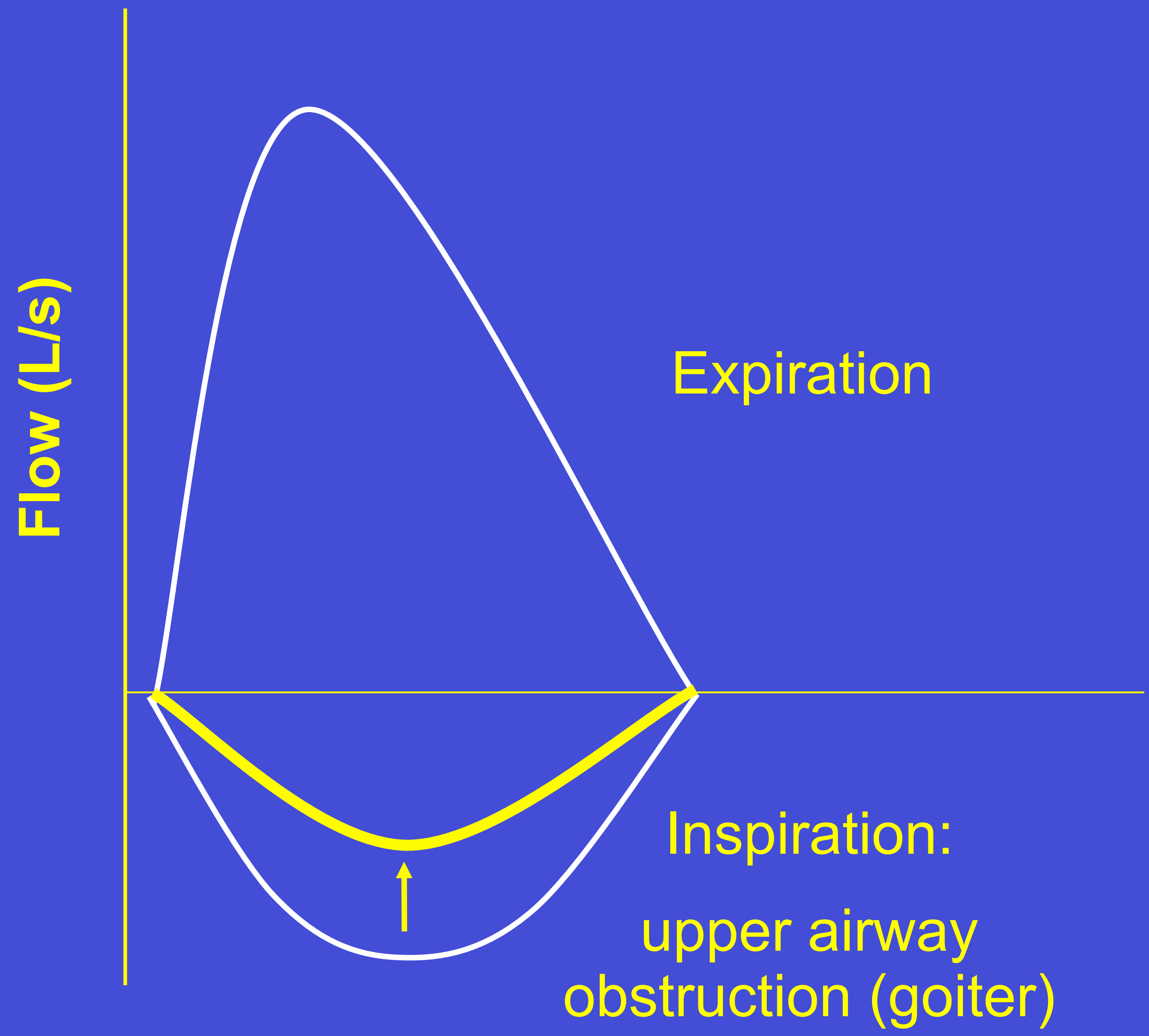
Nielsen et al., Arch Int. Med. 2006 Bonnema et al., JCEM 2007

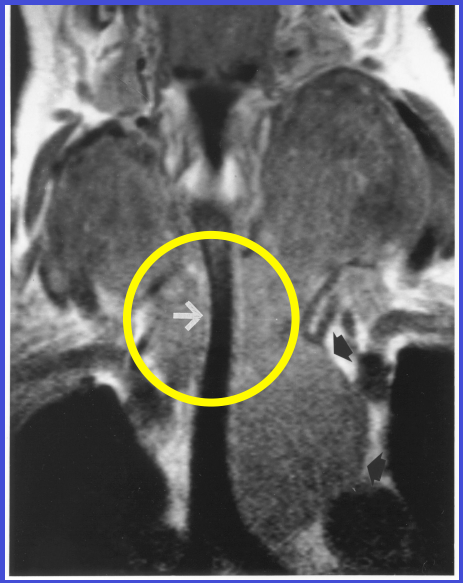
Acute adverse events

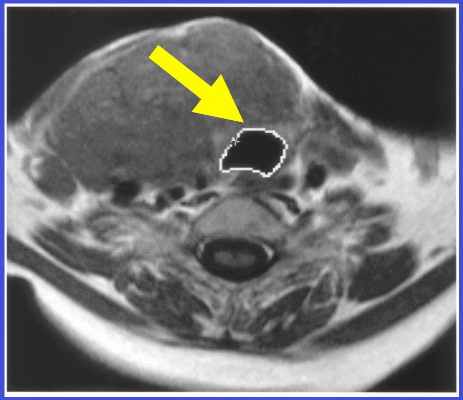
	rhTSH (n=14)	No rhTSH (n=15)	P-value
Hyperthyroid symptoms	4	5	0.55
Cervical pain within the first week	6	1	0.08
Cervical pain after one week	4	2	0.55
Sensation of a tense thyroid gland	5	0	0.04
Oesophagitis	3	0	0.20
Induction of Graves' disease	0	0	-
Other adverse events	4	0	0.09
Total number of adverse effects	26	8	0.02
Prednisolone	2	0	-
Hospitalization	1	0	-
No adverse effects	2	7	0.20

Bonnema et al, JCEM 2007

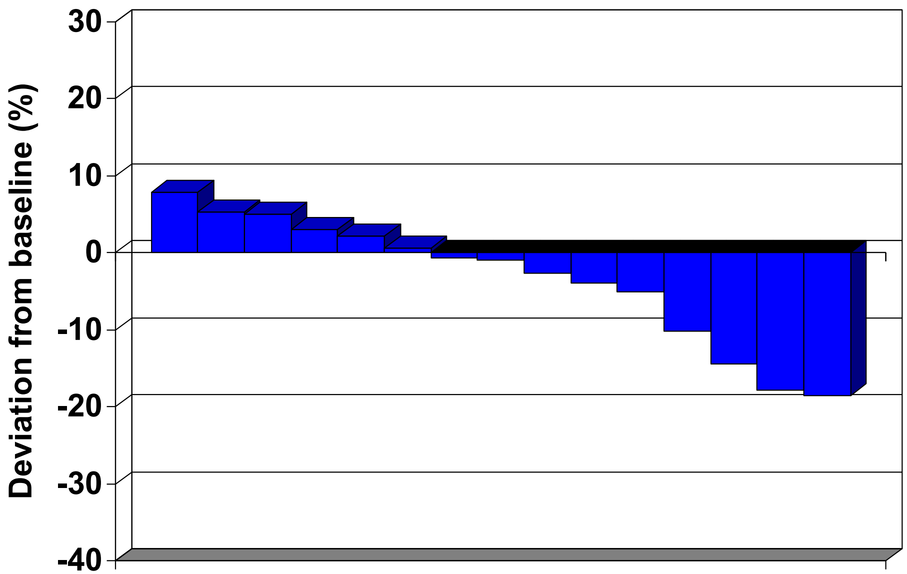
Tracheal compression affects inspiration, not expiration



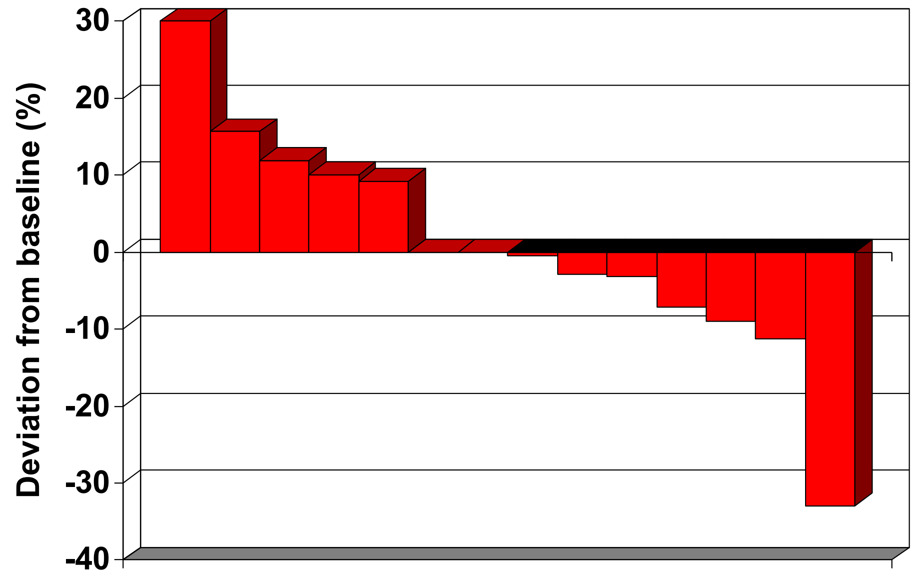




Goiter volume – one week after ^{131}I
Deviation (%) from baseline



Placebo (n=15)

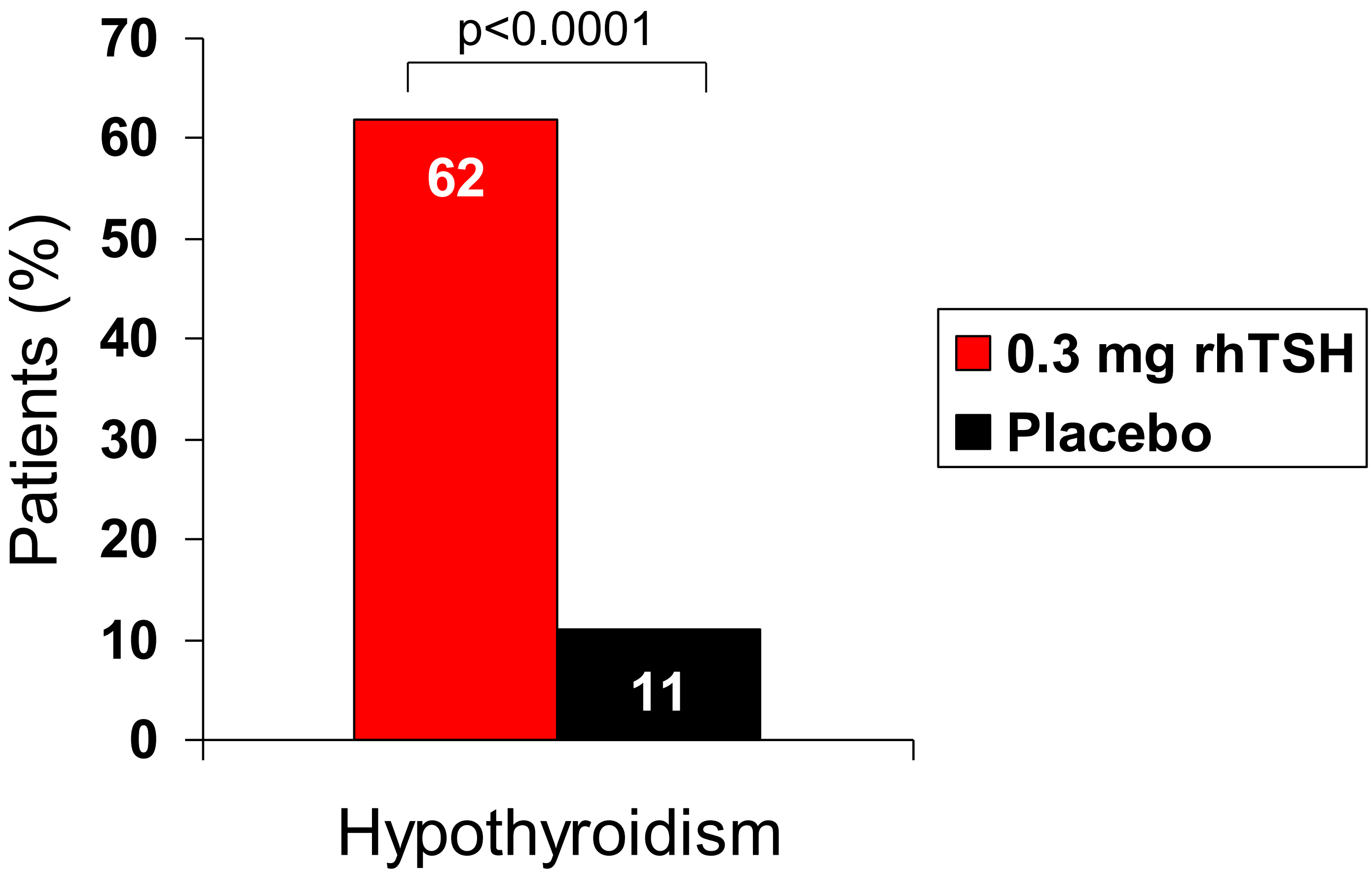


rhTSH (n=14)

P=0.37 between-group

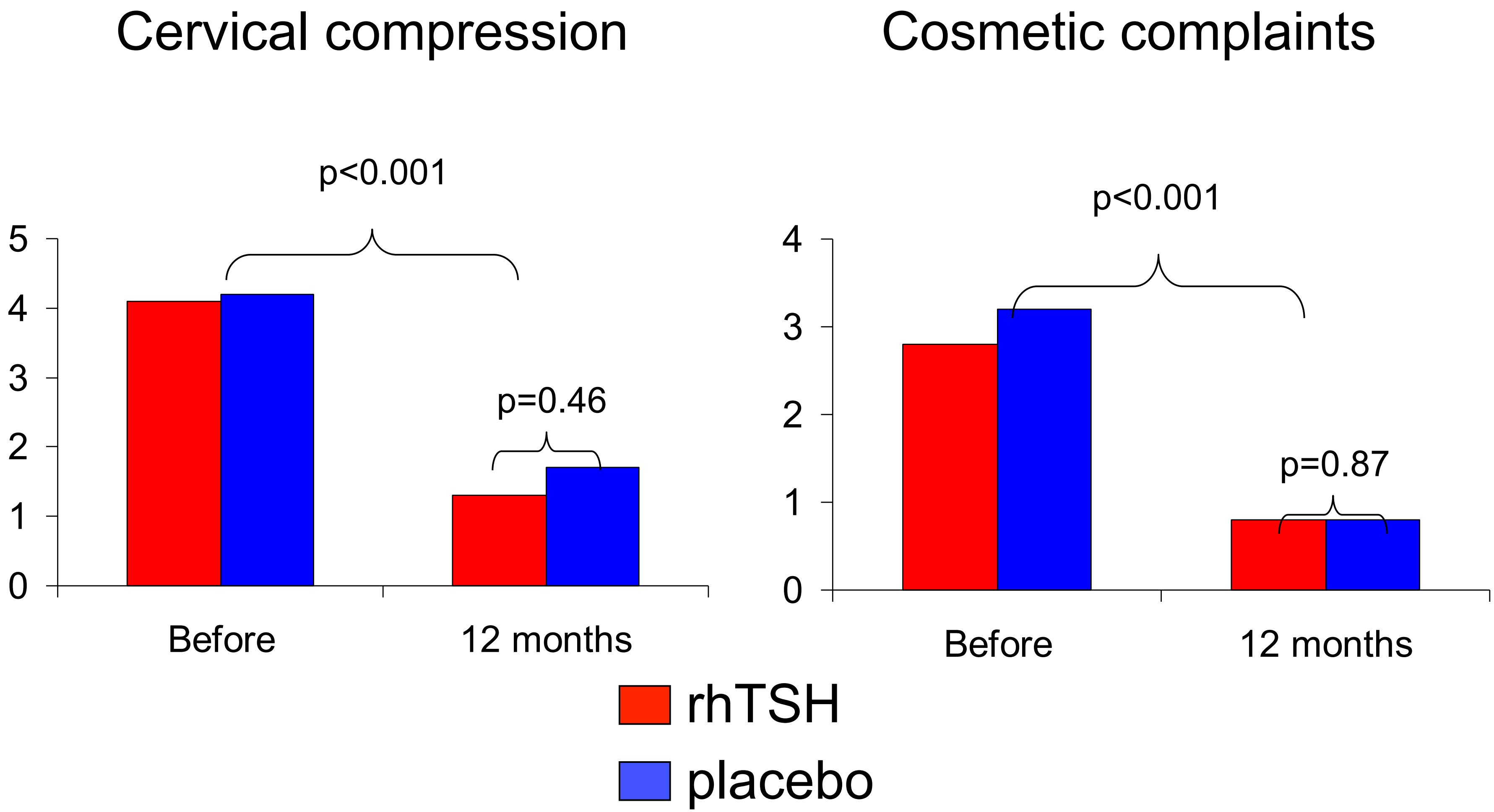
Bonnema et al, JCEM 2007

Hypothyroidism at one year



Nielsen et al., Arch Intern Med 2006

Patient satisfaction - Visual Analogue Scale



Bonnema et al, JCEM 2007

Dilemma with rhTSH-stimulated 131-I therapy

- Increased goiter reduction at one year

versus

- More acute adverse effects
- Higher risk of hypothyroidism
- No improvement in patient satisfaction

Dilemma with rhTSH-stimulated 131-I therapy

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versus

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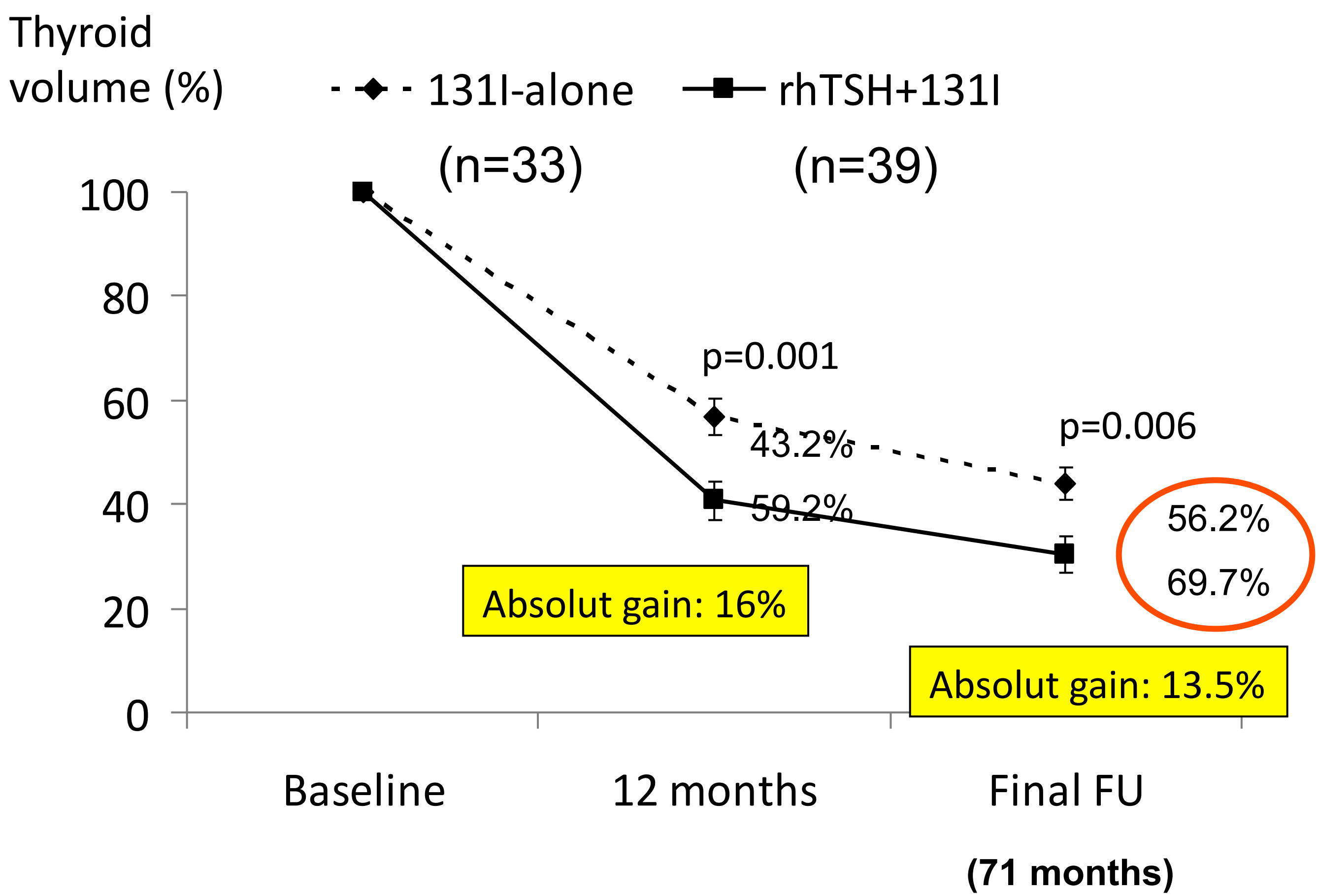
Is it then worthwhile?

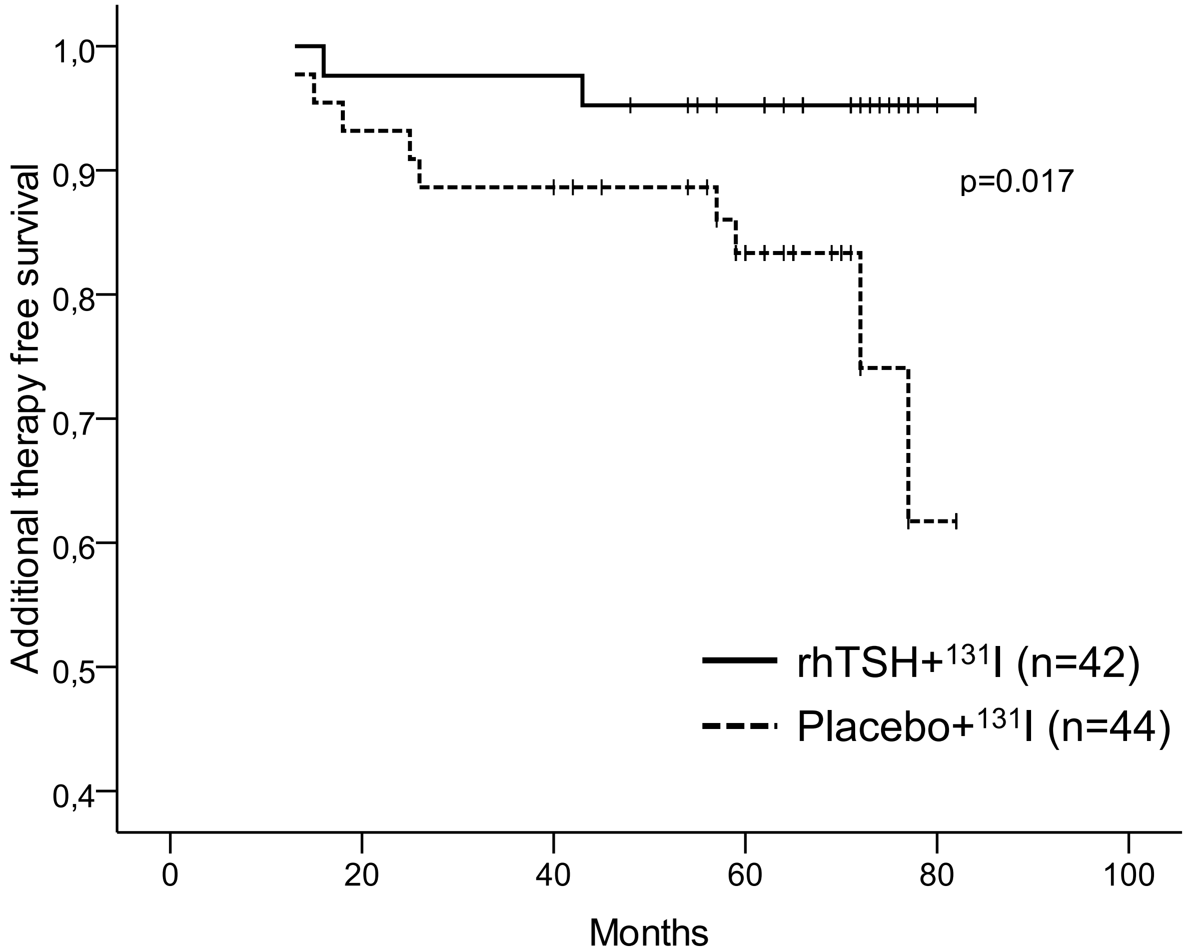
rhTSH-stimulated ^{131}I therapy - long term results



Fast et al., JCEM 2012

rhTSH-stimulated ^{131}I therapy - long term results

Need for additional therapy



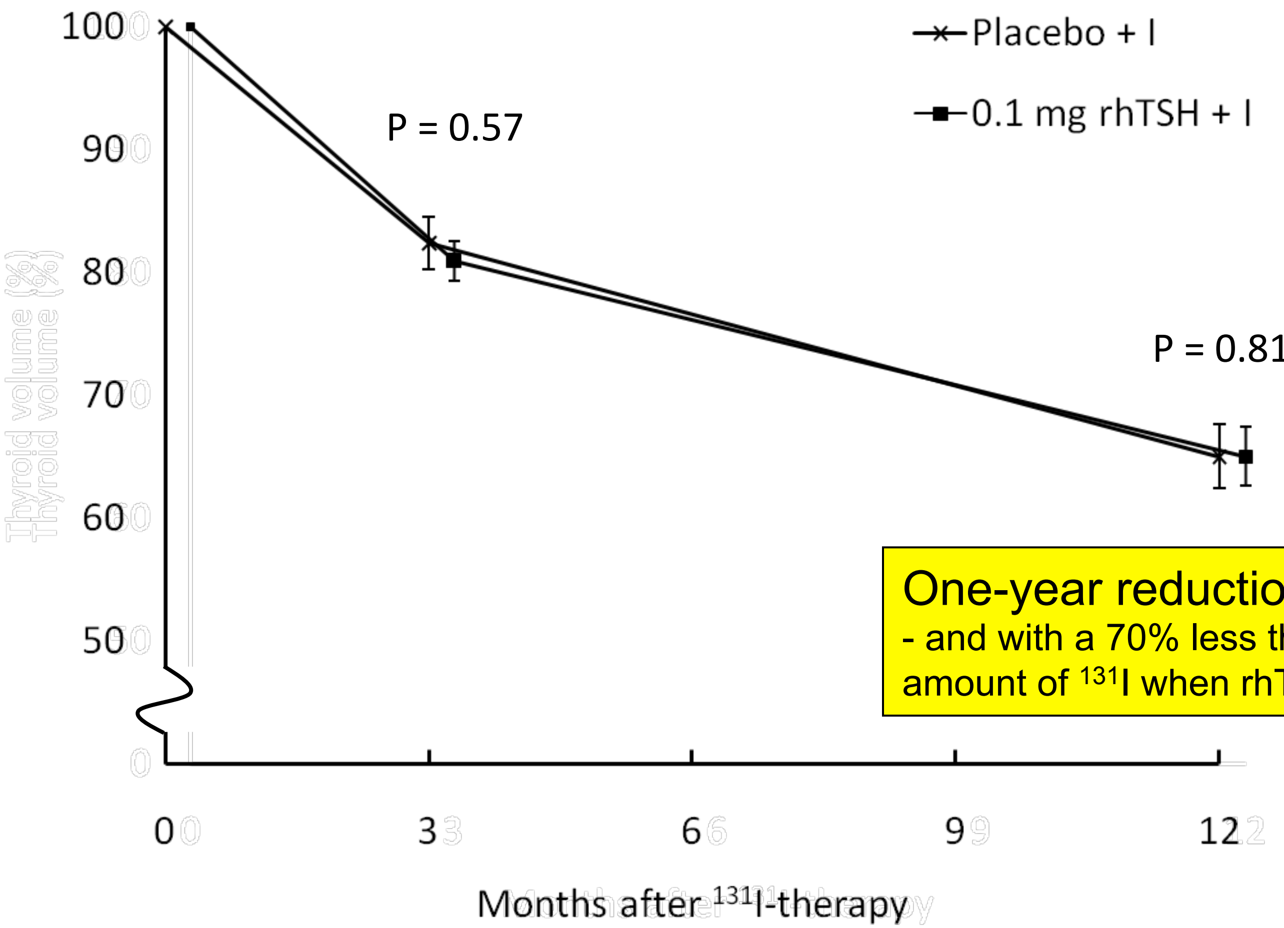
* Each tick (|) denotes a censored patient.

Fast et al., JCEM 2012

Goiter reduction following the equality approach

Identical effect in the rhTSH and the placebo group

Thyroid volume (%)



One-year reduction: 35%
- and with a 70% less than usual amount of ^{131}I when rhTSH stimulated

Fast et al, JCEM, 2010

Key points – Nontoxic nodular goiter

RhTSH-stimulated ^{131}I therapy:

- Improves the goiter reduction, also with long term follow-up
- Especially effective when low thyroid ^{131}I uptake and/or large goiter
- Benefits the upper airways
- More adverse events, to some extent dose dependent
- Two different approaches:
  - Superiority approach (gain in goiter reduction)
  - Equality approach (reduced radiation, recurrence & hospitalization)
- Hindrance for wide-spread use: off-label treatment