Symposium 1

Bari,
7-10 novembre 2013

Medical treatment of nodular goiter: still to be considered?

Yes, may be of use

Salvatore M. Corsello
Rosa Maria Paragliola, Alessandro Prete
Università Cattolica del Sacro Cuore, Roma

Nodular thyroid disease: a common clinical problem

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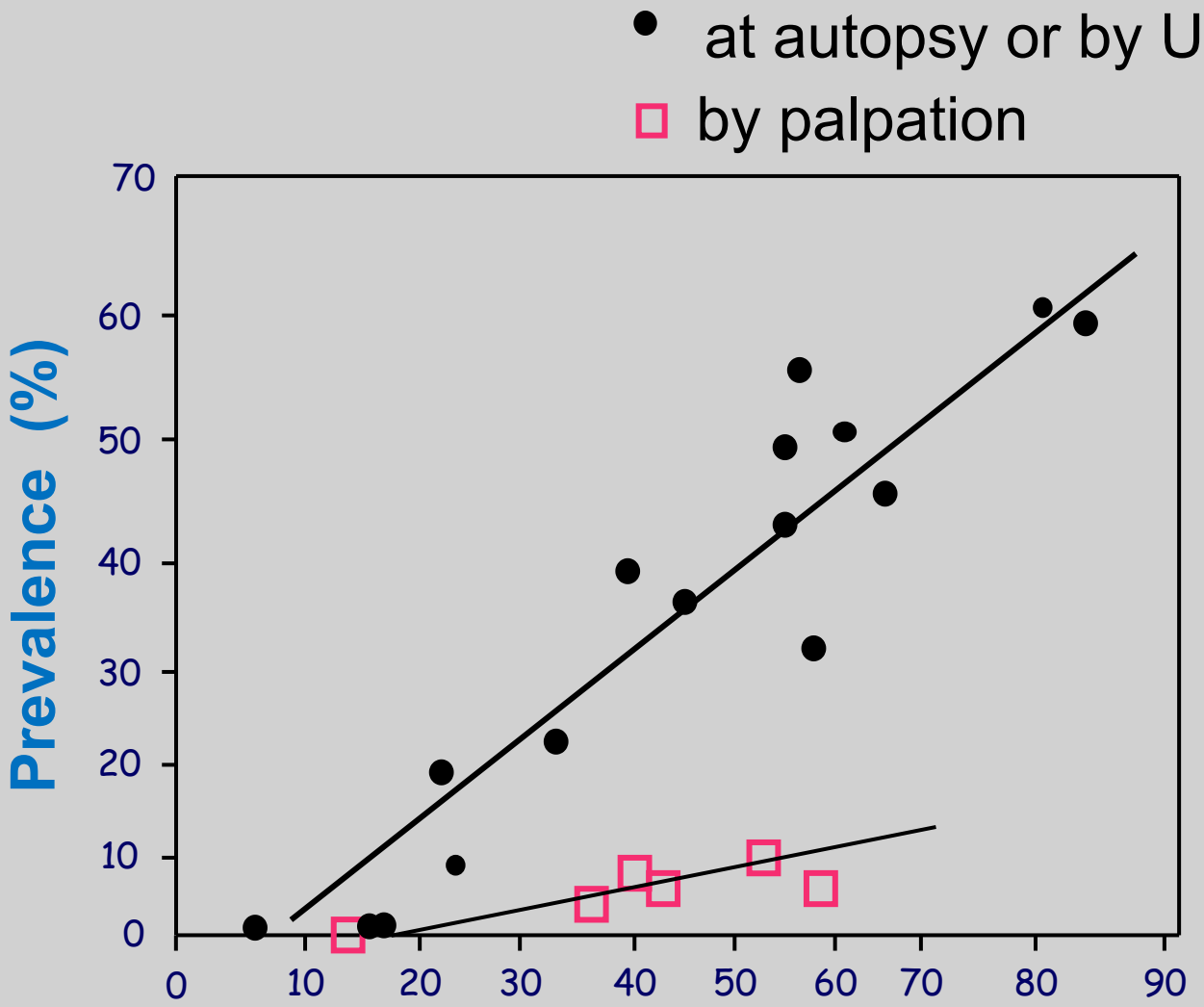
7-10 novembre 2013



Mazzaferri NEJM 1993

Nodular thyroid disease: a common clinical problem

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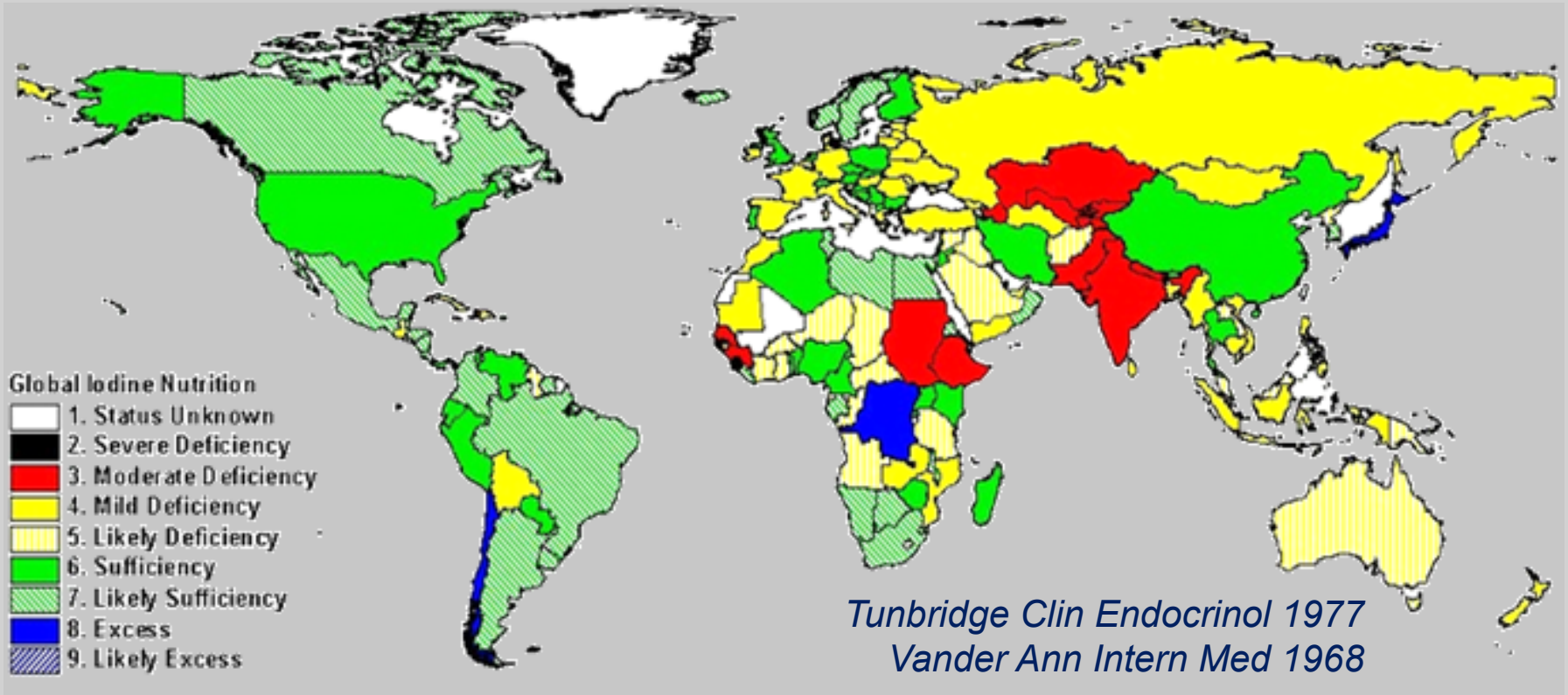
- In iodine-sufficient areas the prevalence of palpable thyroid nodules ranges between 3-7% of the population
- In mild to moderate iodine-deficient areas (i.e.: Italy) the prevalence is higher (~10%)



Tunbridge Clin Endocrinol 1977
Vander Ann Intern Med 1968

Nodular thyroid disease: a common clinical problem

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- The widespread use of ultrasonography (US) has resulted in a dramatic increase in the prevalence of clinically inapparent thyroid nodules
- Prevalence is similar to that reported in autopsy data in patients with no history of thyroid disease
- Thyroid US can detect thyroid nodules in 19%-76% of randomly selected individuals

Mortensen JCEM 1955
Gharib Mayo Clin Proc 1994
Ezzat Arch Intern Med 1994
Tan Ann Intern Med 1997
Hegedus NEJM 2004

Levothyroxine therapy in nodular thyroid disease

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If to treat…why?

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If to treat…why?

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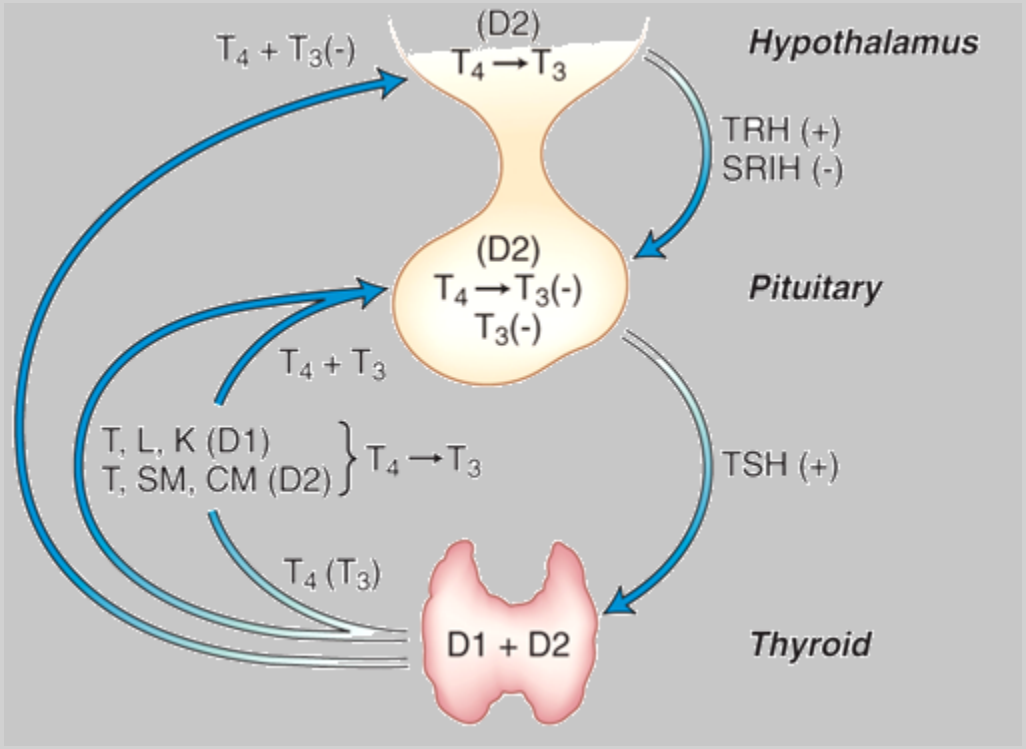
- Even if the pathogenesis of such growth is poorly understood, TSH is considered an important stimulating factor of nodular growth

- Suppression of TSH secretion might be expected to result in a decrease in nodule size or at least prevent any further enlargement



*Suppressive therapy is expected to be **ineffective** in patients in whom serum TSH concentrations are already subnormal due to autonomous thyroid hormone production*

LT4 suppressive therapy in nodular thyroid disease

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Benign nodules can spontaneously grow to more than 15% of their initial size:

- *30% within one year*
- *90% at five years*

if these nodules are not treated

Alexander EK Ann Intern Med 2003

Evidence suggest that LT4 therapy, in doses suppressing serum TSH to subnormal levels:

- may decrease nodule size
- may prevent the appearance of new nodules in regions of the world with borderline / low iodine intake

Zelmanovitz JCEM 1998
Wemeau JCEM 2002
Castro JCEM 2002

LT4 suppressive therapy in nodular thyroid disease

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Data in iodine-sufficient populations are less compelling, suggesting that only about 17–25% of thyroid nodules shrink more than 50% with LT4 suppression of serum TSH.

ATA guidelines (2009)

Routine suppression therapy of benign thyroid nodules in iodine sufficient populations is not recommended

AACE / AME / ETA guidelines (2010)

Routine LT4 treatment in patients with nodular thyroid disease is not recommended. LT4 therapy or iodine supplementation may be considered in:

- Young patients who live in iodine-deficient geographic areas and have small thyroid nodules;
- Young patients who live in iodine-deficient geographic areas and have nodular goiters and no evidence of functional autonomy.

Thyroid hormone suppressive therapy: how frequently used?

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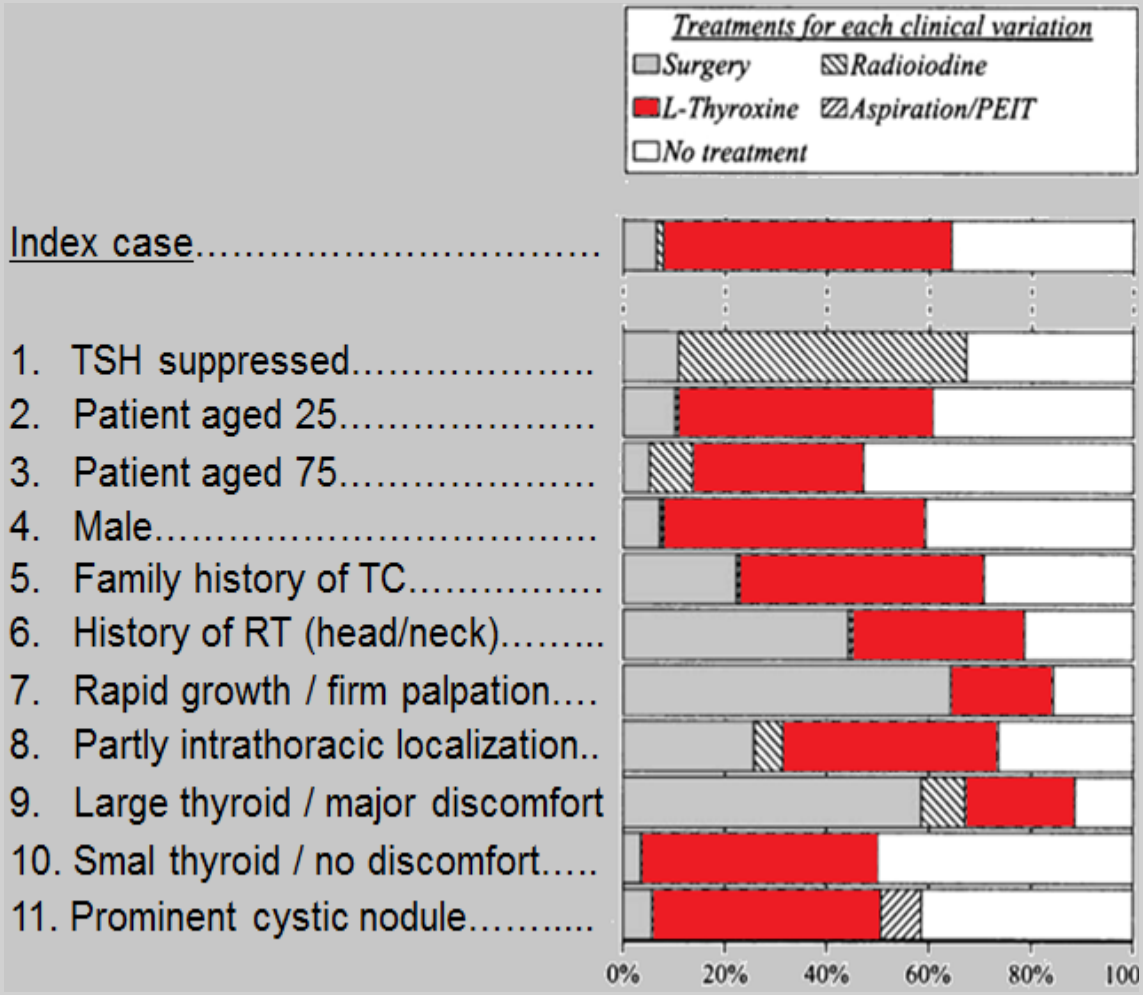
Management of the nontoxic multinodular goiter: a North American survey



Index case: 42-yr-old woman with an irregular, nontender, bilaterally enlarged thyroid of 50–80 g and no clinical suspicion of malignancy or thyroid dysfunction.

- 56,4% would advocate the use of LT4 therapy
- 76% would reach a slightly suppressed serum TSH level (0,1 – 0,3 mcUI/ml)
- 42% would use a long-term LT4 therapy

Bonnema JCEM 2002

Thyroid hormone suppressive therapy: how frequently used?

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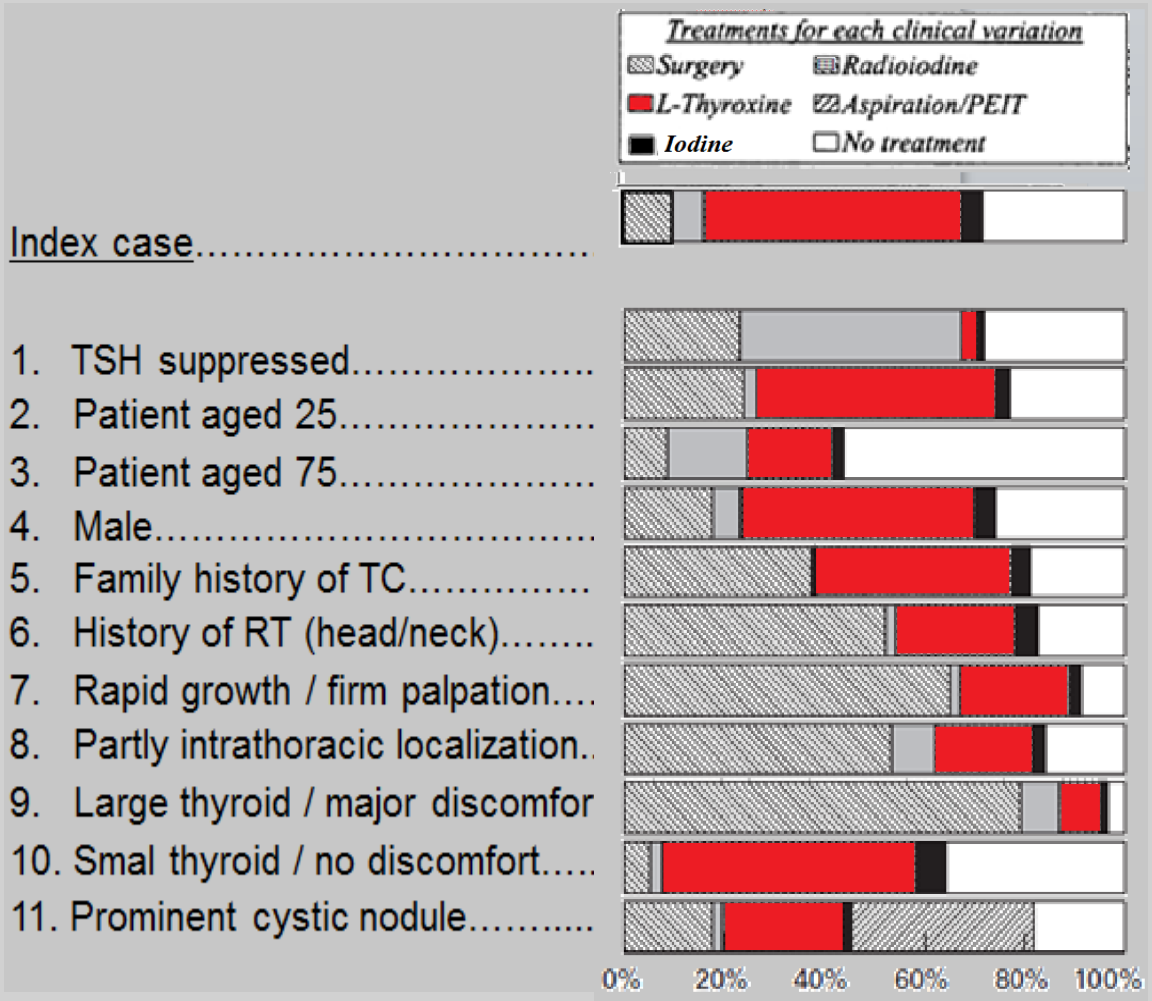
Management of the nontoxic multinodular goiter: a European survey



Index case: 42-yr-old woman with an irregular, nontender, bilaterally enlarged thyroid of 50–80 g and no clinical suspicion of malignancy or thyroid dysfunction.

- 51,6% would advocate the use of LT4 therapy
- 32,3% would reach a slightly suppressed serum TSH level (0,1 – 0,3 mcUI/ml)
- 50% would use a long-term LT4 therapy

Bonnema Clin Endocrinol 2000

Thyroid hormone suppressive therapy: how frequently used?

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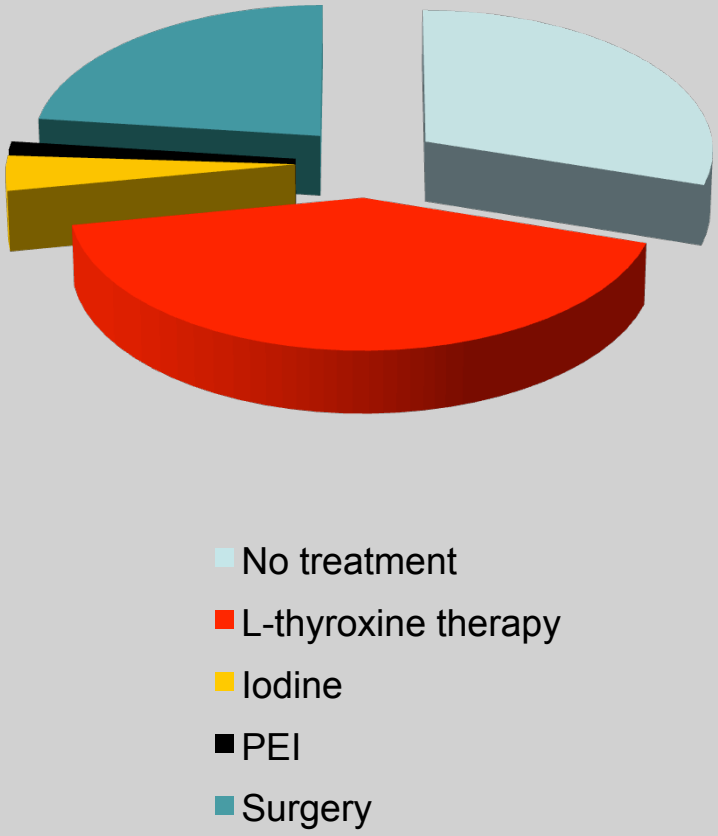
Management of the solitary thyroid nodule: a European survey



Index case: 42-yr-old woman with a solitary 2 x 3 cm thyroid nodule and no clinical suspicion of malignancy

- 40% would advocate the use of LT4 therapy
- 43% would reach a slightly suppressed serum TSH level (0,1 – 0,3 mcUI/ml)
- 62% would use a long-term LT4 therapy

Bennedbæk Clin Endocrinol 1999

Efficacy of TSH suppressive therapy in reducing thyroid nodule

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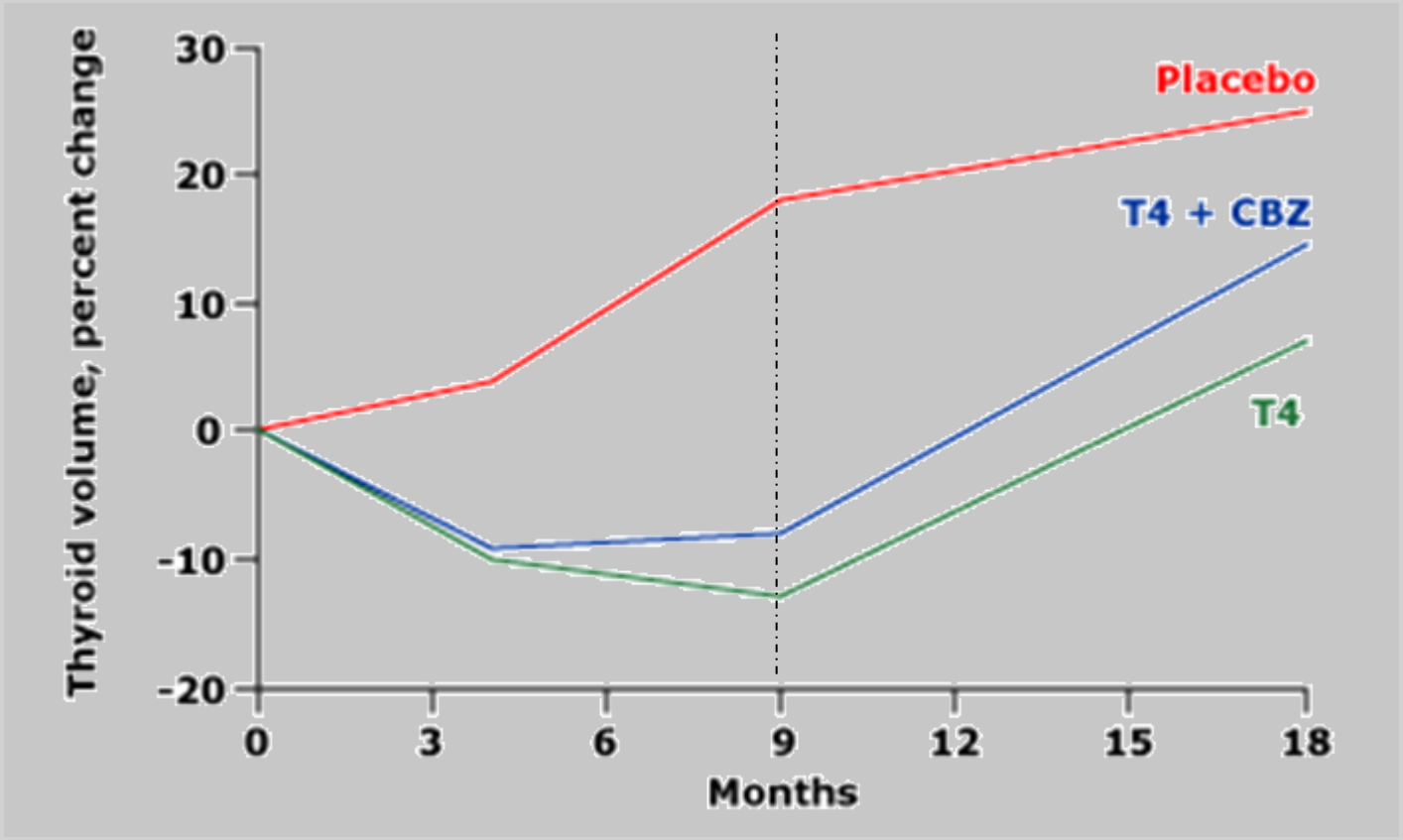
Relative changes in thyroid volume in patients with nontoxic goiter treated with placebo, LT4 + carbimazole and LT4 alone for 9 months, and than followed for other 9 months.



Berghout Lancet 1990

Efficacy of TSH suppressive therapy in reducing thyroid nodule

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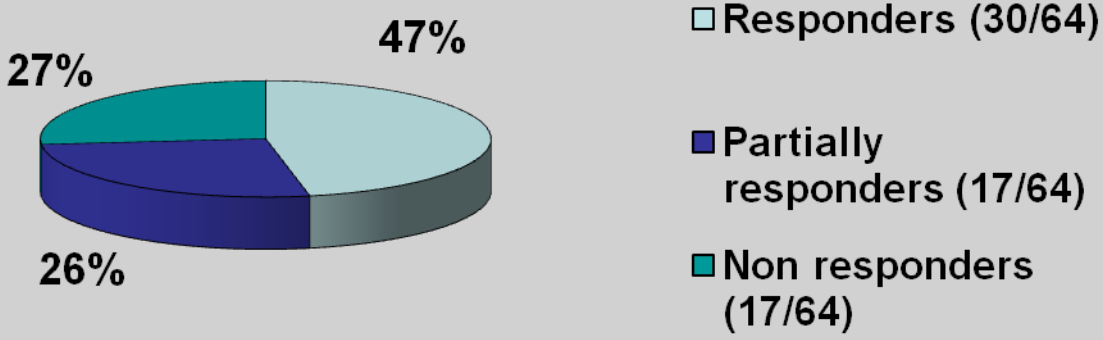
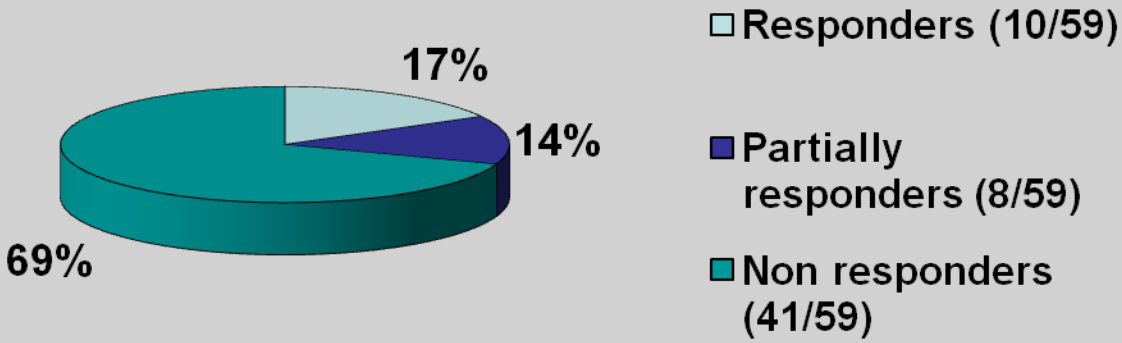
LT4 group



Placebo group



Wemeau JCEM 2002

Efficacy of TSH suppressive therapy in reducing thyroid nodule: meta-analysis

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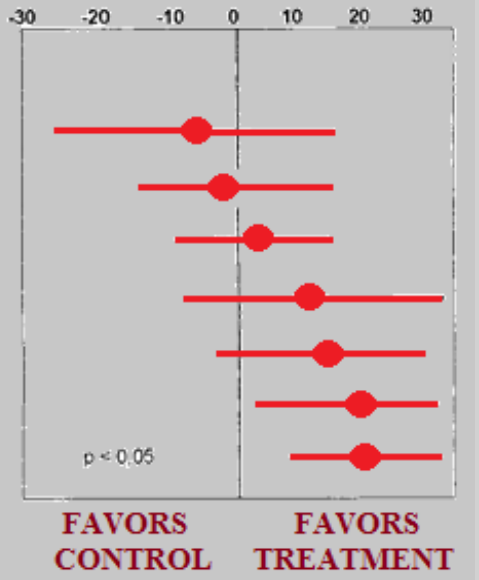
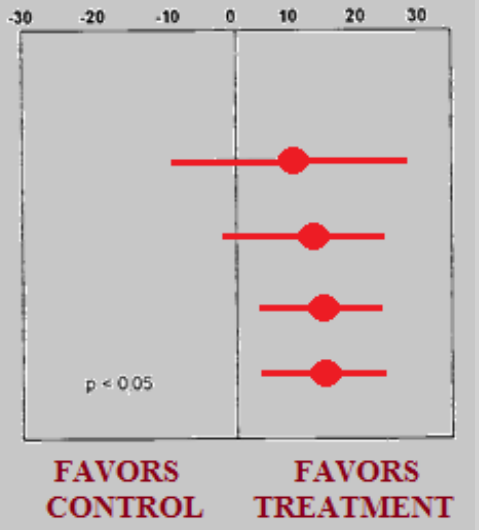
Study	Year	Number of Patients
Gharib et al.	1987	53
Reverter et al.	1992	40
Papini et al.	1993	101
LaRosa et al.	1995	45
Mainini et al.	1995	55
Lima et al.	1997	74
Zelmanovitz et al.	1997	45



Cumulative meta-analysis concerning the capacity of LT4 suppressive therapy to **decrease** a STN volume to less than 50% of its baseline value.

Study	Year	Number of Patients
Gharib et al.	1987	53
Papini et al.	1993	101
LaRosa et al.	1995	45
Zelmanovitz et al.	1997	45



Cumulative meta-analysis concerning the capacity of LT4 suppressive therapy to **arrest** the expansion of a STN volume to less than 50% of its baseline value.

Zelmanovitz JCEM 1998

Efficacy of TSH suppressive therapy in reducing thyroid nodule

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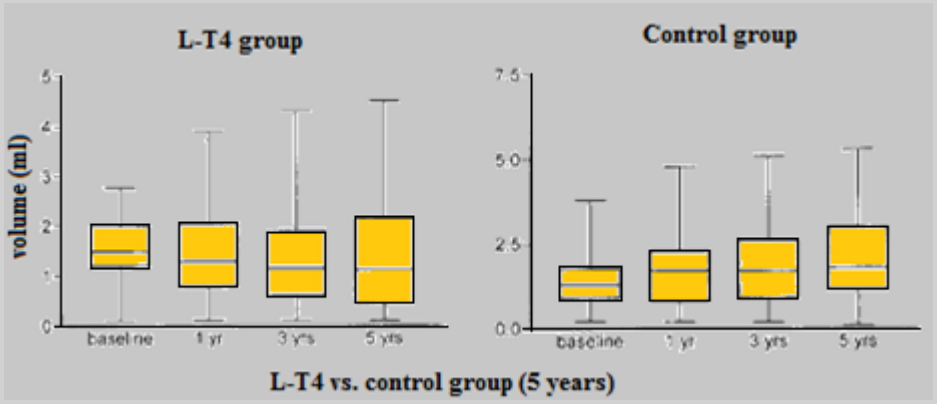
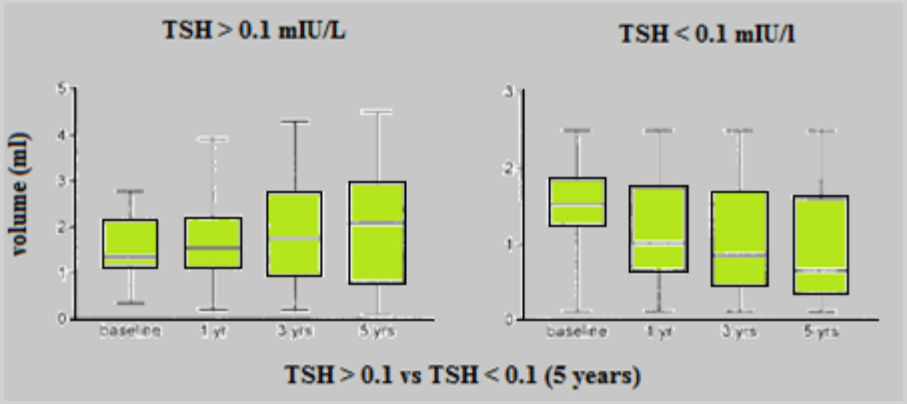
Long-Term Changes in Nodular Goiter: A 5-Year Prospective Randomized Trial of Levothyroxine Suppressive Therapy for Benign Cold Thyroid Nodules

E. PAPINI, L. PETRUCCI, R. GUGLIELMI, C. PANUNZI, R. RINALDI, V. BACCI, A. CRESCENZI, F. NARDI, R. FABBRINI, AND C. M. PACELLA

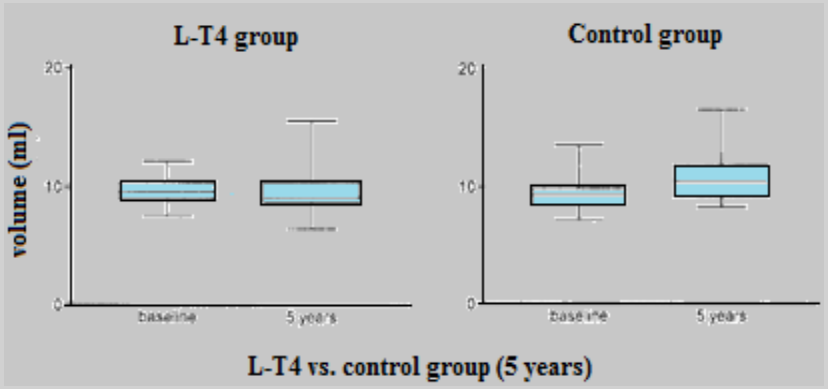
Journal of Clinical Endocrinology and Metabolism



Nodule volume changes in the L-T4 treatment group and in the control group (median and range).



Nodule volume changes in the treatment group: differences between patients with TSH levels greater than 0.1 mU/L and patients with TSH levels less than 0.1 mU/L.



Thyroid volume changes in the L-T4 treatment group and in the control group

Efficacy of TSH suppressive therapy in reducing thyroid nodule

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The characteristics that seem to predict a greater response to TSH suppressive therapy are:

- "Small", solid nodules
- "Recent" nodules
- Nodules with degenerative changes on biopsy/ultrasound
- Nodule with abundant colloid on biopsy/ultrasound
- Nodules without hyperplastic or fibrotic changes on biopsy/ ultrasound

Efficacy of TSH suppressive therapy + iodine in reducing thyroid nodule

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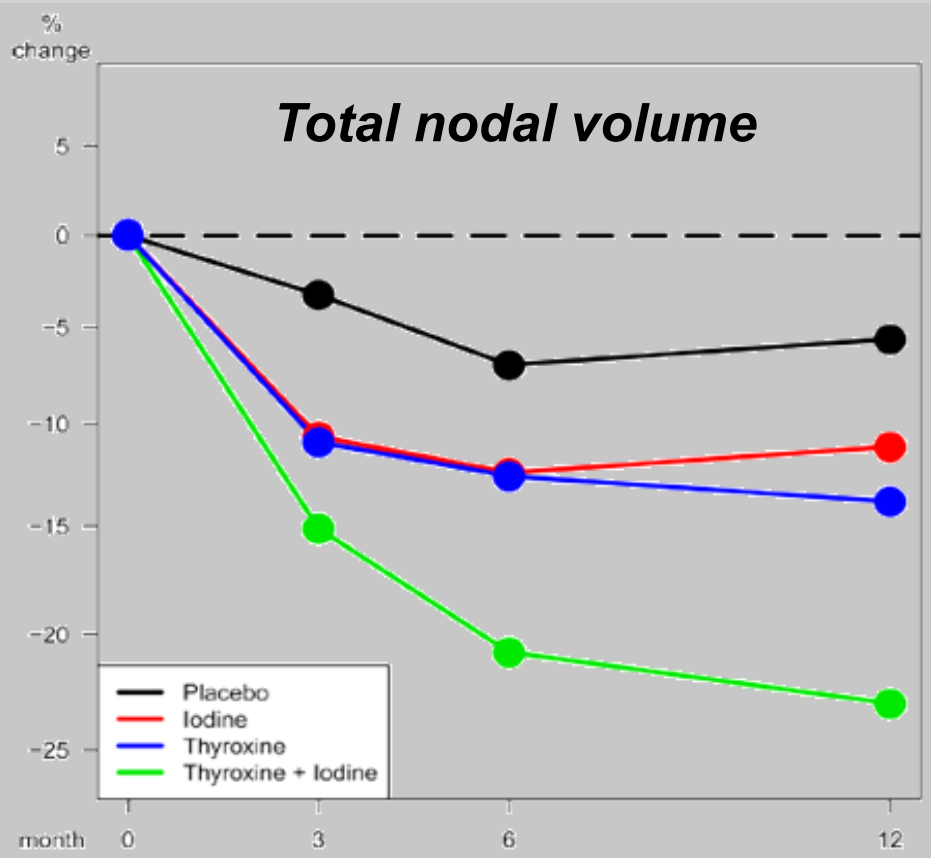
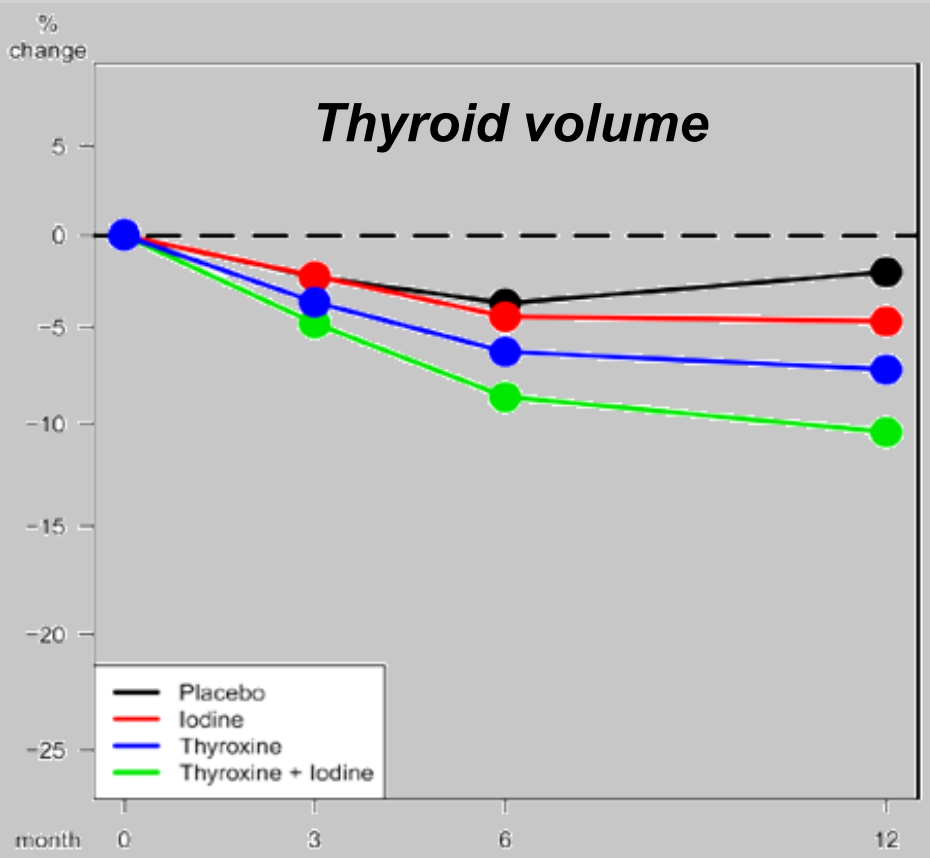
Reduction of Thyroid Nodule Volume by Levothyroxine and Iodine Alone and in Combination: A Randomized, Placebo-Controlled Trial

M. Grussendorf, C. Reiners, R. Paschke, and K. Wegscheider, on behalf of the LISA investigators

J Clin Endocrinol Metab, September 2011, 96(9):2786–2795





Efficacy of TSH suppressive therapy in preventing recurrence after lobectomy

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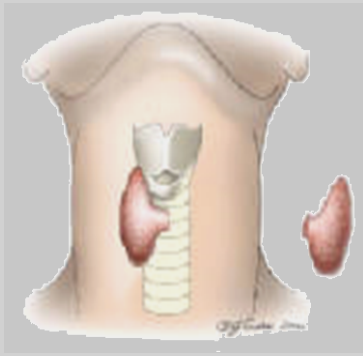
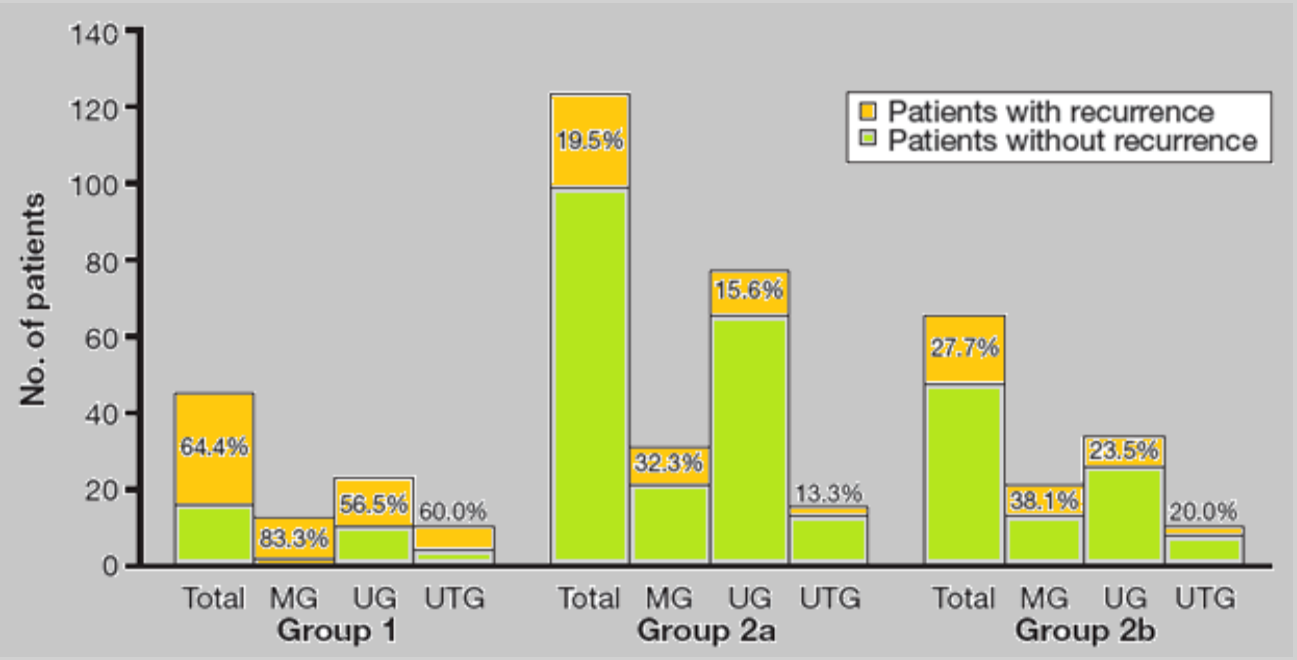
7-10 novembre 2013

Levothyroxine therapy in preventing nodular recurrence after hemithyroidectomy: A retrospective study

M. Alba[1], D. Fintini[2], R.M. Lovicu[1], R.M. Paraqliola[1], G. Papi[3], C.A. Rota[1], A. Pontecorvi[1], and S.M. Corsello[1]

J. Endocrinol. Invest. 32: 330-334, 2009





Patients not receiving LT4

Patients receiving LT4 at substitutive dose

Patients receiving LT4 at suppressive dose

In patients who have undergone hemithyroidectomy for benign monolobar nodular disease, **LT4 therapy may prevent nodular recurrence.**

TSH suppression may not be required for prevention of recurrence

Thyroid nodules and cancer risk

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- Clinically overt thyroid cancer accounts for 1% of all new malignancies in the United States (0.4% of all cancer deaths)

- Thyroid cancer can occur in 5-15% of thyroid nodules

Factors potentially associated to thyroid cancer risk:

- ✓ Age (< 20 or > 70)
- ✓ Male gender
- ✓ Solitary *vs* multiple nodularity (?)
- ✓ Large (4 cm) or rapidly growing nodules (especially during thyroid hormone therapy)
- ✓ Neck irradiation
- ✓ Family history (familiar nonmedullary thyroid carcinoma: ~ 5% of cases)

Yu Thyroid 2010
Frates JCEM 2006
Rago EJE 2010
Hegedus Endocr Rev 2003
Nosè Endocr Pathol 2010

TSH ?

TSH and cancer risk

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- Well-differentiated thyroid cancers express TSH receptors
- Although oncogenes and other growth factors are involved in thyroid cancer growth and development, TSH can act as a cancer stimulus.
- This hypothesis is supported by:

  improved survival in thyroid cancer patients treated with suppressive doses of levothyroxine

  cases of tumor growth post-T4 withdrawal or recombinant TSH

Shi Clin Endocrinol 1993
Derwahl JCEM 1998
Jonklaas Thyroid 2006
Braga JCEM 2001

TSH values and cancer risk: the state of the art

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Serum TSH and Risk of Papillary Thyroid Cancer in Nodular Thyroid Disease

Emilio Fiore and Paolo Vitti

J Clin Endocrinol Metab, April 2012, 97(4):1134–1145

"In the last few years, it has been reported that in patients with nodular thyroid diseases, the risk of thyroid malignancy increases with increasing concentrations of serum TSH, and even within normal ranges, higher TSH values are associated with a higher frequency and more advanced stage of thyroid cancer"

TSH values and cancer risk

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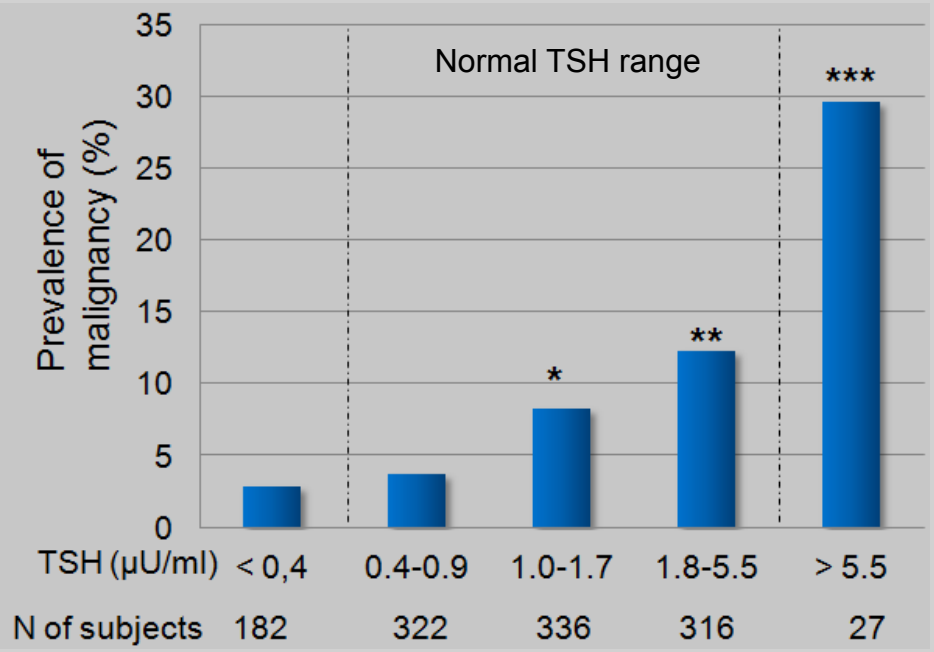
Serum Thyrotropin Concentration as a Novel Predictor of Malignancy in Thyroid Nodules Investigated by Fine-Needle Aspiration

K. Boelaert, J. Horacek, R. L. Holder, J. C. Watkinson, M. C. Sheppard, and J. A. Franklyn

The Journal of Clinical Endocrinology & Metabolism 91(11):4295–4301



Variable	Adjusted odds ratio	95% CI	P value
Male gender	1.80	1.80 - 3.10	0.036
Decreasing age (overall annual decrement)	1.08	1.01 - 1.15	0.025
Solitary nodule	2.53	1.50 - 4.28	0.001
TSH (µU/ml)			
Less than 0.4	1.00		
0.4-0.9	1.31	0.45 - 3.81	0.622
1.0-1.7	2.72	1.02 - 7.27	0.046
1.8-5.5	3.88	1.48 -10.19	0.006
> 5.5	11.18	3.23 - 38.63	<0.001

**** P 0.05; ** P 0.01; *** P 0.001, compared with TSH less than 0.4* µU/ml.**

TSH values and cancer risk

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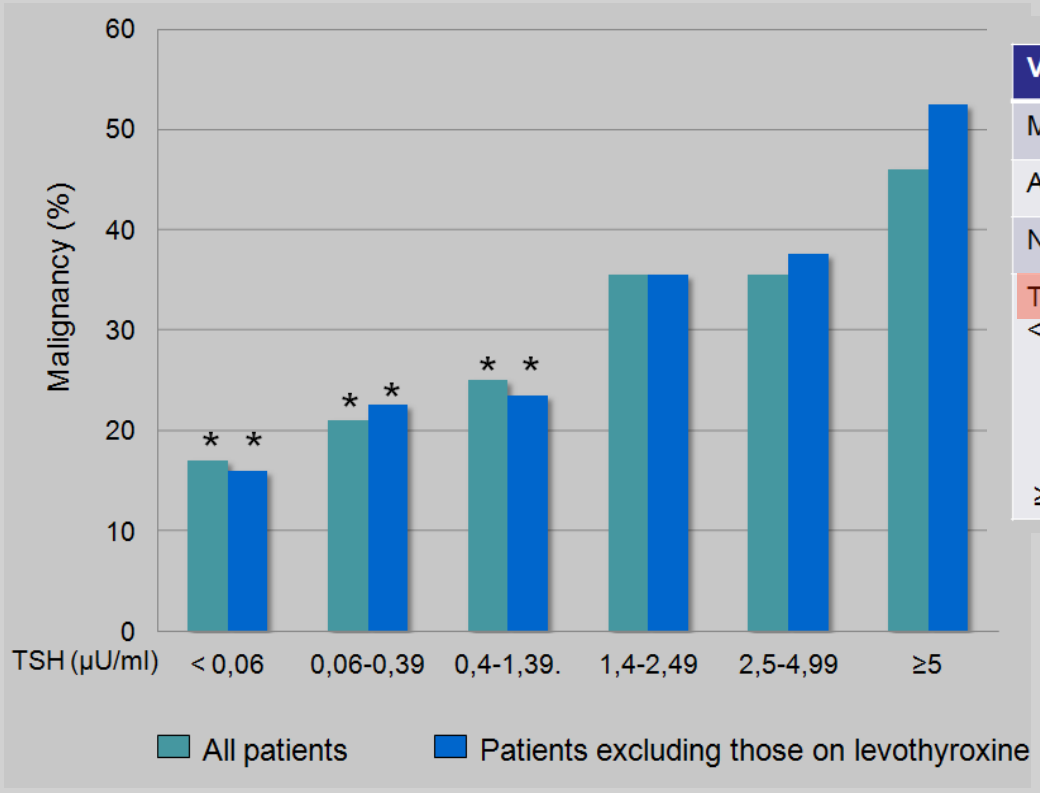
Higher Serum Thyroid Stimulating Hormone Level in Thyroid Nodule Patients Is Associated with Greater Risks of Differentiated Thyroid Cancer and Advanced Tumor Stage

Megan Rist Haymart, Daniel John Repplinger, Glen E. Leverson, Diane F. Elson, Rebecca S. Sippel, Juan Carlos Jaume, and Herbert Chen

(*J Clin Endocrinol Metab* 93: 809–814, 2008)



Variable	Adjusted odds ratio	95% CI	P value
Male gender	2.32	1.51 - 3.58	<0.0001
Age	0.98	0.97 - 0.99	0.01
Nodule size	0.77	0.69 - 0.87	<0.0001
TSH (µU/ml)			
<0.06	1		
0.06-0.39	1.65	0.59 - 4.60	0.34
0.40-1.39	1.39	0.59 - 3.27	0.44
1.40-2.49	2.50	1.04 - 6.04	0.04
2.50-4.99	3.52	1.37 - 9.04	0.009
≥5.00	4.56	1.35 -15.45	0.01

TSH and cancer stage

TNM stage	No. of patients	Mean TSH	*P* value
I and II	204	2.1 ± 0.24	0.002
III and IV	35	4.9 ± 1.59	

TSH values and cancer risk

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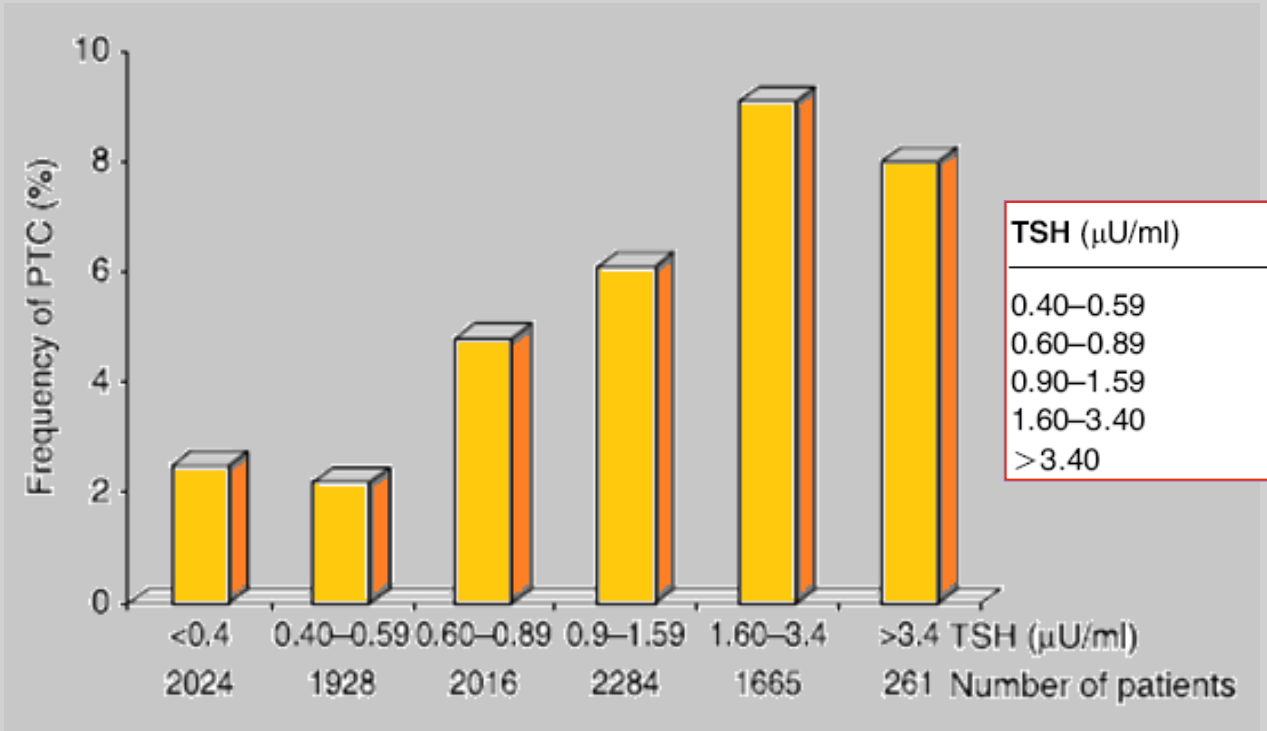
Lower levels of TSH are associated with a lower risk of papillary thyroid cancer in patients with thyroid nodular disease: thyroid autonomy may play a protective role

E Fiore, T Rago, M A Provenzale, M Scutari, C Ugolini[1], F Basolo[1], G Di Coscio[2], P Berti[3], L Grasso, R Elisei, A Pinchera and P Vitti

Endocrine-Related Cancer (2009) **16** 1251–1260



TSH (μU/ml)	OR	95% CI	*P* value[a]
0.40–0.59	0.80	0.51–1.27	0.18
0.60–0.89	2.01	1.46–2.77	<0.0001
0.90–1.59	2.66	1.98–3.58	<0.0001
1.60–3.40	4.29	3.17–5.08	<0.0001
>3.40	3.50	2.10–5.83	0.0011

Levothyroxine therapy in nodular thyroid disease: for many, but not all!

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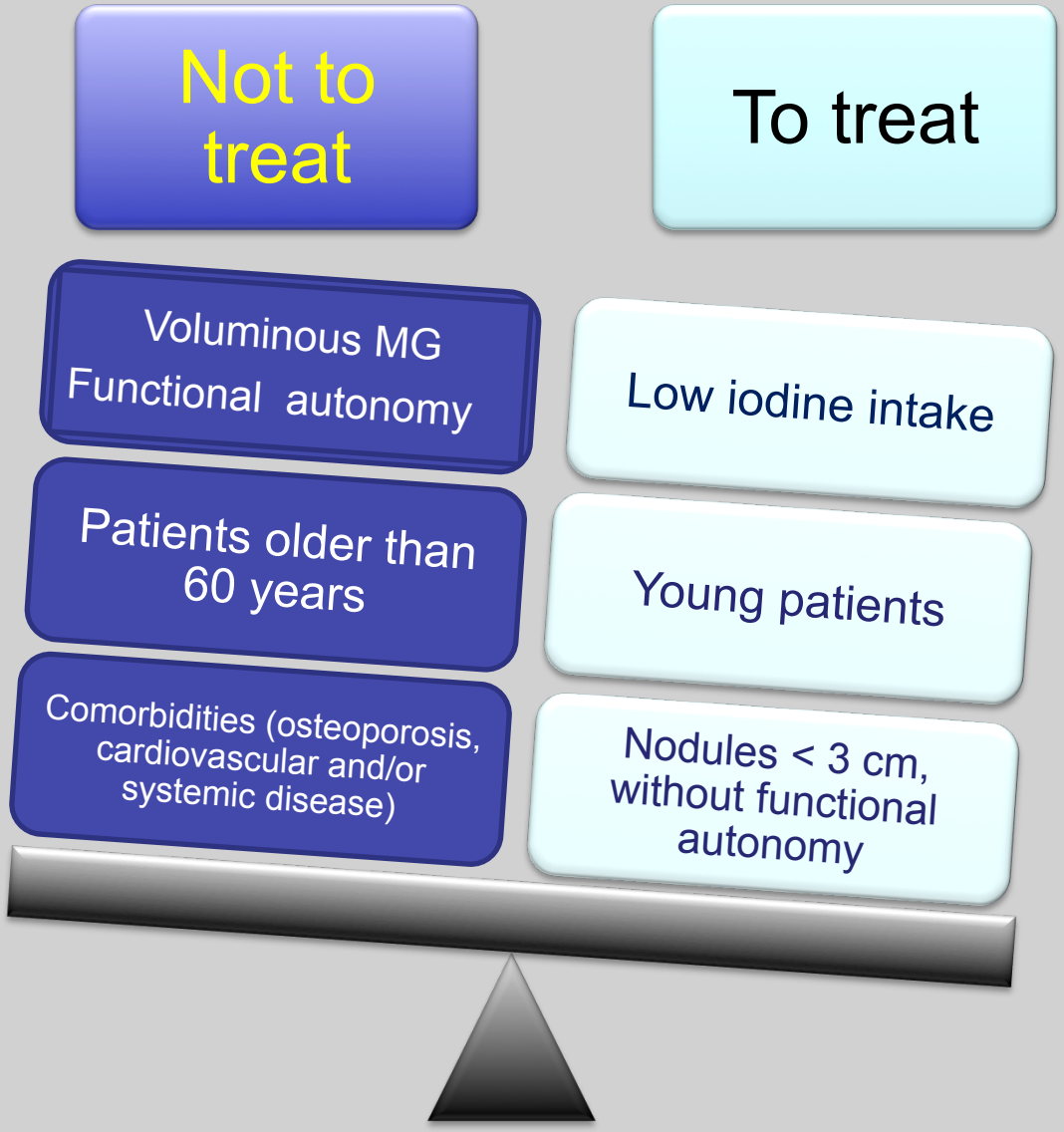

Levothyroxine therapy & heart damage: YES, BUT…

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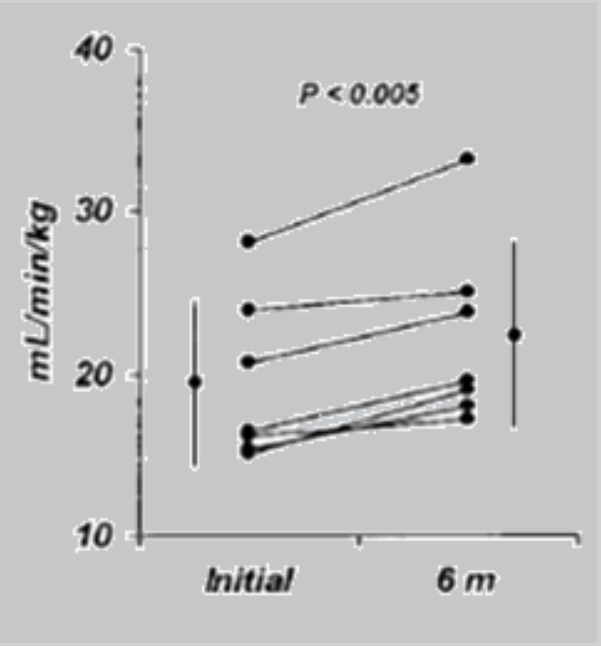
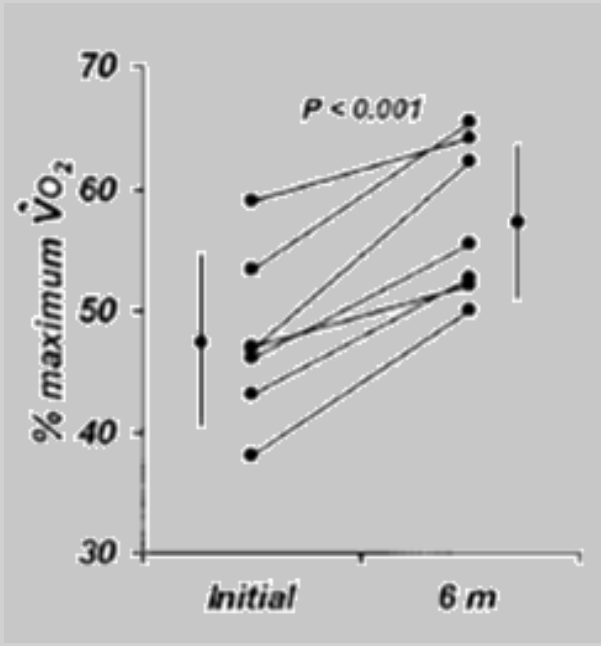
- Abnormalities of heart morphology associated with impaired exercise performance occur as a consequence of long term therapy with fixed TSH-suppressive doses of LT4
- these abnormalities improve or disappear after careful tailoring of TSH-suppressive therapy



Oxygen consumption

Individual tailoring of the TSH-suppressive LT4 dose was in all cases associated with normalization of all echocardiographic and ergometabolic parameters

Mercuro JCEM 2000



Anaerobic treshold

Levothyroxine therapy & bone damage: YES, BUT…

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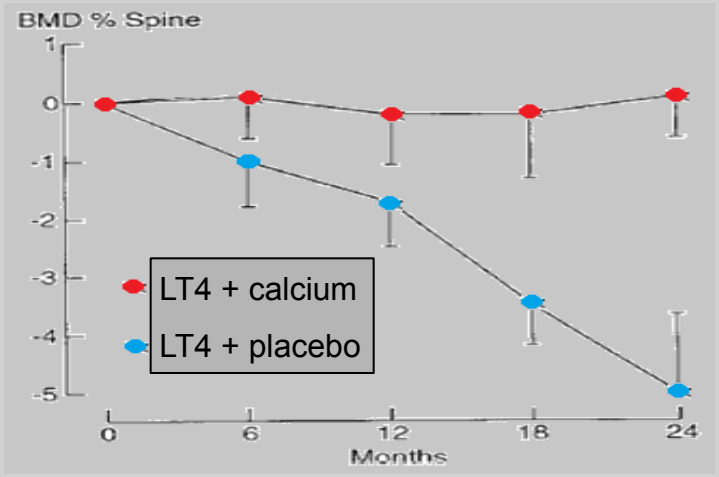
- No change in the mean bone mineral density of women after 1 yr of l-T4 therapy for benign solitary thyroid nodules (mean TSH < 0.3 mIU/liter).

  Zelmanovitz, JCEM, 1998

- A significantly increased risk for new hip and vertebral fractures was shown in women older than 65 yr of age who had low TSH levels, <u>but not in those with LT4 therapy</u>.

  Bauer, Ann Intern Med, 2001

- LT4-suppressive therapy is associated with bone loss in post-menopausal women. Anyway, this can be easily prevented by adding dietary calcium supplementation (1'000 mg/die).



Kung JCEM 1996

Levothyroxine therapy & long-term continuation: YES, BUT…

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Several studies show goiter recurrence few months after LT4 discontinuation

TSH suppressive therapy is generally supposed to be of indefinite duration

YES, BUT…

- Patients in clinical studies sometimes undergo LT4 therapy for a short period of time (months)
- Studies generally include only young patients
- Increasing age is accompanied by reduction of several stimuli to thyroid nodule growth: **BMI**; **GH**; **IGF1**; **estrogens**

Levothyroxine therapy in nodular thyroid disease

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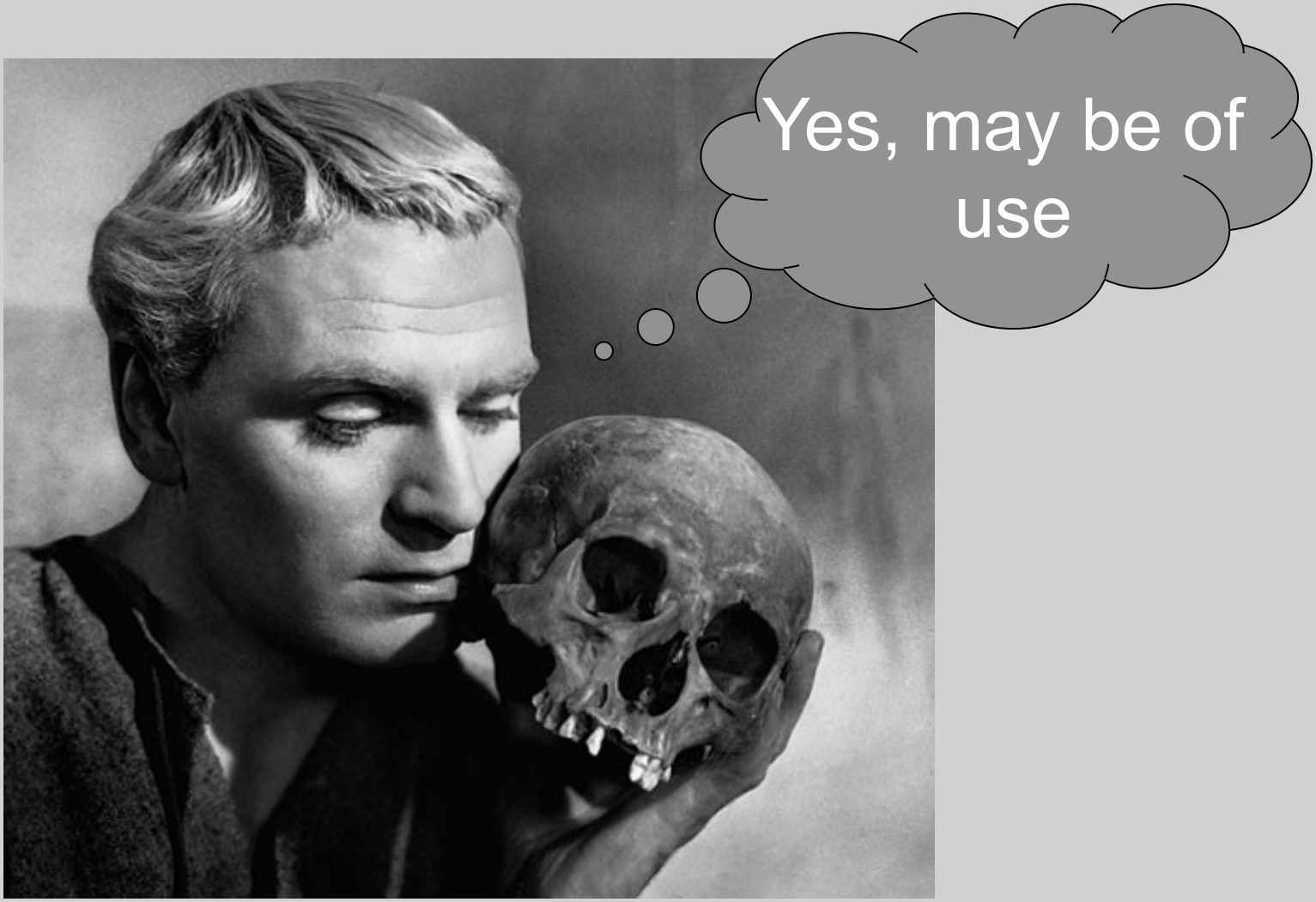

Thank you!