MAYO CLINIC

The Year in Thyroid

17th AME Italian Congress

Rome
November 8-11, 2018

Hossein Gharib, MD, MACP, MACE
Professor, Mayo Clinic College of Medicine
Past President, American Thyroid Association
Past President, American Association of Clinical Endocrinologists

AME ~ Rome ~ 2016

Disclosures

- None

Thanks

- My sincere thanks for the invitation to attend AME & AACE Italian Chapter Conference and for the honor of speaking to your group again

Paper Selection

- Published 2017-2018
- Appeared in major medical or endocrine journals
- Impact on thyroid practice
- Answered questions for patient management

Is Thyroid Hormone Therapy Useful in SCHypo?

Thyroxine Therapy in SCHypo

Background

- Subclinical hypothyroidism is a purely biochemical diagnosis
- Data conflicting on impact of LT4 Rx on morbidity and mortality
- Razvi et al, JCEM 2007, showed beneficial effect on CV risk factors and QOL
- Guidelines suggest Rx if TSH >10; consider Rx if TSH 5-10 with $TPOAb^{+}$, CAD, Sx or hyperlipidemia

0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(5):1715–1723

doi: 10.1210/jc.2006-1869

The Beneficial Effect of L-Thyroxine on Cardiovascular Risk Factors, Endothelial Function, and Quality of Life in Subclinical Hypothyroidism: Randomized, Crossover Trial

Salman Razvi, Lorna Ingoe, Gill Keeka, Crispian Oates, Carolyn McMillan, and Jolanta U. Weaver

Design: This was a randomized, double-blind, crossover study of L-thyroxine and placebo.

Setting: The study was conducted with community-dwelling patients.

Patients: One hundred patients [mean age (SD) 53.8 (12) yr, 81 females] with SCH [mean TSH 6.6 (1.3) mIU/liter] without previously treated thyroid or vascular disease.

and improved FMD from 4.2 to 5.9%, $P < 0.001$. Multivariate analysis showed that increased serum free T_4 level was the most significant variable predicting reduction in TC or improvement in FMD. Furthermore, the symptom of tiredness improved on L-thyroxine therapy, but other patient-reported outcomes were not significantly different after correction for multiple comparisons.

Conclusion: SCH treated by L-thyroxine leads to a significant improvement in CV risk factors and symptoms of tiredness. The CV

- **Population-based study of 100 pt**
- **Serum TSH >4 (mean 6.6); normal FT4**
- **Randomized to 100 mcg T4 and placebo for 12 wk; crossed over to other Rx**

sion 2; TC, total cholesterol; TFT, thyroid function test; TG, triglyceride; ThyDQoL, Underactive Thyroid-Dependent QoL; ThySC, Underactive Thyroid Symptom Checklist; ThyTSQ, Underactive Thyroid Treatment Satisfaction Questionnaire; TPO, thyroid peroxidase autoantibody.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

contribute to CV risk in SCH, including body mass index, fat distribution, lipid profile, and vascular dysfunction (16). The present study was designed to evaluate whether L-thyroxine treatment improves CV risk profile in people with SCH. In addition, the effect of L-thyroxine on patient-reported outcomes was also investigated.

ORIGINAL ARTICLE

Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism

D.J. Stott, N. Rodondi, P.M. Kearney, I. Ford, R.G.J. Westendorp, S.P. Mooijaart, N. Sattar, C.E. Aubert, D. Aujesky, D.C. Bauer, C. Baumgartner, M.R. Blum, J.P. Browne, S. Byrne, T.-H. Collet, O.M. Dekkers, W.P.J. den Elzen, R.S. Du Puy, G. Ellis, M. Feller, C. Floriani, K. Hendry, C. Hurley, J.W. Jukema, S. Kean, M. Kelly, D. Krebs, P. Langhorne, G. McCarthy, V. McCarthy, A. McConnachie, M. McDade, M. Messow, A. O'Flynn, D. O'Riordan, R.K.E. Poortvliet, T.J Quinn, A. Russell, C. Sinnott, J.W.A. Smit, H.A. Van Dorland, K.A. Walsh, E.K. Walsh, T. Watt, R. Wilson, and J. Gussekloo, for the TRUST Study Group*

the Thyroid Hormone Replacement for Untreated Older Adults with Subclinical Hypothyroidism — A Randomized Placebo Controlled Trial (TRUST) is pro-

clinical hypothyroidism (thyrotropin level, 4.60 to 19.99 mIU per liter, free thyroxine level within the reference range). A total of 368 patients were assigned to receive levothyroxine (at a starting dose of 50 μg daily, or 25 μg if the body weight was <50 kg

- **Double-blind, randomized, placebo-controlled study**
- **737 adults ≥65 years**
- **Median TSH 6-4 mIU/L**
- **Score after 1 year on LT4 or placebo**
- **No difference in hypothyroid symptoms**

Stott et al: NEJM 376:26, 2017

Table 2. **Outcomes at 12 Months and Extended Follow-up.***

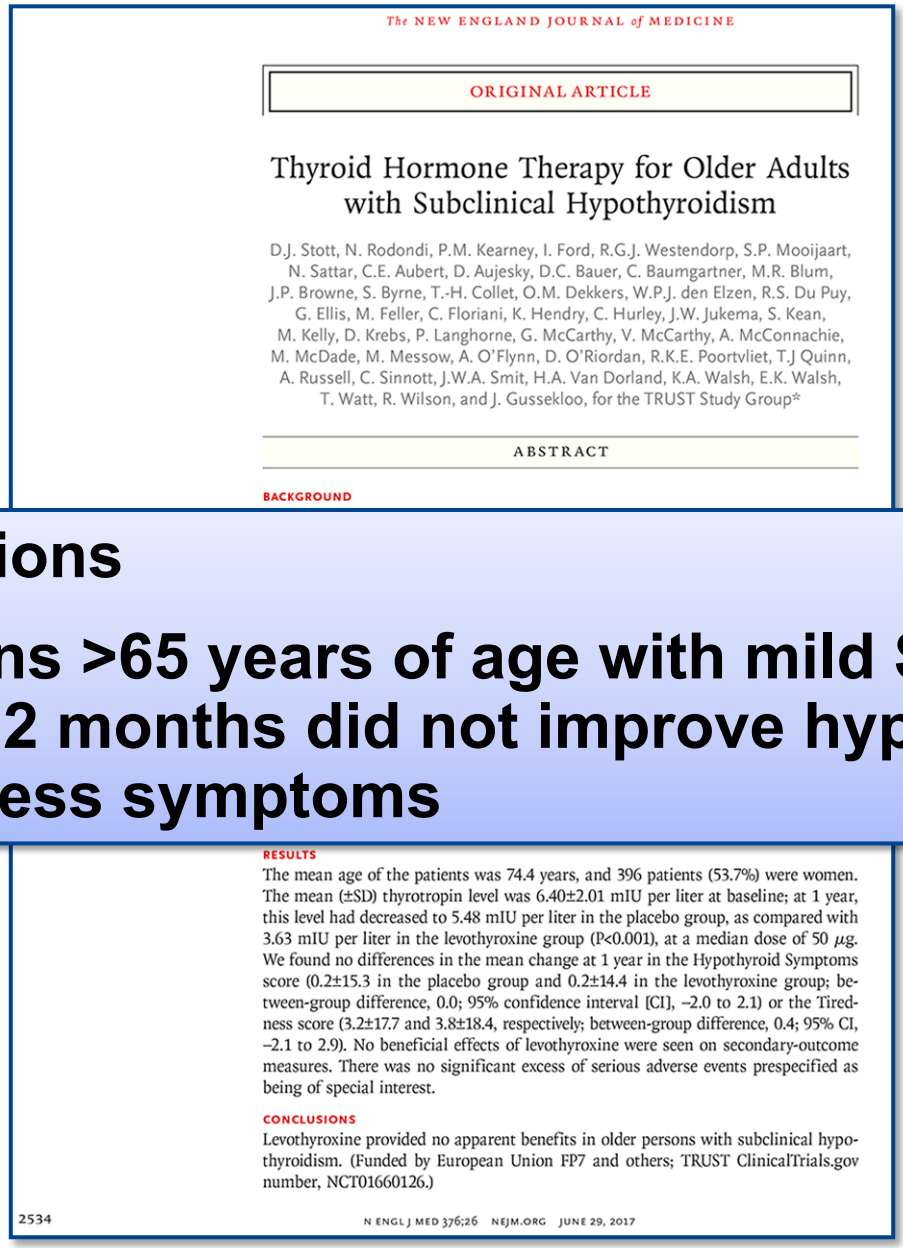
Variable	Baseline		At 12 Mo						
	Placebo (N=369)	Levothyroxine (N=368)				Levothyroxine (N=318)	Difference (95% CI)	P Value	
Thyrotropin — mIU/liter	6.38±2.01	6.41±2.01				3.63±2.11	−1.92 (−2.24 to −1.59)	<0.001	
score					(−2.0 to 2.1)			(−1.9 to 3.9)	
Tiredness score	25.5±20.3	25.9±20.6	28.6±19.5	28.7±20.2	0.4 (−2.1 to 2.9)	0.77	31.9±22.1	30.2±20.5	−3.5 (−7.0 to 0.0)	0.05
Secondary outcomes									
EQ-5D descriptive score	0.847±0.171	0.846±0.187	0.853±0.191	0.833±0.212	−0.025 (−0.050 to 0.000)	0.05	0.829±0.209	0.864±0.188	0.040 (0.005 to 0.075)	0.03
EQ VAS score	76.5±16.3	78.4±15.3	77.4±13.7	77.3±15.6	−1.3 (−3.2 to 0.6)	0.18	77.2±13.5	76.8±14.2	−0.8 (−3.2 to 1.7)	0.56
Hand-grip strength — kg	27.5±11.3	28.0±10.2	27.1±11.2	27.5±10.5	−0.1 (−0.9 to 0.7)	0.84	24.9±10.6	24.4±10.1	−0.6 (−1.7 to 0.6)	0.34
Blood pressure — mm Hg										
Systolic	140.4±18.9	141.2±18.7	138.4±17.8	138.3±18.7	0.1 (−2.1 to 2.4)	0.90	137.5±19.2	136.8±17.6	1.1 (−4.1 to 2.1)	0.51
Diastolic	74.8±11.7	74.1±11.6	73.5±11.1	72.8±11.4	−0.1 (−1.5 to 1.3)	0.93	72.3±11.4	72.0±11.5	0.5 (−1.4 to 2.4)	0.59
Body-mass index	27.7±4.6	28.1±5.3	27.7±4.6	27.9±5.1	0.0 (−0.2 to 0.2)	0.89	27.2±4.5	27.9±4.9	0.2 (−0.1 to 0.5)	0.30
Waist circumference — cm	97.5±12.8	98.5±13.6	96.8±13.1	98.0±13.2	0.4 (−0.4 to 1.3)	0.34	96.0±13.8	97.6±13.4	0.3 (−0.9 to 1.5)	0.66
Adverse symptom assessment									
Hyperthyroid Symptoms score§	10.5±11.2	10.5±11.2	10.3±11.3	10.5±10.8	0.6 (−0.7 to 1.9)	0.35	9.8±11.0	11.1±11.7	0.7 (−1.2 to 2.5)	0.46

Clinical Outcomes and Adverse Events

Variable	All patients (n=737)	Placebo group (n=369)	Levothyroxine group (n=368)	HR (95% CI)
Clinical outcome, no. (%)				
Fatal or nonfatal CV event	38 (5.2)	20 (5.4)	18 (4.9)	0.89 (0.47-1.69)
CV death	3 (0.4)	1 (0.3)	2 (0.5)	–
Death from any cause	15 (2.0)	5 (1.4)	10 (2.7)	1.91 (0.65-5.60)
Serious adverse events				
Pt with ≥1 event, no. (%)	181 (24.6)	103 (27.9)	78 (21.2)	0.94 (0.88-1.00)*
Events, no.	343	201	142	–
Adverse event of special interest, no. (%)				
New onset AF	24 (3.3)	13 (3.5)	11 (3.0)	0.80 (0.35-1.80)
Heart failure	9 (1.2)	6 (1.6)	3 (0.8)	–
Fracture	17 (2.3)	8 (2.2)	9 (2.4)	1.06 (0.41-2.76)
New Dx of osteoporosis	7 (0.9)	4 (1.1)	3 (0.8)	–
Withdrawal, no. (%)				
Permanent discontinuation of trial regimen	160 (21.7)	79 (21.4)	81 (22.0)	1.06 (0.78-1.44)
Withdrawal from follow-up	41 (5.6)	22 (6.0)	19 (5.2)	0.84 (0.46-1.56)

*P=0.5

Stott et al: NEJM 376:2534, 2017



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism

D.J. Stott, N. Rodondi, P.M. Kearney, I. Ford, R.G.J. Westendorp, S.P. Mooijaart, N. Sattar, C.E. Aubert, D. Aujesky, D.C. Bauer, C. Baumgartner, M.R. Blum, J.P. Browne, S. Byrne, T.-H. Collet, O.M. Dekkers, W.P.J. den Elzen, R.S. Du Puy, G. Ellis, M. Feller, C. Floriani, K. Hendry, C. Hurley, J.W. Jukema, S. Kean, M. Kelly, D. Krebs, P. Langhorne, G. McCarthy, V. McCarthy, A. McConnachie, M. McDade, M. Messow, A. O'Flynn, D. O'Riordan, R.K.E. Poortvliet, T.J Quinn, A. Russell, C. Sinnott, J.W.A. Smit, H.A. Van Dorland, K.A. Walsh, E.K. Walsh, T. Watt, R. Wilson, and J. Gussekloo, for the TRUST Study Group*

ABSTRACT

BACKGROUND

RESULTS

The mean age of the patients was 74.4 years, and 396 patients (53.7%) were women. The mean (±SD) thyrotropin level was 6.40±2.01 mIU per liter at baseline; at 1 year, this level had decreased to 5.48 mIU per liter in the placebo group, as compared with 3.63 mIU per liter in the levothyroxine group (P<0.001), at a median dose of 50 μg. We found no differences in the mean change at 1 year in the Hypothyroid Symptoms score (0.2±15.3 in the placebo group and 0.2±14.4 in the levothyroxine group; between-group difference, 0.0; 95% confidence interval [CI], −2.0 to 2.1) or the Tiredness score (3.2±17.7 and 3.8±18.4, respectively; between-group difference, 0.4; 95% CI, −2.1 to 2.9). No beneficial effects of levothyroxine were seen on secondary-outcome measures. There was no significant excess of serious adverse events prespecified as being of special interest.

CONCLUSIONS

Levothyroxine provided no apparent benefits in older persons with subclinical hypothyroidism. (Funded by European Union FP7 and others; TRUST ClinicalTrials.gov number, NCT01660126.)

- **Conclusions**
- **In persons >65 years of age with mild SCHypo, LT4 for 12 months did not improve hypothyroid or tiredness symptoms**

Stott et al: NEJM 376:26, 2017

Replacement Therapy for Primary & Central Hypothyroidism

MAYO CLINIC

Review | G A de Carvalho and others | Pitfalls in hypothyroidism therapy | 178:6 | R231–R244

MANAGEMENT OF ENDOCRINE DISEASE

Pitfalls on the replacement therapy for primary and central hypothyroidism in adults

Gisah Amaral de Carvalho[1], Gilberto Paz-Filho[2], Cleo Mesa Junior[1] and Hans Graf[1]

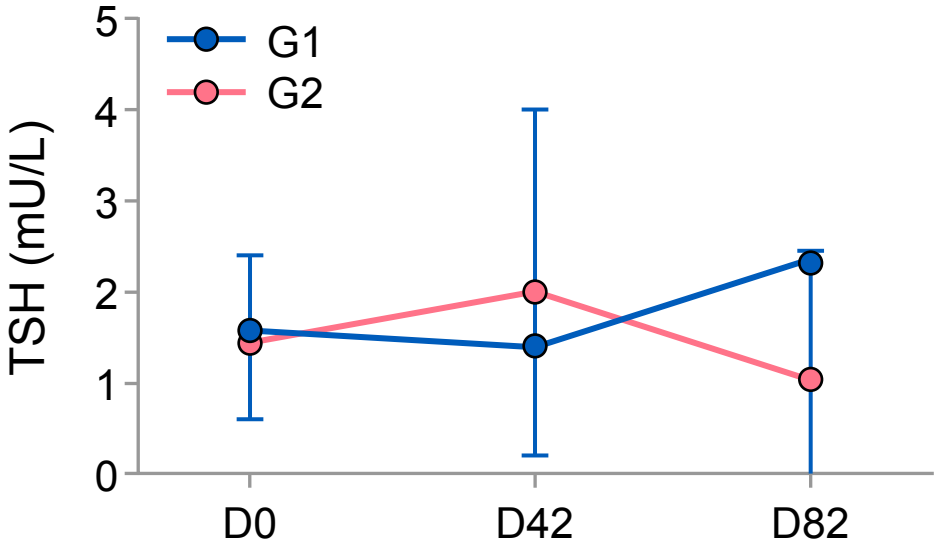
[1]Department of Endocrinology and Metabolism, SEMPR, Hospital de Clínicas, Federal University of Paraná, Curitiba, Brazil and [2]Janssen-Cilag Australia, Sydney, Australia

monotherapy with LT4 due to its efficacy, long-term experience, favorable side effect profile, ease of administration, good intestinal absorption, long serum half-life and low cost. Despite being easily treatable with a daily dose of LT4, many patients remain hypothyroid due to malabsorption syndromes, autoimmune gastritis, pancreatic and liver disorders, drug interactions, polymorphisms in DIO2 (iodothyronine deiodinase 2), high fiber diet, and more

https://doi.org/10.1530/EJE-17-0947 Printed in Great Britain

- Review and analysis of practice
- LT4 is standard Rx for hypothyroidism
- Discussion of causes of under- and over-treatment
- Discussion of combination T4 plus T3
- Use of FT4, not TSH, to monitor central hypothyroidism
- Oncologic hypothyroidism

"Weekly administration of LT4 was safe, well-tolerated and without evidence of Rx toxicity, including cardiac effects."



- Changes in TSH serum levels with daily and weekly regimens of LT4
- G1: D0-D42 of daily regimen of LT4 (TSH 2.03±1.40 mIU/L) and weekly regimen of LT4 (TSH 2.39±1.19 mIU/L)
- G2: D0-D42 of weekly regimen of LT4 (TSH 3.32±3.10 mIU/L) and daily regimen of LT4 (TSH 2.38±1.37 mIU/L)

P>0.05 for all comparisons between groups and within same group
de Carvalho et al: Eur J Endocrinol 178:R231, 2018

Main GI Disorders That Interfere With LT4 Absorption

- Atrophic gastritis
- H. pylori infection
- Celiac disease
- Lactose intolerance
- Bowel resection

Central Hypothyroidism

- In contrast to primary hypothyroidism, TSH is not useful for LT4 dosing
- Monitor FT4 for LT4 changes
- Central hypothyroidism is rare and usually isolated deficiency
- Caution is necessary when central hypothyroidism is associated with adrenal insufficiency
- Estrogen replacement can ↑ LT4 requirement and dose

What You Should Know About LT4

- Up to 40% of patients are under-treated
- When TSH is ↑, look for non-compliance, interfering drugs, food/fasting, GI disorders
- Bariatric surgery and LT4 absorption requirements often ↓ because of massive weight loss
- Daily dose vs weekly dose

What's New in SCHypo in Pregnancy

MAYO CLINIC

SCHypo in Pregnancy

- Common problem
- Changing recommendations for Rx
- New normal TSH results
- Remains controversial

THYROID
Volume 27, Number 3, 2017

DOI: 10.1089/thy.2016.0457

SPECIAL ARTICLE

2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum

Erik K. Alexander,[1,*] Elizabeth N. Pearce,[2,*] Gregory A. Brent,[3] Rosalind S. Brown,[4] Herbert Chen,[5] Chrysoula Dosiou,[6] William A. Grobman,[7] Peter Laurberg,[8,†] John H. Lazarus,[9] Susan J. Mandel,[10] Robin P. Peeters,[11] and Scott Sullivan[12]

Background: Thyroid disease in pregnancy is a common clinical problem. Since the guidelines for the management of these disorders by the American Thyroid Association (ATA) were first published in 2011, significant clinical and scientific advances have occurred in the field. The aim of these guidelines is to inform clinicians, patients, researchers, and health policy makers on published evidence relating to the diagnosis and management of thyroid disease in women during pregnancy, preconception, and the postpartum period.

- **12 authors; 74 pages; 621 references**
- **Evidence-based guidelines; 97 recommendations**
- **For management of thyroid disease during pregnancy and postpartum**
- **Published 2017**

[5]Department of Surgery, University of Alabama at Birmingham, Birmingham, Alabama.
[6]Division of Endocrinology, Stanford University School of Medicine, Stanford, California.
[7]Department of Obstetrics and Gynecology, Northwestern University, Chicago, Illinois.
[8]Departments of Endocrinology & Clinical Medicine, Aalborg University Hospital, Aalborg, Denmark.
[9]Institute of Molecular Medicine, Cardiff University, Cardiff, United Kingdom.
[10]Division of Endocrinology, Diabetes and Metabolism, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.
[11]Department of Internal Medicine and Rotterdam Thyroid Center, Erasmus Medical Center, Rotterdam, The Netherlands.
[12]Department of Obstetrics and Gynecology, Medical University of South Carolina, Charleston, South Carolina.
*Co-chairpersons: Erik K. Alexander and Elizabeth N. Pearce. Excepting the co-chairpersons, the authors are listed in alphabetical order and were appointed by the ATA to independently formulate the content of this manuscript. None of the scientific or medical content of the manuscript was dictated by the ATA.
†Deceased.

Debate | I Velasco and P Taylor | Subclinical hypothyroidism in pregnancy | 178:1 | D1–D12

Identifying and treating subclinical thyroid dysfunction in pregnancy: emerging controversies

Inés Velasco[1] and **Peter Taylor**[2]

[1]Pediatrics, Gynecology & Obstetrics Unit, Riotinto Hospital, Huelva, Spain and [2]Thyroid Research Group, Systems Immunity Research Institute, Cardiff University School of Medicine, Cardiff, UK

Correspondence should be addressed to I Velasco
Email:
inesvelas@msn.com

risk of thyroid dysfunction during pregnancy remains unresolved. Despite this, levothyroxine is also now regularly prescribed by gynaecologists and centres for reproductive medicine. In this context, there is increasing concern regarding the risk of over diagnosis and subsequent potential overtreatment. Taken together, we need to reconsider how thyroid dysfunction should be identified in pregnant women and highlight the arguments for and against the

- **Analysis of data**
- **Criteria for screening**
- **LT4 therapy: Pros and cons**
- **Conclusions**

www.eje-online.org
https://doi.org/10.1530/EJE-17-0598

Published by Bioscientifica Ltd.

SCHypo and Pregnancy

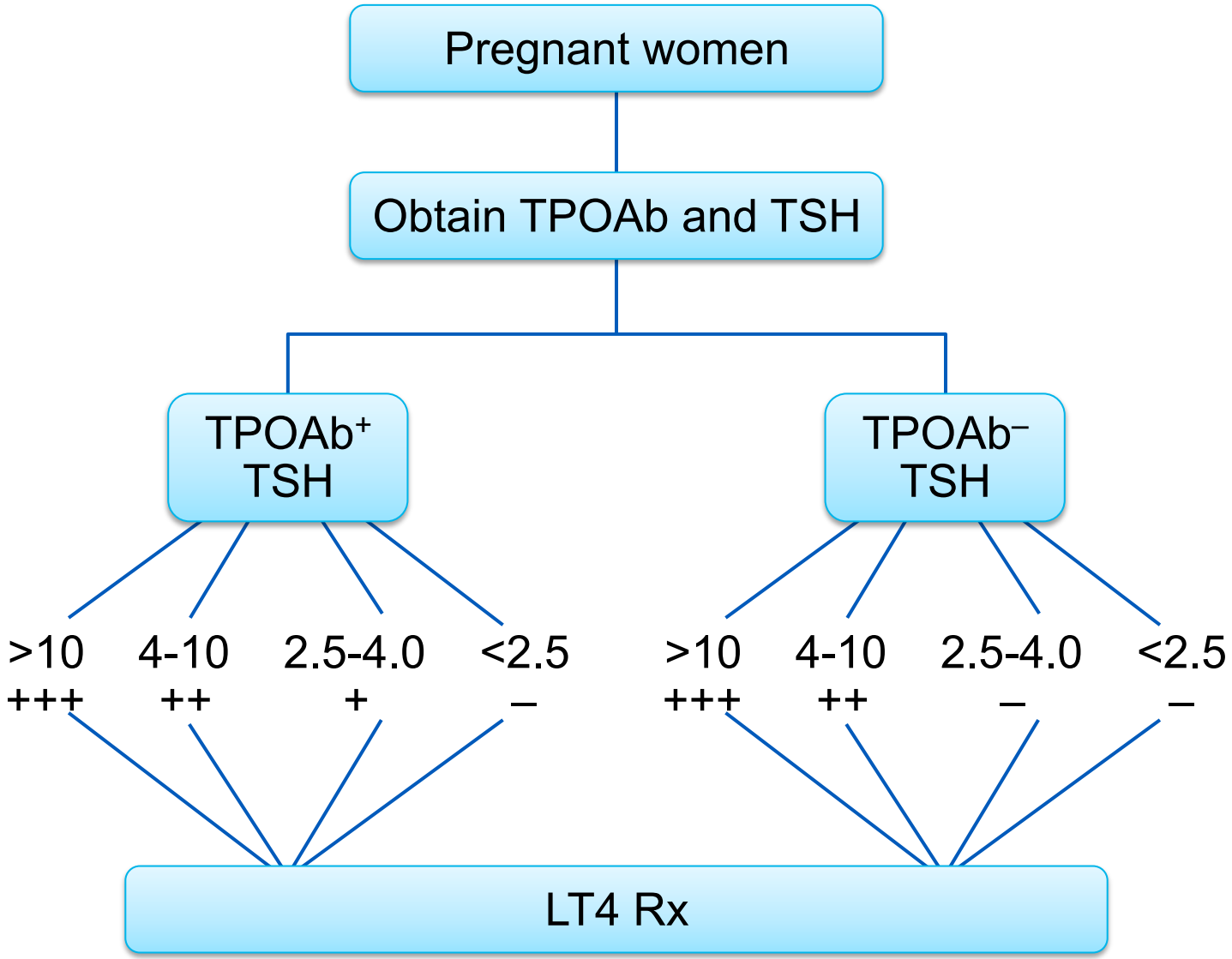
- Numerous studies demonstrate adverse pregnancy and neonatal outcomes: Miscarriage, preterm delivery, pre-eclampsia, growth restrictions, perinatal mortality
- Combination of SCH and AITD is more likely associated with poor outcomes
- New TSH ranges offered
- Screen women with infertility or recurrent abortions

Criteria for screening by Wilson and Junger

1. Is it an important health problem?
2. Is there an accepted treatment?
3. Are facilities for diagnosis and treatment available?
4. Is there a recognizable latent stage where symptoms are lacking?
5. Is there a suitable test or examination?
6. Is the test acceptable to the general population?
7. Is the natural history of the condition, including development from latent to declared disease understood?
8. Is there an agreed policy on whom to treat as patients?
9. Is the cost of case finding (including diagnosis and treatment of patients diagnosed) economically appropriate?
10. Case finding should be a continuing process and not a “once and for all” project

Screen summary

- Important health problem?
- Suitable Dx test?
- Cause of serious complications
- Rx available



SCHypo in Pregnancy

- Iodine deficiency affects TSH levels; American guidelines cannot be applied universally
- Upper limit of pregnancy TSH was changed from 2.5 mIU/L (2011) to 4.0 mIU/L (2017)
- 2 large-scale studies (Lazarus, 2012; Casey, 2017) failed to show significant effect of LT4 on newborn IQ
- There is need for well-defined criteria for diagnosis in a single population

Is Combined Therapy Effective?

MAYO CLINIC

Original Article

ITALIAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS STATEMENT–REPLACEMENT THERAPY FOR PRIMARY HYPOTHYROIDISM: A BRIEF GUIDE FOR CLINICAL PRACTICE

Rinaldo Guglielmi, MD[1]; Andrea Frasoldati, MD[2]; Michele Zini, MD[2]; Franco Grimaldi, MD[3]; Hossein Gharib, MD, FACE, MACE[4]; Jeffrey R. Garber, MD, FACE[5]; Enrico Papini, MD, FACE[1]

Dos

- LT4 is first choice
- Therapeutic target TSH 1-3 mIU/L
- Use generic or brand LT4
- Initial T4 dose 25-50 mcg if CAD, old or fragile patient, or profound hypothyroidism
- Liquid LT4 with poor compliance or dec GI absorption

Guglielmi et al: Endocr Pract, 2016

Italian AACE Recommendations

Don’ts

- Combined Rx in fragile patient, with CV disease, or in pregnancy
- LT3 as sole replacement
- LT4 use in biochemically euthyroid, symptomatic patient
- Thyroid extracts
- Switch Rx when one is working well

Combination LT4 Plus LT3 Rx

- May be necessary in some patients with persistent symptoms
- R/o non-thyroid problems
- Consider combination Rx

Possible Approach to Shift from LT4 Monotherapy to Combined LT4/LT3 Therapy*							
LT4 monotherapy	LT4 (μg/day)	75	100	125	150	175	200
Combined LT4/LT3	LT4 (μg)	70	88	100	125	150	175
	LT3 (μg)	5	5	7.5	7.5	10	10
LT4:LT3 ratio		14.0	17.5	13.5	16.5	15.0	17.5

*Suggested LT4 and LT3 daily doses are targeted to maintain LT4:LT3 ratio within a 10:1 to 20:1 range. LT3 should be prescribed, if possible in divided doses. Due to greater potency of T3 vs T4 (estimates ranging from 3:1 to 4:1), the proposed combined Rx may result in a change in thyroid status and, therefore, should be considered starting points that may have to be modified on basis of clinical and laboratory parameters EP 2016

Review | W M Wiersinga | T4+T3 combination therapy | 177:6 | R287–R296

THERAPY OF ENDOCRINE DISEASE

T4+T3 combination therapy: is there a true effect?

Wilmar M Wiersinga

Department of Endocrinology and Metabolism, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

Correspondence should be addressed to W M Wiersinga
Email
w.m.wiersinga@amc.uva.nl

to T3 conversion in cell cultures. Peripheral tissue function tests such as serum cholesterol reflect thyroid hormone action in target tissues. Using such biochemical markers, patients who had a normal serum TSH during postoperative T4 monotherapy, were mildly hypothyroid, whereas those with a TSH 0.03–≤0.3 mU/L were closest to euthyroidism.

- **5-10% of hypothyroid patients on LT4 complain of symptoms**
- **Escobar-Morreale et al in 1995 showed that serum TSH may not reflect tissue TSH**
- **Attempts to improve results include T4 plus T3 combination**

Wiersinga: Eur J Endocrinol 177:R287, 2017

Combination T4 plus T3

Is an attempt to simulate normal physiology of 2 hormone production

Thyroid Hormone Replacement Therapy in Primary Hypothyroidism: A Randomized Trial Comparing L-Thyroxine plus Liothyronine with L-Thyroxine Alone

Héctor F. Escobar-Morreale, MD, PhD; José I. Botella-Carretero, MD; Manuel Gómez-Bueno, MD; José M. Galán, MD; Vivencio Barrios, MD, PhD; and José Sancho, MD, PhD

Conclusions: Physiologic combinations of L-thyroxine plus liothyronine do not offer any objective advantage over L-thyroxine alone, yet patients prefer combination treatment

ronine in hypothyroid patients that match the proportions present in normal secretions of the human thyroid gland.

Design: Randomized, double-blind, crossover trial.

Setting: Academic research hospital.

Participants: 28 women with overt primary hypothyroidism.

Intervention: Crossover trial comparing treatment with L-thyroxine, 100 μg/d (standard treatment), versus treatment with L-thyroxine, 75 μg/d, plus liothyronine, 5 μg/d (combination treatment), for 8-week periods. All patients also received L-thyroxine, 87.5 μg/d, plus liothyronine, 7.5 μg/d (add-on combination treatment), for a final 8-week add-on period.

Measurements: Primary outcomes included serum thyroid hormone levels, results of quality-of-life and psychometric tests, and patients' preference. Multiple biological thyroid hormone end points were studied as secondary outcomes.

Results: Compared with standard treatment, combination treatment led to lower free thyroxine levels (decrease, 3.9 pmol/L [95% CI, 2.5 to 5.3 pmol/L]), slightly higher serum levels of total score increased slightly (0.6 digit [CI, 0.1 to 1.0 digit] and 0.8 digit [CI, 0.2 to 1.4 digits], respectively). The add-on combination treatment resulted in overreplacement. Levels of thyroid-stimulating hormone decreased by 0.85 mU/L (CI, 0.27 to 1.43 mU/L) and serum free triiodothyronine levels increased by 0.8 pmol/L (CI, 0.1 to 1.5 pmol/L) compared with standard treatment; 10 patients had levels of thyroid-stimulating hormone that were below the normal range. Twelve patients preferred combination treatment, 6 patients preferred the add-on combination treatment, 2 patients preferred standard treatment, and 6 patients had no preference ($P = 0.015$).

Limitations: Treatment with L-thyroxine, 87.5 μg/d, plus liothyronine, 7.5 μg/d, was an add-on regimen and was not randomized.

Conclusions: Physiologic combinations of L-thyroxine plus liothyronine do not offer any objective advantage over L-thyroxine alone, yet patients prefer combination treatment.

Ann Intern Med. 2005;142:412-424. www.annals.org

For author affiliations, see end of text.

The recommended treatment for hypothyroidism is oral L-thyroxine sodium. This treatment is administered with the aim of restoring clinical euthyroidism and well-being and maintaining normal serum levels of thyroid-stimulating hormone (TSH) (1). However, triiodothyronine is the most active thyroid hormone because its affinity for the nuclear thyroid hormone receptor is 10- to 20-fold that of thyroxine (2, 3). The current practice of using L-thyroxine alone as replacement therapy for hypothyroidism assumes that peripheral conversion of thyroxine into triiodothyronine is able to restore normal triiodothyronine concentrations in target tissues. However, no experimental data support this assumption. On the contrary, we found that infusion of thyroxine alone into thyroidectomized rats was not able to restore euthyroidism (4); this was possible only by infusing combinations of thyroxine and triiodothyronine in proportions similar to those secreted by the rat thyroid gland (5).

An early study in hypothyroid patients compared treatment with the usual daily L-thyroxine dose, consisting of two or three 100-μg tablets, versus the same number of tablets, each containing 80 μg of L-thyroxine and 20 μg of liothyronine (6). Although patients were probably overtreated throughout the study, adverse events were more frequent during treatment with the L-thyroxine–liothyronine combination (6), probably because of the excessive amount of liothyronine administered. More recently, several studies have evaluated combined levothyroxine–liothyronine treatment using a "triiodothyronine substitution" approach, in which a small yet supraphysiologic amount of liothyronine, ranging from 10 μg/d to 15 μg/d, was substituted for 50 μg of the total L-thyroxine dose (7–10). Bunevicius and colleagues (7, 8) reported that triiodothy-

See also:

Print
Editors' Notes 413
Summary for Patients I-55

Web-Only
Appendix Table
Conversion of figures and tables into slides

MAYO CLINIC

Escobar-Morreale et al: Ann Intern Med 142:412, 2005

0021-972X/06/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 91(7):2592–2599

doi: 10.1210/jc.2006-0448

Thyroxine-Triiodothyronine Combination Therapy *Versus* Thyroxine Monotherapy for Clinical Hypothyroidism: Meta-Analysis of Randomized Controlled Trials

Simona Grozinsky-Glasberg, Abigail Fraser, Ethan Nahshoni, Abraham Weizman, and Leonard Leibovici

scanned for additional studies. We put no restrictions on language, year of publication, or publication status.

Study Selection: All randomized trials that compared the effective-

serum cholesterol, triglyceride levels, low-density lipoprotein, and high-density lipoprotein. Adverse events did not differ between regimens.

Conclusions: T_4 monotherapy should remain the treatment of choice

- **Meta-analysis of 11 studies and 1,216 patients**
- **Randomized trials comparing T4 & T3 to T4 therapy**
- **Endpoints included bodily pain, depression, anxiety, fatigue, QOL, weight and lipid profiles**
- **Adverse effects were similar**
- **No difference between T4 & T3 vs T4 therapy**
- **T4 monotherapy should remain the Rx of choice for hypothyroidism**

MAYO CLINIC

Grozinsky-Glasberg et al: JCEM 91:2592, 2006

Results of Randomized-Controlled Trials of T4 + T3 vs T4 Alone

Study (year)	Outcome	Pt preference
Bunevicius et al: 1999	T4 + T3 > T4	T4 + T3 > T4
Walsh et al: 2002	No difference	No difference
Escobar-Morreale et al: 2005	No difference	T4 + T3 > T4
Appelhof et al: 2005	No difference	T4 + T3 > T4

Combination Rx Results in < T4 and > T3 Serum Levels Compared to T4 Monotherapy

	Baseline under T4	T4 monotherapy	T4 + T3 combination	P value T4 vs T4 + T3
TSH (mU/L)	1.10 (0.5-2.2)	0.99 (0.6-1.9)	0.76 (0.2-1.8)	0.07
T4 (nmol/L)	124±29	123±30	77±32	<0.001
T3 (nmol/L)	1.6±0.4	1.7±0.6	2.4±1.0	<0.001

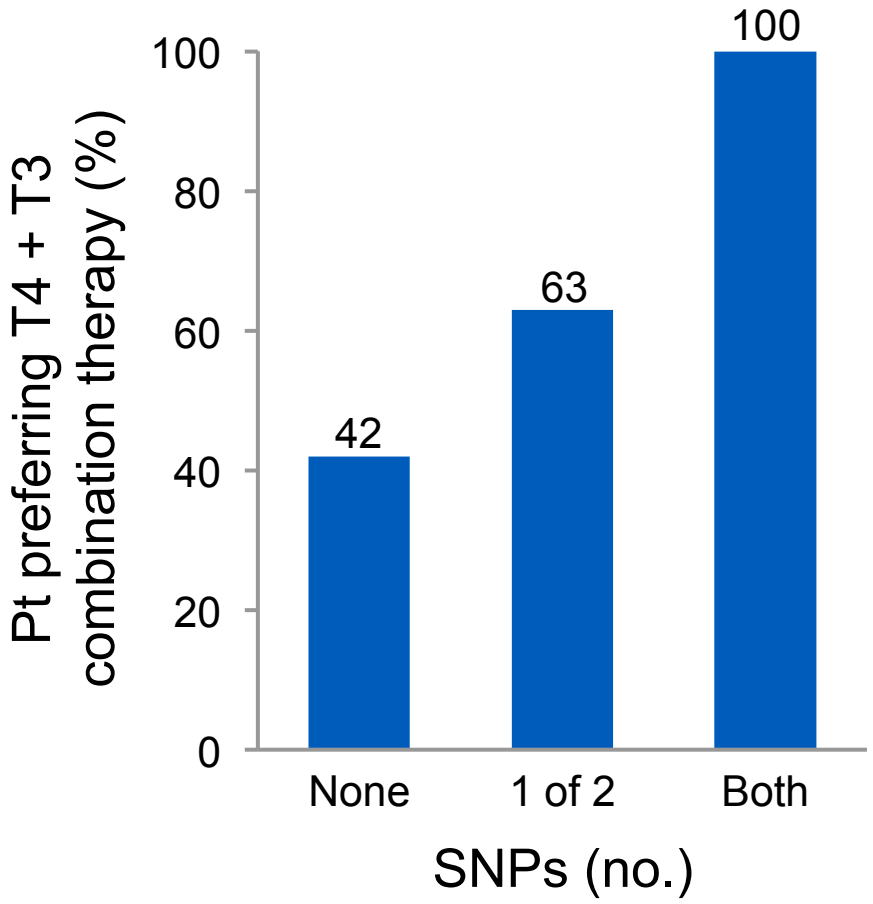
Nygaard et al: Eur J Endocrinol 161:895, 2009

Combination Rx Results in Serum FT3, FT4 and FT3/FT4 Ratios More Closely to Healthy Subjects

	Serum FT3 (pmol/L)	Serum FT4 (pmol/L)	FT3/FT4 ratio
Euthroid controls	4.47	13.8	0.32 (IQR 0.27-0.37)
Hypothyroid on T4	3.70	15.4	0.24 (IQR 0.20-0.28)
Randomized to T4 monotherapy	4.40	20.2	0.24 (range 0.18-0.25)
Randomized to T4 + T3 combination	4.70	14.7	0.30 (range 0.25-0.45)

Wiersinga et al: Eur J Endocrinol 177:R287, 2017

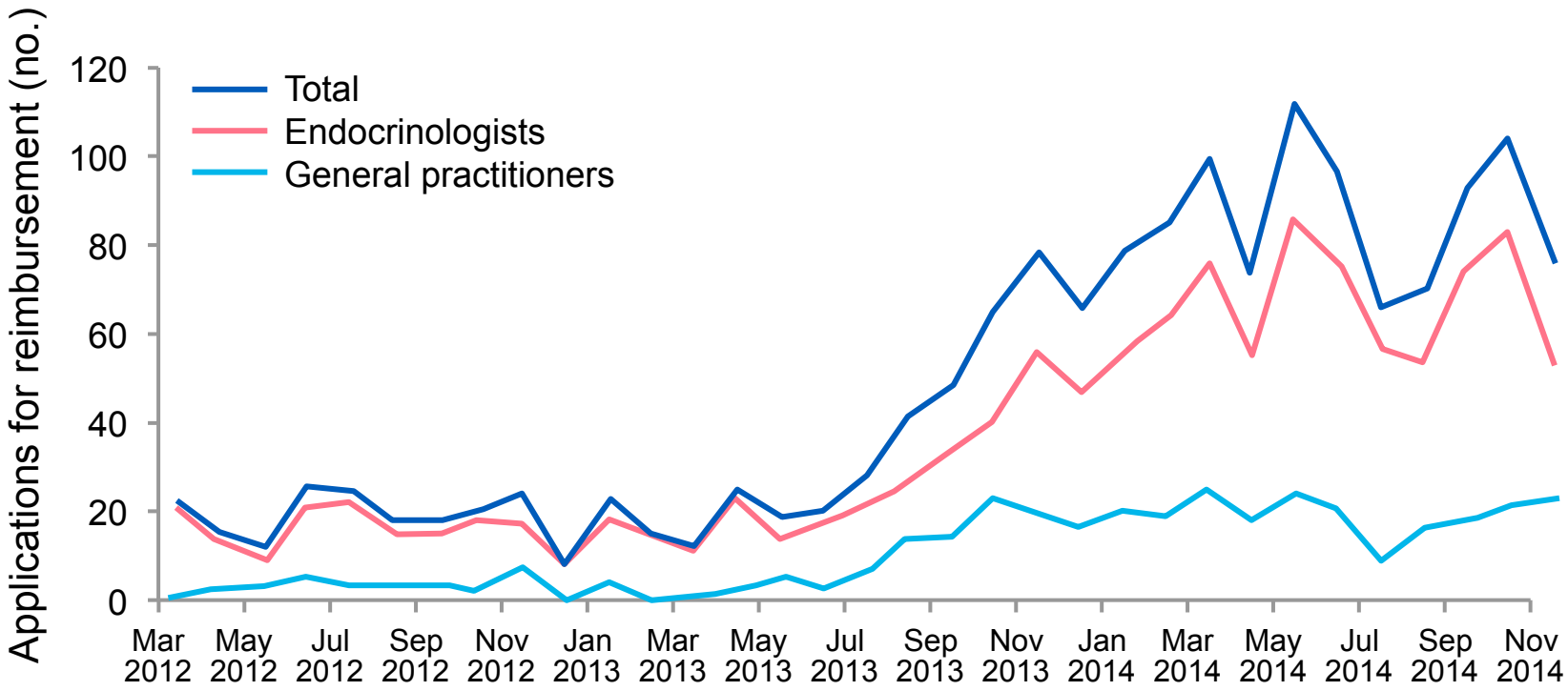
Preference of Hypothyroid Patients for T4 + T3 Combination Therapy Over T4 Monotherapy



- Polymorphisms in DIO2 after T4 + T3 metabolism
- These may account for poor response to LT4 Rx
- Polymorphisms in thyroid hormone transporters and deiodinases is associated with a preference for T4 + T3 Rx

Wiersinga et al: Eur J Endocrinol 177:R287, 2017

Preference of Hypothyroid Patients for T4 + T3 Combination Therapy Over T4 Monotherapy



- In Denmark, sales of T3 increased x 6
- Number of reimbursements for T4 + T3 Rx rose x 3.8 2013-2014

Wiersinga et al: Eur J Endocrinol 177:R287, 2017

Conclusions

- LT4 monotherapy is (still) standard of care
- Only ETA has guidelines for clinical Rx
- 1/20th of T4 dose = T3 dose in µg/day
- Polymorphisms likely account for poor response to T4 alone
- Patient advocacy groups influence management
- It is recognized that many experienced clinicians may not agree with T4 + T3 Rx

Preop US & Thyroidectomy for PTC

MAYO CLINIC

THYROID
Volume 27, Number 12, 2017

DOI: 10.1089/thy.2017.0457

Individualizing Surgery in Papillary Thyroid Carcinoma Based on a Detailed Sonographic Assessment of Extrathyroidal Extension

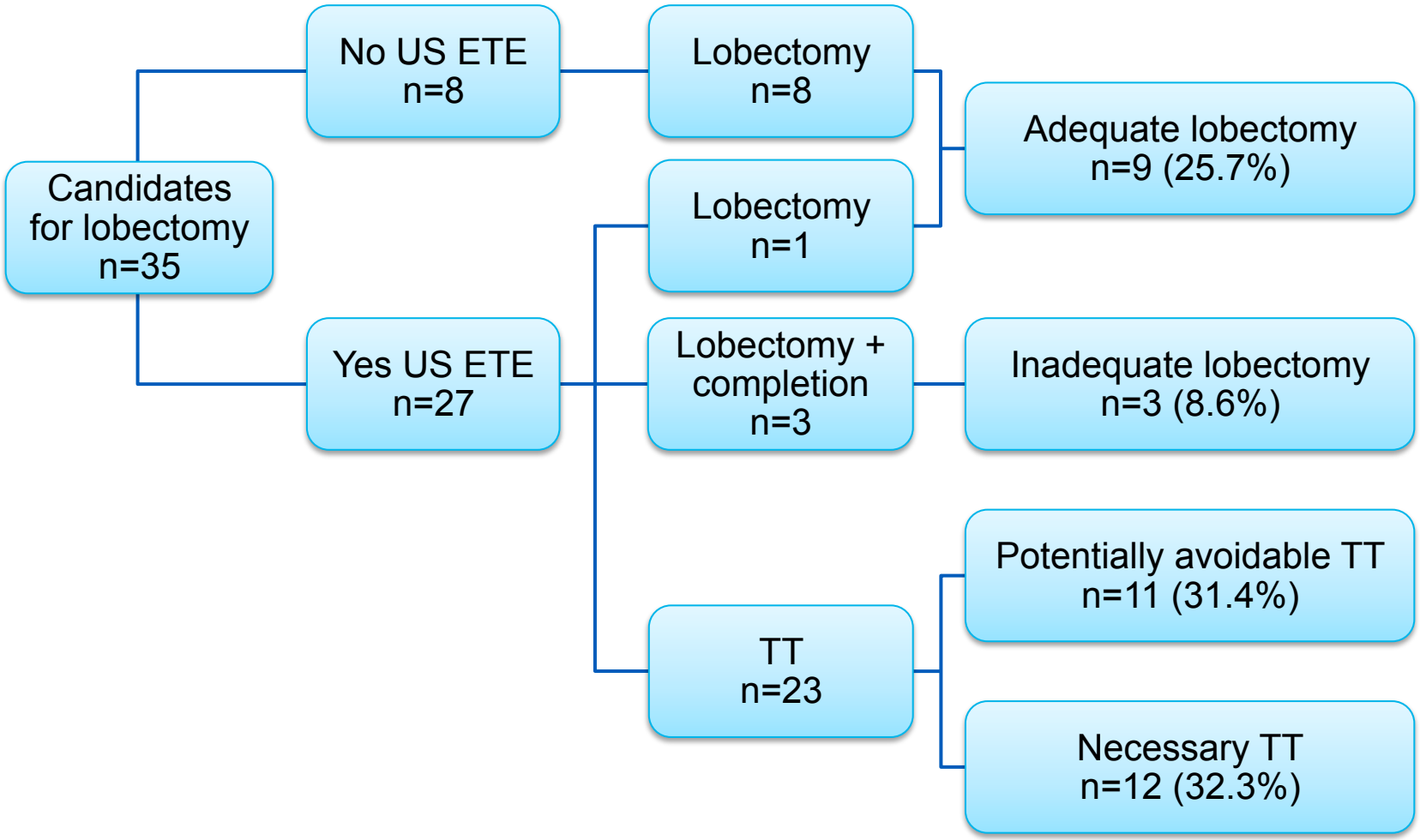
Eric J. Kuo, William J. Thi, Feibi Zheng, Kyle A. Zanocco, Masha J. Livhits, and Michael W. Yeh

acteristics. A detailed sonographic assessment of extrathyroidal extension (ETE) included surgeon-performed evaluation of thyroid capsular distortion, a long interface between tumor and thyroid capsule, irregular or indistinct tumor margins abutting the thyroid capsule, or a tracheal footprint.
Results: Of 141 patients with PTC, 35 (25%) patients were candidates for lobectomy, and 105 (75%) patients were not candidates for lobectomy because of non-tumor ($n=46$) or tumor ($n=59$) characteristics. Of the 35

- **Recent ATA guidelines recommend lobectomy for 1-4 cm PTC if no ETE or lymph nodes**
- **Study evaluates value of preop US in determining ETE**
- **Retrospective study in a single, high-volume endocrine surgery center**
- **Of 141 patients with PTC, 35 (25%) were candidates for lobectomy**
- **PPV was 52% and NPV 100% for US findings of ETE**

Kuo et al: Thyroid 27:1544, 2017

Application of Sonographic ETE to Surgical Decision Making



Kuo et al: Thyroid 27:1544, 2017

Table 1. Comparison of Studies Analyzing Actual Versus Hypothetical Implementation of the 2015 ATA Guidelines into Clinical Practice

Study	*Current study*	*Kluijfhout* et al. *(8)*	*Lang* et al. *(10)*
Study design	Actual implementation of ATA guidelines	Hypothetical implementation of ATA guidelines	Hypothetical implementation of ATA guidelines
Sample size	141	1000	1513
Histology	PTC	WDTC	PTC
Preoperative candidates for lobectomy	Inclusions: • Unilateral • ≤3 cm • cN0 Exclusions: • FH thyroid cancer • Hx radiation • Hx hyper- or hypothyroidism	Inclusions: • Unilateral • T1–T2 • cN0 Exclusions: • FH thyroid cancer • Hx radiation	Inclusions: • Unilateral • T1–T2 • cN0 Exclusions: • FH thyroid cancer • Hx radiation
Postoperative features requiring total thyroidectomy	• ETE • ≥5 central neck metastases • ≥1 lateral neck metastases • Aggressive histology • Vascular invasion • Contralateral carcinoma >1 cm	• ETE • ≥1 central neck metastases • ≥1 lateral neck metastases • Aggressive histology • Vascular invasion • Contralateral carcinoma • Positive margins	• ETE • pN1 >0.5 cm • Aggressive histology • Vascular invasion • Multifocality >1 cm • Positive margins
% of patients with PTC that are preoperative candidates for lobectomy	35/141	25%	38%
% of lobectomy candidates where total thyroidectomy necessary	(42.9%)	43%	43%
Rate of inadequate thyroid lobectomy	8.6%	43%[a]	43%[a]
Rate of potentially avoidable total thyroidectomy	31.4%	57%[b]	57%[b]

[a]Assuming a hypothetical strategy of routine thyroid lobectomy.
[b]Assuming a hypothetical strategy of routine total thyroidectomy.
ATA, American Thyroid Association; PTC, papillary thyroid carcinoma; WDTC, well-differentiated thyroid cancer; FH, family history; ETE, extrathyroidal extension.

Conclusions

- This study validates use of US to access ETE
- NPV is high when US performed by experienced team
- Clinical significance of microscopic ETE is unknown and more studies are needed to evaluate

Recurrent vs Persistent PTC

Disease-Free Status

- Not clearly defined
- ATA guidelines
  - No clinical evidence of tumor
  - No evidence of tumor by WBS and/or US
  - Unstim Tg <0.2 or stim Tg <1 ng/mL

Surgery 163 (2018) 118–123

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/ymsy

Thyroid

Back so soon? Is early recurrence of papillary thyroid cancer really just persistent disease?

Maria F. Bates, MD *, Marcos R. Lamas, MD, Reese W. Randle, MD, Kristin L. Long, MD, Susan C. Pitt, MD, MPHS, David F. Schneider, MD, MS, and Rebecca S. Sippel, MD

curred within 1 year. Only 3 operations met criteria for true "recurrence," while 71 operations were categorized as persistent disease.

Conclusion. Many reoperations for papillary thyroid carcinoma are for management of persistent disease. More than half of the patients required reoperation within the first 2 years, which suggests strongly that improvements in the preoperative assessment and adequacy of initial operative therapy need to be made

- **Retrospective study of 69 PTC patients from 2000-2016**
- **"Recurrence" if negative US + Tg 1 year postop**
- **"Persistence" if abnormal US, positive Tg or TgAb**
- **77% had postop ^{131}I**
- **Most patients have persistent rather than recurrent PTC**

Bates et al: Surgery 163:118, 2018

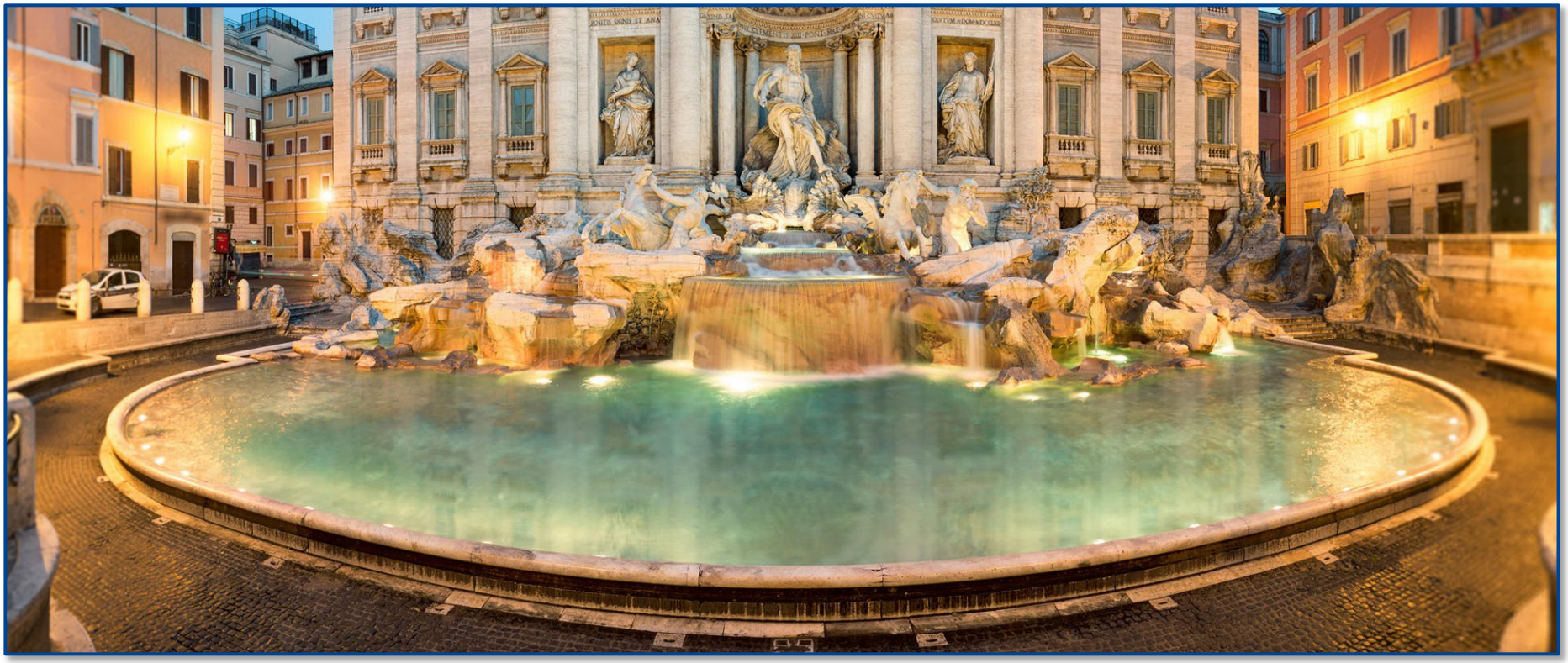
Table II
Patient demographics and characteristics of initial operation.

Variables	All patients ($n = 69$)	%
Sex, *n* (%)		
Male	21	30.4
Female	48	69.5
Age, *n* (%)		
Mean age, y (SD)	42.4 (±14.6)	
<45	38	55.0
>45	31	44.9
Family history PTC	19	27.5
History of radiation	2	2.9
Location of original operation		
Referring facility	54	78.2
University of Wisconsin, Madison	15	21.7
Primary tumor		
Histologic subtype		
Classical PTC	56	81.2
Follicular variant	6	8.6
Tall cell	5	7.2
Sclerosing	2	3.0
Mean size, cm (SD)	2.66 (±1.55)	
Multifocality	35	50.7
Capsular invasion	24	34.7
Extrathyroidal extension	29	42.0
Lympho-vascular invasion	21	30.4
ATA risk stratification		
Low	11	15.9
Intermediate	39	56.5
High	10	14.4
Postoperative RAI	53	76.8

SD, Standard deviation, *PTC*, Papillary thyroid cancer; *ATA*, American Thyroid Association; *RAI*, Radioactive iodine.

Conclusions

- Often difficult to separate persistence from recurrence
- Report implies that in some cases initial Rx may have been inadequate
- It is imperative to perform appropriate surgery for more extensive, advanced disease
- Detection of Tg may represent abnormal thyroid tissue
- All recurrent cancers are persistence of some kind



NIFTP

MAYO CLINIC

PRACTICE GUIDELINES

WILEY

AHNS Series: Do you know your guidelines? AHNS Endocrine Section Consensus Statement: State-of-the-art thyroid surgical recommendations in the era of noninvasive follicular thyroid neoplasm with papillary-like nuclear features

Robert L. Ferris MD, PhD[1] | Yuri Nikiforov MD, PhD[2] | Davis Terris MD[3] |
Raja R. Seethala MD[2] | J. Andrew Ridge MD, PhD[4] | Peter Angelos MD, PhD[5] |
Quan-Yang Duh MD[6] | Richard Wong MD[7] | Mona M. Sabra MD[8] |
James A. Fagin MD[8] | Bryan McIver MD, PhD[9] | Victor J. Bernet MD[10] |
R. Mack Harrell MD[11] | Naifa Busaidy MD[12] | Edmund S. Cibas MD[13] |
William C. Faquin MD, PhD[14,19] | Peter Sadow MD, PhD[14,19] |
Zubair Baloch MD, PhD[15] | Maisie Shindo MD[16] | Lisa Orloff MD[17] |
Louise Davies MD, MS[18] | Gregory W. Randolph MD[19]

- American Head and Neck Society statement
- NIFT-P is a premalignant neoplasm
- Cannot be diagnosed preop; FNA is suspicious or PTC
- NIFT-P Dx is surgical; lobectomy is sufficient
- RAS is positive in 36-57%
- See in consultation with endocrinologist
- Accounts for 10,000 (15%) of 65,000 TC patients in U.S.

Ferris et al: Head Neck, 2018

TABLE 2 Preoperative features that may indicate noninvasive follicular thyroid neoplasm with papillary-like nuclear features diagnosis and are permissive of offering hemithyroidectomy initially

I. Physical examination characteristics

1. No lymph node metastasis
2. No fixation
3. No voice abnormalities
4. No vocal cord paralysis

II. Ultrasound characteristics (see also Table 2)

1. Low and intermediate nodule findings: isoechoic or hypoechoic, oval to round, sharp regular margin, hypoechoic rim
2. Not taller than wide
3. No microcalcifications
4. No contralateral lobe nodules
5. No extrathyroidal extension
6. No posterior abutment
7. No lymph node metastasis
8. No fixation
9. No vocal cord paralysis

III. Cytology characteristics (see also Table 1)

Bethesda III, IV, or V with:

+ Follicular pattern
+ Hypercellular
+ Microfollicular architecture
+ Sheet-like architecture
- No papillae
- No psammomatous calcifications
- No prominent nuclear pseudoinclusions
- No prominent nuclear grooves
- No necrosis or mitoses

IV. Molecular characteristics

1. May have RAS, THADA fusion, or PAX8-PARG
2. Should not have BRAF, RET fusion, TERT promoter, or other high-grade mutation

V. Patient/endocrine characteristics

1. Willing to have second surgery if needed
2. Medically fit for possible second anesthesia
3. Endocrinologist in agreement with initial lobectomy surgery

Ferris et al: Head Neck, 2018

Box 2. Diagnostic Criteria for NIFTP

1. Encapsulation or clear demarcation[a]
2. Follicular growth pattern[b] with
   - <1% Papillae
   - No psammoma bodies
   - <30% Solid/trabecular/insular growth pattern
3. Nuclear score 2-3
4. No vascular or capsular invasion[c]
5. No tumor necrosis
6. No high mitotic activity[d]

[a] Thick, thin, or partial capsule or well circumscribed with a clear demarcation from adjacent thyroid tissue.

[b] Including microfollicular, normofollicular, or macrofollicular architecture with abundant colloid.

[c] Requires adequate microscopic examination of the tumor capsule interface.

[d] High mitotic activity defined as at least 3 mitoses per 10 high-power fields (400×).

JAMA Oncol. 2016;2(8):1023-1029. doi:10.1001/jamaoncol.2016.0386
Published online April 14, 2016. Corrected on May 12, 2016.

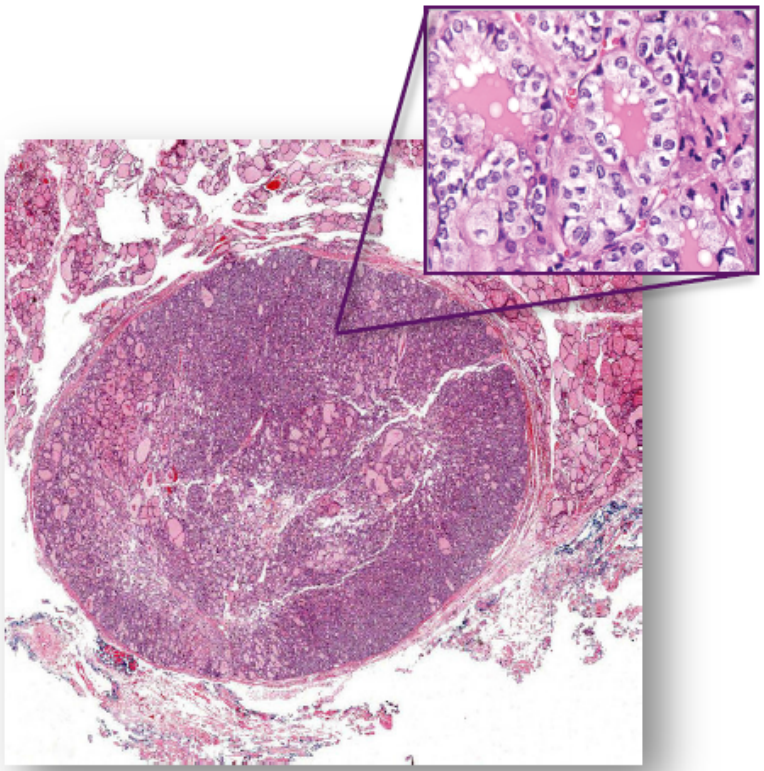
3477 Euler Way, Room 8031,
Pittsburgh, PA 15213 (nikiforovye@upmc.edu).

MAYO CLINIC

Nikiforov et al: JAMA Oncol 2:1023, 2016

NIFTP

Non-Invasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features



- Previously known as encapsulated follicular variant of papillary carcinoma
- If no invasion upon removal – very low (<1%) risk of recurrence
- Best viewed as “premalignant” equivalent of “carcinoma in situ”
- Still requires surgical resection, but lobectomy likely sufficient surgery
- RAS and RAS-like mutations common, but BRAF V600E, TERT not seen

Nikiforov et al: JAMA Oncol 2:1023, 2016

NIFTP as a Putative Premalignant Lesion

Putative Scheme of Thyroid Carcinogenesis

Pattern	Nuclear Features of PTC	Main Oncogene		
Papillary	Yes	*BRAF*	Papillary microcarcinoma	Classic PTC
Follicular	Yes	*RAS*	NIFTP	Invasive EFVPTC
Follicular	No	*RAS*	Follicular adenoma	Follicular thyroid carcinoma

EFVPTC indicates encapsulated follicular variant of PTC; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; PTC, papillary thyroid carcinoma

Nikiforov et al: JAMA Oncol 2:1023, 2016

Surgery 163 (2018) 60–65

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/ymsy

Thyroid

Evaluating the projected surgical impact of reclassifying noninvasive encapsulated follicular variant of papillary thyroid cancer as noninvasive follicular thyroid neoplasm with papillary-like nuclear features

Rajshri Mainthia, MD [a], Heather Wachtel, MD [a], Yufei Chen, MD [a], Elizabeth Mort, MD, MPH [b], Sareh Parangi, MD [a], Peter M. Sadow, MD, PhD [c], and Carrie C. Lubitz, MD, MPH [a,d,*]

- **164 patients of 1,335 cases of PTC met criteria for NIFT-P**
- **79 patients (48%) had initial lobectomy**
- **43 patients (54%) or 3.2% of all PTC pt had subsequent Tx**
- **In this surgical series, the impact of NIFT-P diagnosis was very small**
- **However, the impact was measured in the context of overall PTC at their center, not just on FVPTC**

Mainthia et al: Surgery 163:60, 2018

Conclusions

- NIFT-P is a new diagnosis (EFVPTC)
- Considered premalignant
- FNA is usually suspicious
- Pathology shows encapsulated PTC with follicular features
- Rx is lobectomy
- Will not recur or metastasize
- Positive RAS in 30-50%

Compare Different Thyroid US Classifications

MAYO CLINIC

AACE Thyroid US ROM

US features (ROM)	High (70-90%)	Intermediate (5-15%)	Low (<1%)
Mostly cystic >50%			✓
Isoechoic			✓
Spongiform			✓
Hypoechoic	✓	✓	✓
Intranodular vascularization		✓	✓
Smooth/ill-defined margins		✓	✗
Marked hypoechogenicity	✓	✗	✗
Spiculated margins	✓	✗	✗
Microcalcifications	✓	✗	✗
Taller, than wide	✓	✗	✗
ETE and/or nodes	✓	✗	✗

Comparison of the 2016 AACE/AME & 2015 ATA Nodule Ultrasound Classification Systems

AACE/ACE-AME	ATA
1. Low-risk lesion • Cysts (fluid component >80%) • Mostly cystic nodules with reverberating artifacts and not associated with suspicious US signs • Isoechoic spongiform nodules, either confluent or with regular halo. <1%	**Benign** 1% Purely cystic nodules (no solid component) **Very low suspicion** 3% Spongiform or partially cystic nodules without any of the US features described in low-, intermediate- or high-suspicion patterns **Low suspicion** 5-10% Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid area without: • Microcalcifications • Irregular margin • Extrathyroidal extension • Taller than wide shape
2. Intermediate-risk thyroid lesion Slightly hypoechoic (vs. thyroid tissue) or isoechoic nodules, with ovoid-to-round shape, smooth or ill-defined margins May be present: • Intranodular vascularization • Elevated stiffness at elastography, • Macro or continuous rim calcifications • Indeterminate hyperechoic spots 5-15%	**Intermediate suspicion** Hypoechoic solid nodule with smooth margins without: • Microcalcifications • Extrathyroidal extension • Or taller than wide shape 10-20%
3. High-risk thyroid lesion (50-90%) Nodules with at least 1 of the following features: • Marked hypoechogenicity (vs. prethyroid muscles) • Spiculated or lobulated margins • Microcalcifications • Taller-than-wide shape (AP>TR) • Extrathyroidal growth • Pathologic adenopathy Expected risk of malignancy in accordance with the presence of 1 or more suspicious findings. 50-90%	**High suspicion** Solid hypoechoic nodule or solid hypoechoic component of partially cystic nodule with 1 or more of the following features: • Irregular margins (infiltrative, microlobulated) • Microcalcifications • Taller than wide shape • Rim calcifications with small extrusive soft tissue component • Evidence of extrathyroidal extension >70%

Clinical Study | A Lauria Pantano, E Maddaloni and others | Thyroid US classifications and cytology | 178:6 | 595–603

Differences between ATA, AACE/ACE/AME and ACR TI-RADS ultrasound classifications performance in identifying cytological high-risk thyroid nodules

A Lauria Pantano[1,*], E Maddaloni[1,*], S I Briganti[1], G Beretta Anguissola[1], E Perrella[2], C Taffon[2], A Palermo[1], P Pozzilli[1], S Manfrini[1] and A Crescenzi[2]

and ACR TI-RADS ultrasound classifications by an automated algorithm. Odds ratios (ORs) and receiver operating characteristic (ROC) curves for high-risk cytology categories (TIR3b, TIR4 and TIR5) were calculated for the different US categories and compared.

Results: Cytological categories of risk increased together with all US classifications' sonographic patterns ($P < 0.001$). The diagnostic performance (C-index) of ACR TI-RADS and AACE/ACE/AME significantly improved when adding

- Thyroid US is crucial for management of thyroid nodules
- This study compares performance of ATA, AACE/ACE/AME and ACR TI-RADS US classifications
- 1,077 TNs undergoing FNA were classified according to each classification
- Sensitivity, specificity, PPV and NPV of all categories were evaluated
- ACR TI-RADS classification has the highest area under ROC (receiving operator characteristic) curve; ATA leaves unclassified nodules at high risk

Pantano et al: Eur J Endocrinol 178:595, 2018

Table 1 ATA US classification system in relation to cytology.

	ATA unclassified	Benign	Very low suspicion	Low suspicion	Intermediate suspicion	High suspicion	Tot
TIR1C	1	4	9	7	6	2	29
TIR2	35	2	175	132	323	61	728
TIR3A	9	0	32	33	111	22	207
TIR3B	2	0	2	8	19	6	37
TIR4	1	0	2	3	5	9	20
TIR5	6	0	2	0	16	32	56
Tot	54	6	222	183	480	132	1.077

TIR1 nodules were excluded. *P* value for distribution of proportions among categories: <0.001.

Table 2 AACE/ACE/AME US classification system in relation to cytology.

	AACE/AME/FNC unclassified	Class I	Class II	Class III	Tot
TIR1C	7	12	4	6	29
TIR2	17	120	347	244	728
TIR3A	3	19	83	102	207
TIR3B	1	1	13	22	37
TIR4	0	2	4	14	20
TIR5	0	0	5	51	56
Tot	28	154	456	439	1.077

TIR1 nodules were excluded. *P* value for distribution of proportions among categories: <0.001.

Table 3 ACR TI-RADS US classification system in relation to cytology.

	TR1 (benign)	**TR2** (not suspicious)	**TR3** (mildly suspicious)	**TR4** (moderately suspicious)	**TR5** (highly suspicious)	Tot
TIR1C	17	4	1	4	3	29
TIR2	38	158	149	332	51	728
TIR3A	6	33	33	113	22	207
TIR3B	1	2	10	18	6	37
TIR4	1	2	1	8	8	20
TIR5	0	1	2	20	33	56
Tot	63	200	196	495	123	1.077

TIR1 nodules were excluded. *P* value for distribution of proportions among categories: <0.001.

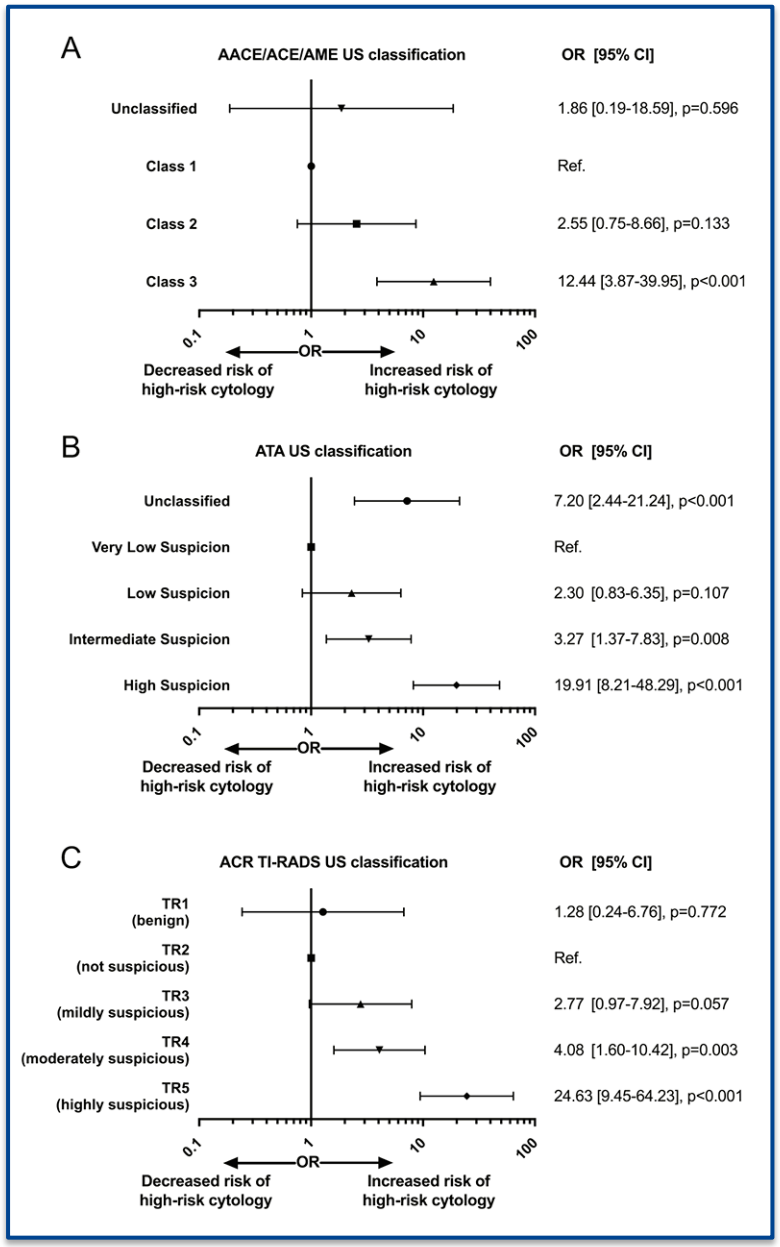


Figure 1

Odds ratio for cytological high-risk nodules by AACE/ACE/AME (A), ATA (B) and ACR TI-RADS (C) US classification systems. (A) Class III nodules showed a significant increased risk for cytological malignancy as defined in the text compared to class I. (B) Intermediate- and high-suspicion nodules had increased risk for cytological malignancy as defined in the text. As well, also unclassified nodules were 7 times more likely to be cytologically malignant than very low-suspicion nodules. (C) A stepwise increased risk of malignancy was found for nodules categorized within the TR3, TR4 and TR5 categories when compared to not suspicious nodules.

Table 4 Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values for malignant cytology of the ATA sonographic patterns. Data are presented as percentages.

	ATA unclassified	Benign	Very low suspicion	Low suspicion	Intermediate suspicion	High suspicion
Sensitivity	8.0	0.0	5.3	9.7	35.4	41.6
Specificity	95.3	99.4	77.6	82.2	54.4	91.2
PPV	16.7	0.0	2.7	6.0	8.3	35.6
NPV	89.8	89.4	87.5	88.6	87.8	93.0

Table 5 Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values for malignant cytology of the AACE/ACE/AME US categories. Data are presentad as percent ages.

	AACE/ACE/AME unclassified	Class I	Class II	Class III
Sensitivity	0.9	2.7	19.5	77.0
Specificity	97.2	84.3	55.0	63.5
PPV	3.6	1.95	4.8	19.8
NPV	89.3	88.1	85.3	95.9

Table 6 Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values for malignant cytology of the ACR TI-RADS US categories. Data are presented as percentages.

	TR1 (benign)	**TR2** (not suspicious)	**TR3** (mildly suspicious)	**TR4** (moderately suspicious)	**TR5** (highly suspicious)
Sensitivity	1.7	4.4	11.3	40.9	41.7
Specificity	93.7	79.8	81.0	53.4	92.1
PPV	3.2	2.5	6.6	9.5	38.7
NPV	88.9	87.5	88.4	88.3	93.0

ROC

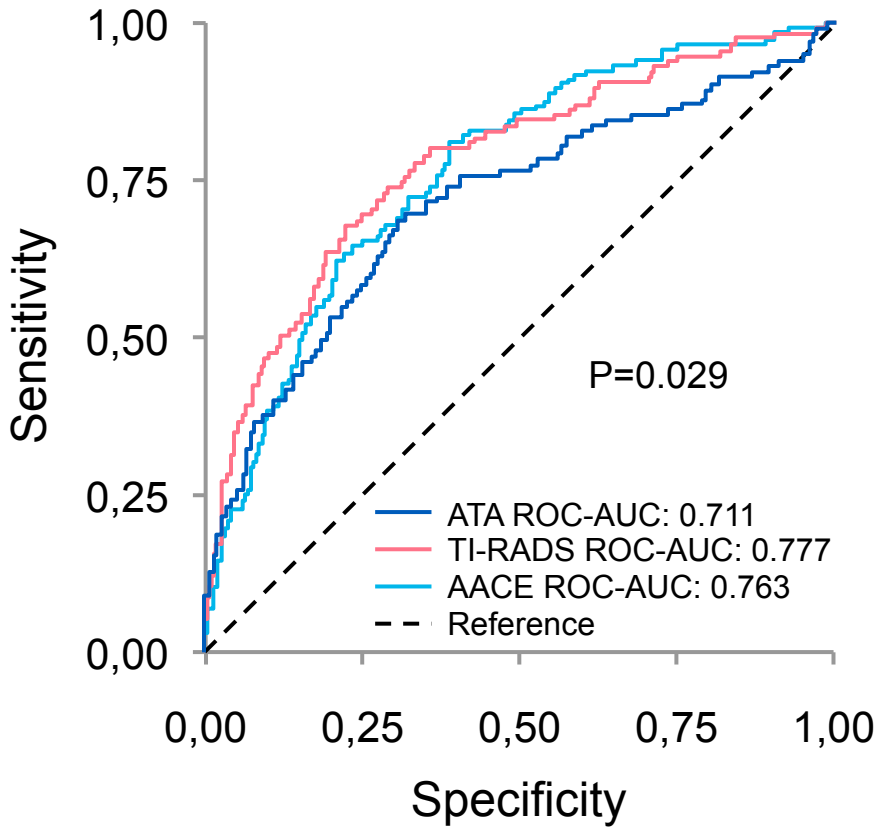


Figure 2

Receiver operating characteristic (ROC) curves for the diagnosis of cytological high-risk malignant nodules. The areas under the ROC curve of regression models accounting for age and gender *plus* US categories from ATA classification (gray circles) or AACE/ACE/AME classification (black squares) or ACR TI-RADS classification (white triangles) are shown. The addition of ACR TI-RADS categories resulted in the highest nominal ROC-AUC value (0.777 (95% CI: 0.729–0.825)). This was similar to the ROC-AUC value obtained when AACE/ACE/AME categories were used (0.763 (95% CI: 0.718–0.808), $P=0.287$ vs ACR TI-RADS ROC-AUC). The addition of categories from the ATA classification resulted in the lowest ROC-AUC value (0.711 (95% CI: 0.655–0.767), $P=0.008$ vs ACR TI-RADS and $P=0.036$ vs AACE/ACE/AME). *P-value for differences between the three models.

Schmidt et al: Thyroid 28:842, 2018

Conclusions

- US classification improves and standardizes care
- All 3 classifications reviewed here provide effective malignancy risk stratification, but have significant differences
- ACR TI-RADS and AACE/AME have highest C-index but significantly higher than ATA scheme
- ACR TI-RADS has the highest ROC-AUC for identifying high-risk nodules

Grazie!

Rome ~ 2016

MAYO CLINIC

Thank You