Recent Developments and Future Challenges in Thyroidology: Clinical Endocrine Review

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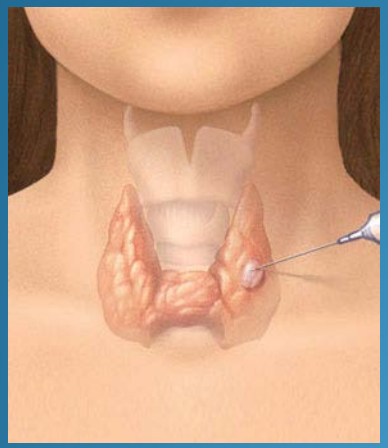
Disclosure:

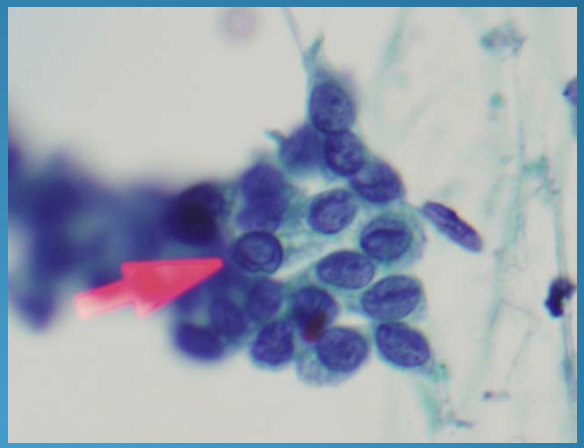
Nothing to Disclose

Learning Objectives

- Thyroid cancer
  - diagnosis
  - prognosis
  - treatment
  - follow-up
- Thyroid function
  - older patients
  - pregnancy

Thyroid Cancer Diagnosis





Thyroid Cancer Diagnosis: Nodules

Table 5. Accuracy of Several Definitions of an Abnormal Ultrasound Examination Result[a]

Definition	Sensitivity	False-Positive Rate	Likelihood Ratio (Predictive Values)		Risk of Cancer (Predictive Values)		No. Needed to Biopsy to Diagnose a Cancer
			Characteristic Present	Characteristic Absent	Characteristic Present	Characteristic Absent	
Any 1 suggestive ultrasound imaging characteristic (microcalcification or solid nodule or size >2 cm)	0.88 (0.80-0.94)	0.44 (0.43-0.45)	2.0 (1.8-2.2)	0.21 (0.19-0.23)	0.018 (0.015-0.022)	0.002 (0.001-0.003)	56 (45-67)
Solid nodule	0.77 (0.68-0.85)	0.32 (0.31-0.33)	2.4 (2.1-2.7)	0.34 (0.30-0.38)	0.021 (0.017-0.027)	0.003 (0.002-0.005)	48 (37-59)
Size >2 cm	0.39 (0.30-0.49)	0.21 (0.20-0.21)	1.9 (1.6-2.3)	0.76 (0.65-0.90)	0.017 (0.012-0.024)	0.007 (0.005-0.009)	59 (42-83)
Microcalcification or solid nodule and >2 cm	0.54 (0.44-0.64)	0.08 (0.08-0.09)	6.7 (5.8-7.7)	0.50 (0.43-0.57)	0.058 (0.044-0.075)	0.005 (0.003-0.006)	17 (13-23)
Any 2 suggestive ultrasound imaging characteristics (microcalcification or solid nodule or size >2 cm)	0.52 (0.42-0.62)	0.07 (0.07-0.08)	7.1 (6.2-8.2)	0.52 (0.45-0.60)	0.062 (0.047-0.080)	0.005 (0.004-0.006)	16 (13-21)
Microcalcification	0.39 (0.30-0.49)	0.04 (0.04-0.05)	9.7 (8.3-11.4)	0.63 (0.54-0.74)	0.082 (0.059-0.110)	0.006 (0.004-0.007)	12 (9-17)
All 3 suggestive ultrasound imaging characteristics (microcalcification and solid nodule and size >2 cm)	0.07 (0.03-0.14)	0.00 (0.00-0.00)	28 (23.0-34.0)[b]	0.93 (0.77-1.10)	1.0 (0.826-1.0)	0.008 (0.007-0.010)	1 (1-1.2)

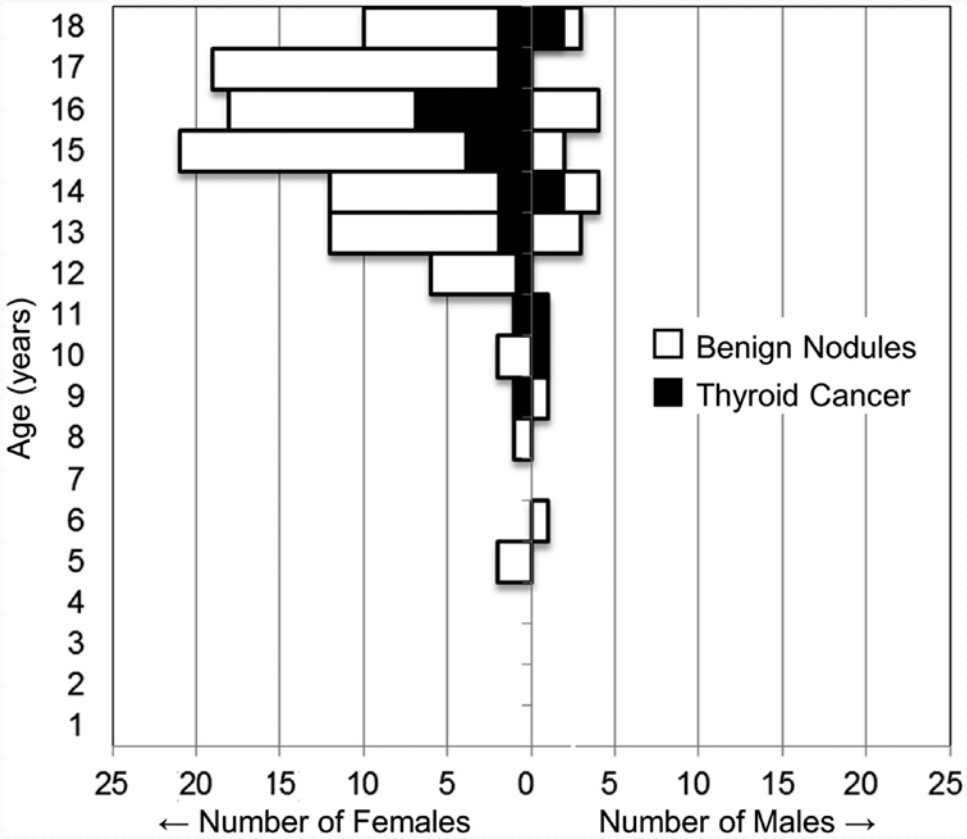
[a] Numbers in parentheses are 95% CIs.

[b] 0.25 Was added to zero cells to calculate accuracy statistics.

Smith-Bindman R, et al JAMA Intern Med Epub ahead of print Aug 13, 2013

Thyroid Cancer Diagnosis: Nodules

Age and gender distribution of benign and cancerous nodules.



Gupta A, et al. JCEM 2013;98:3238-3245

The Journal of Clinical Endocrinology & Metabolism

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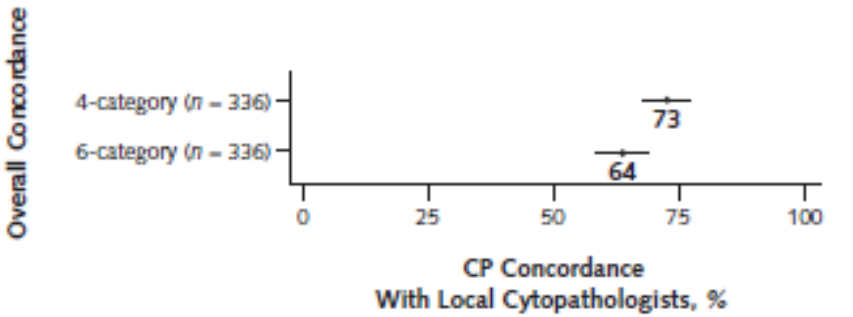
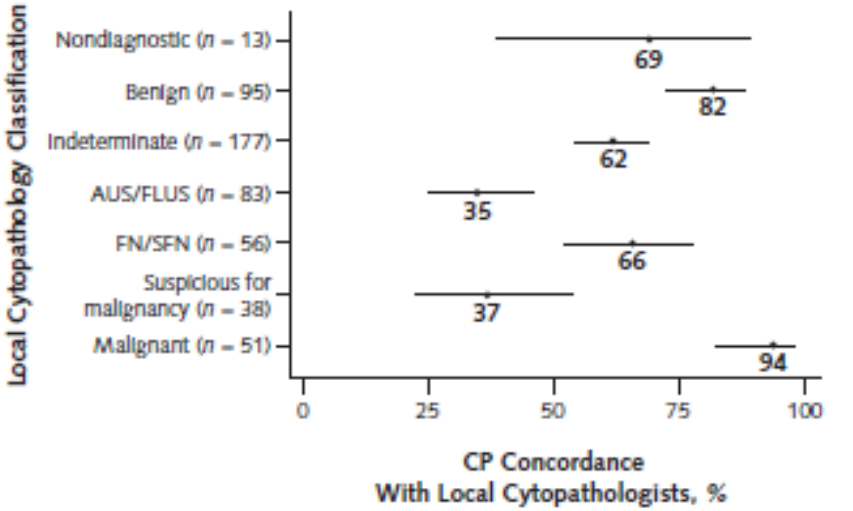
Thyroid Cancer Diagnosis: Nodules

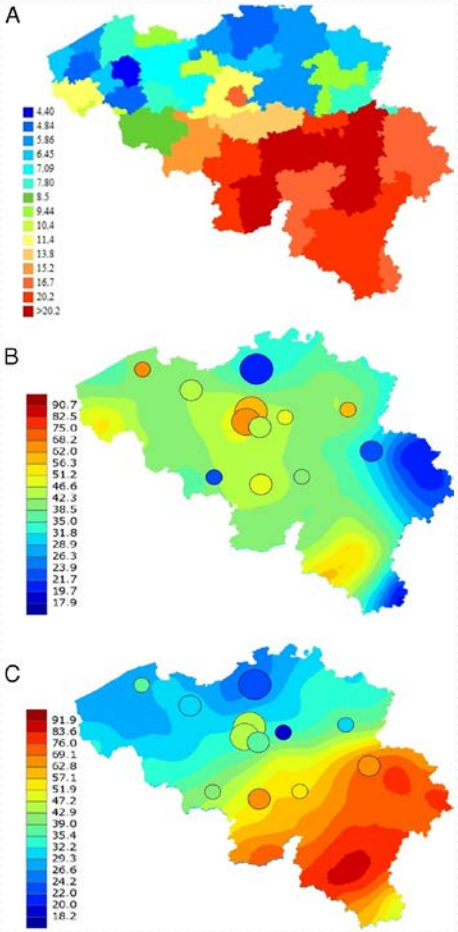
Figure 2. **Interobserver concordance of thyroid FNA cytopathologic diagnoses.**





Cibas ES, et al. Ann Intern Med 2013;159:325-32

Thyroid Cancer Diagnosis: Over diagnosis?

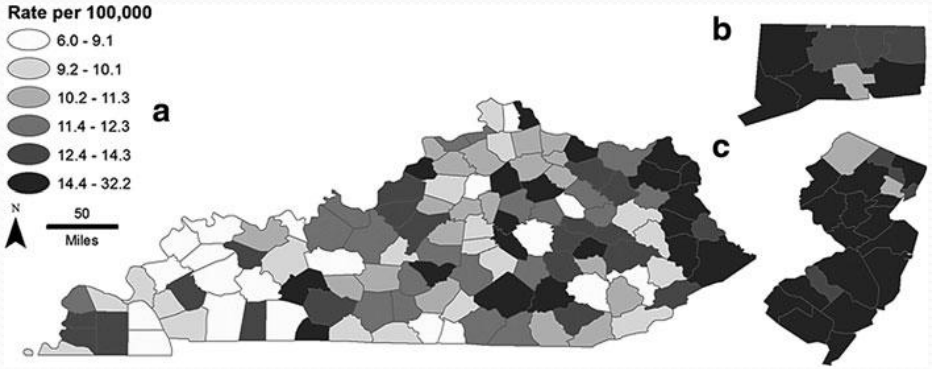


Rates of neck US

Rates of FNA

Rates of Surgery

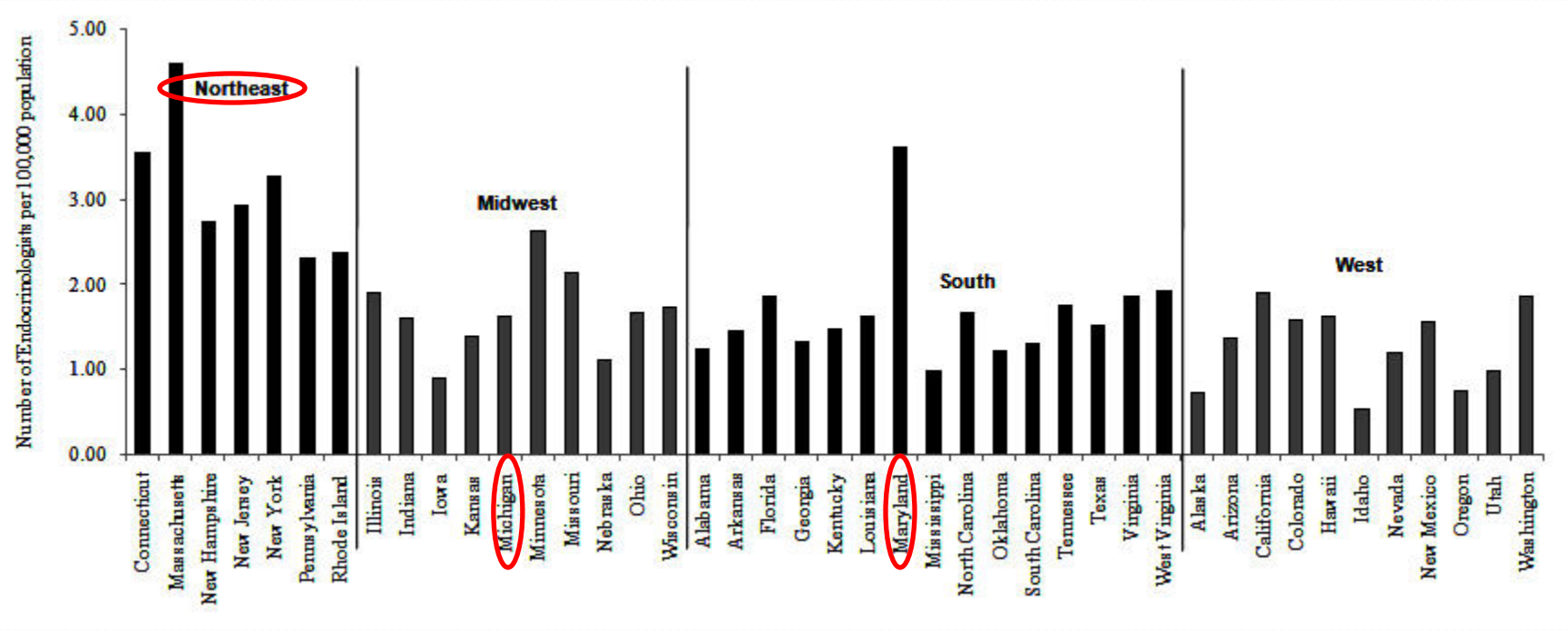
Van den Bruel A. JCEM epub ahead of print Aug 21, 2013



Incidence of PTC: Kentucky, Connecticut, New Jersey

Morris LGT, et al. Thyroid 2013;7:885-889

Thyroid Cancer Diagnosis: Over diagnosis?



Density of endocrinologists

Udelsman R, et al. Thyroid epub ahead of print Aug 12, 2013

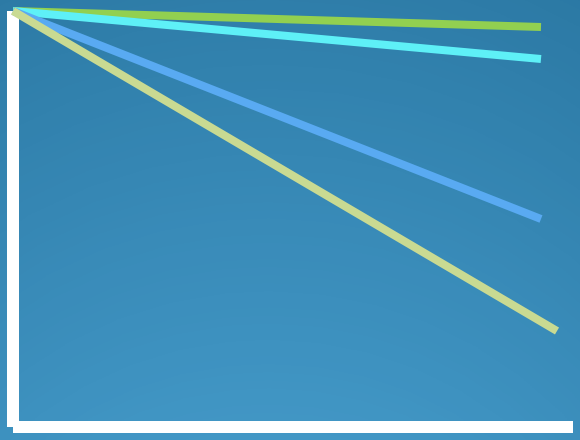
Summary of Studies on Thyroid Cancer Diagnosis

- Recent Development: US criteria may help reduce the number of FNAs we perform.
- Future Challenges: Additional supportive studies are needed.

- Recent Development: US guided FNA is standard for diagnosing thyroid cancer (even in children).
- Future Challenges: There is heterogeneity in cytopathology interpretation. What are the implications?

- Recent Development: There is variation in the incidence of thyroid cancer with correlative studies suggesting over diagnosis
- Future Challenges: These studies are only correlative. How do we establish cause?

Thyroid Cancer Prognosis



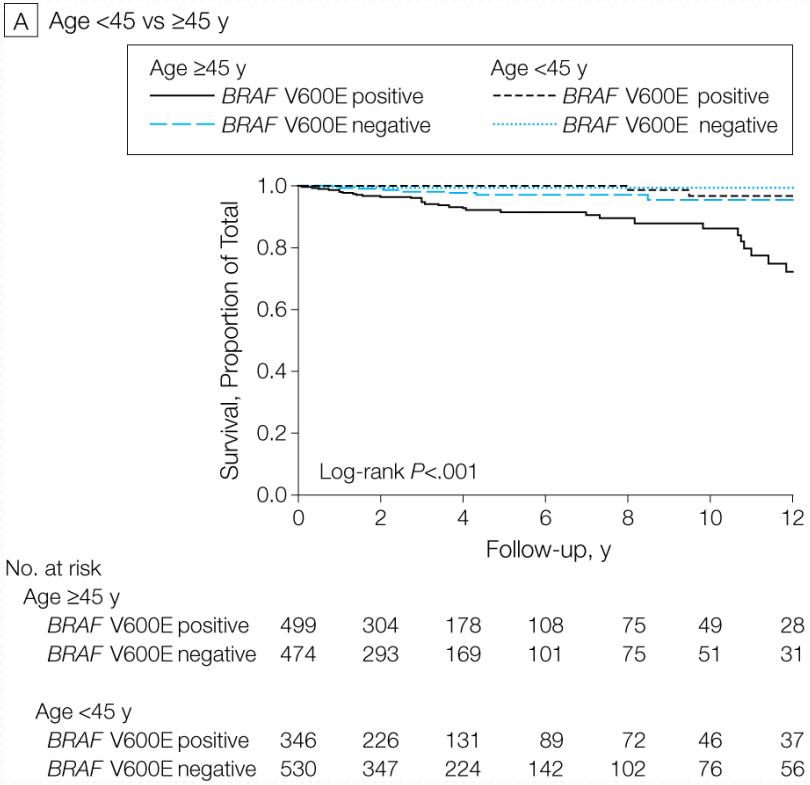
Thyroid Cancer Prognosis: Age and mPTC progression

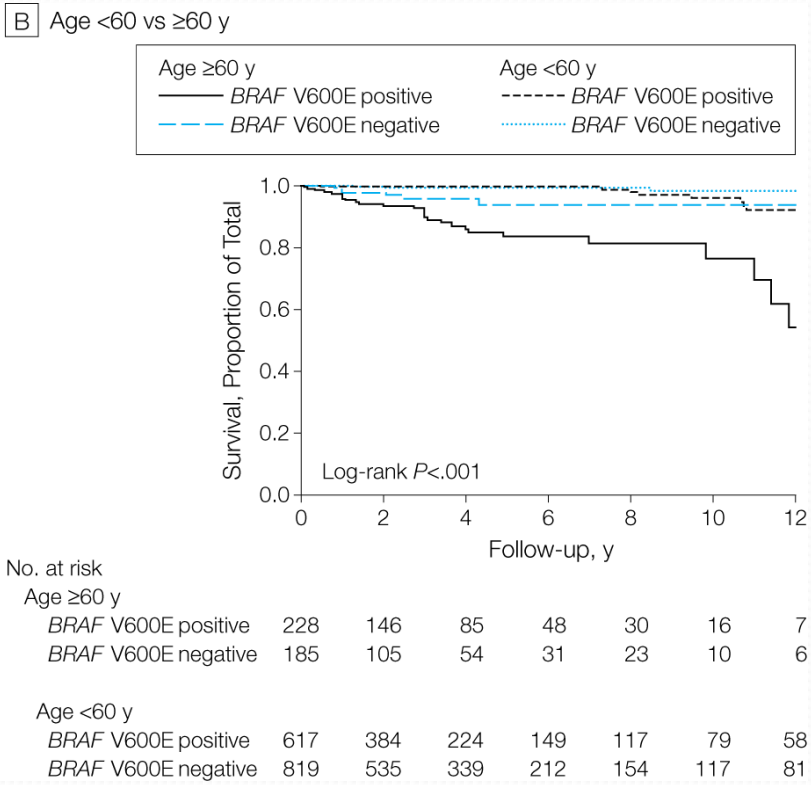
Patient Age	< 40 (N=169)	40-59 (N=570)	≥ 60 (N=496)	Total (N=1,235)
Size increase	14 (5.9%)	33 (5.7%)	11 (2.2%)	58 (p=0.0014)
New LN mets	9 (5.3%)	8 (1.4%)	2 (0.4%)	19 (p<0.0001)
New clinical disease	15 (8.9%)	20 (3.5%)	8 (1.6%)	43 (p<0.0001)

An increase in tumor size was defined of as an increase in size by 3mm or more, 1-2 times/year US was used to detect suspicious lymph nodes and then patients underwent FNA with measurement of thyroglobulin in needle washout, new clinical disease was classified as the tumor size reaching 12 mm or larger OR the appearance of new lymph node metastasis.

Ito Y, et al. Thyroid epub ahead of print Sep 3, 2013

Thyroid Cancer Prognosis: BRAF





Retrospective study of 1849 patients with median follow-up of 33 months. BRAF V600E was associated with increased cancer-related mortality and had an additive interaction with several conventional risk factors, including age. The relationship with mortality was NOT independent of tumor features.

Xing M, et al JAMA 2013;309:1493-1501

Thyroid Cancer Prognosis: BRAF

Controversy over high risk

- 314/429 (73%) with BRAF mutation
- In multivariate analysis BRAF was not significantly associated with high risk features such as larger tumor size, extrathyroidal extension, lymph node involvement, or positive margins

Gouvia C, et al. JAMA Otolaryngol Head and Neck Surg epub ahead of print September 12, 2013

Controversy over CLND

- 388 patients from 4 tertiary endocrine surgery clinics. BRAF + 80% CVPTC , + 40% FVPTC, and + 87% aggressive variant PTC
- For CVPTC- BRAF mutation was not associated with aggressive features including LN mets. There was an association between BRAF and LN mets in FVPTC and aggressive variant PTC

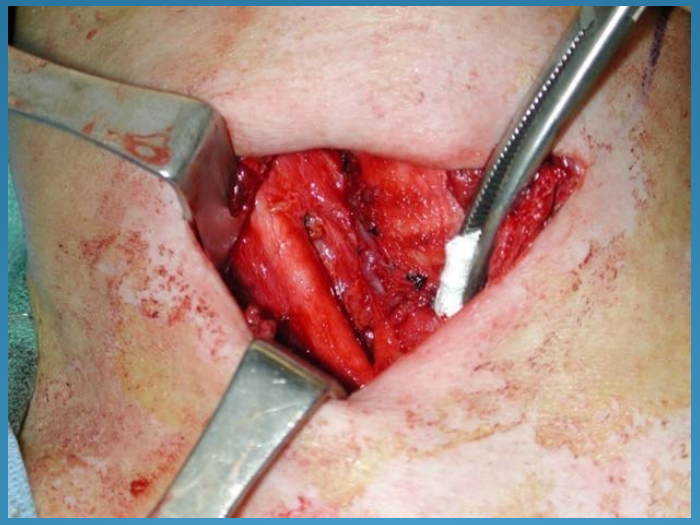
Li C, et al. JCEM 2013;98:3702-3712

Summary of Studies on Thyroid Cancer Prognosis

- Recent Developments: Older patients with small tumors may be more likely to have indolent cancers. BRAF V600E is associated with increased mortality.

- Future Challenges: How do we delineate the indolent disease from the potentially aggressive disease?
- Future Challenges: How to use BRAF V600E in prognostication or in the treatment plan for patients with thyroid cancer remains unclear.

Thyroid Cancer Treatment



Thyroid Cancer Treatment

Compliance with existing guidelines?

- SEER database was used to evaluate compliance with the 2006 ATA guidelines (R26, R27, R32)
- Compliance with all but lymphadenectomy was associated with improved disease specific survival
- Older age was associated with guideline discordance for total thyroidectomy and RAI treatment

Goffredo P, et al. Thyroid
Epub ahead of print Aug 26, 2013

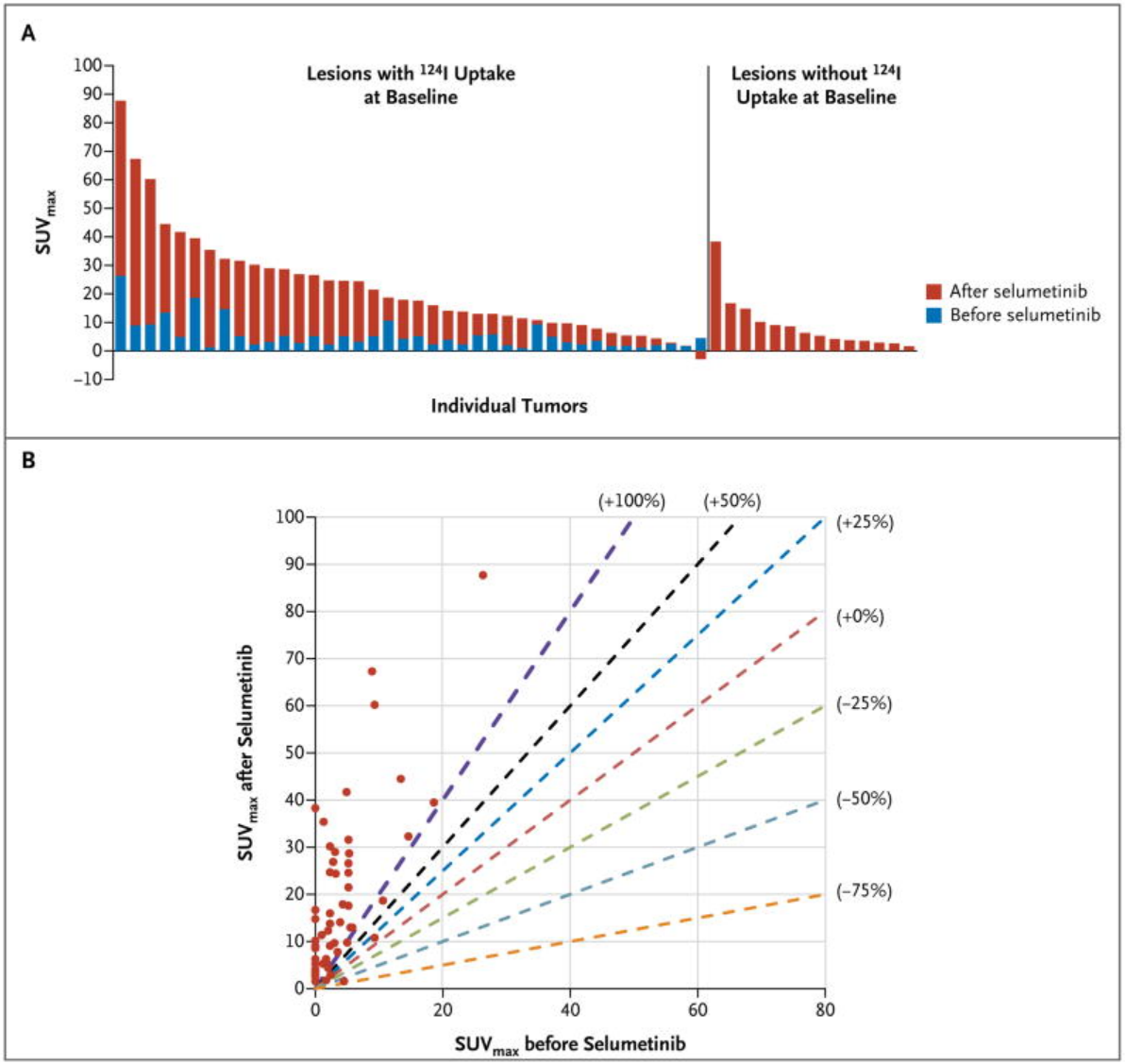
Moving targets?

- T1 or T2NOMO WDTC (N=107)
- One group received RAI a median of 3 months post op (<4.7 months) and a second group received RAI a median of 6 months post surgery (4.8-30 months)
- Long term outcome (median follow up 87 months) didn't differ

Tsirona S, et al. Clinical Endocrinology
Epub ahead of print July 29, 2013

Thyroid Cancer Treatment

Selumetinib -Enhanced RAI Uptake in Advanced Thyroid Cancer



Ho AL, et al NEJM 2013;368:623-632

Thyroid Cancer Treatment

Cabozantinib for progressive MTC

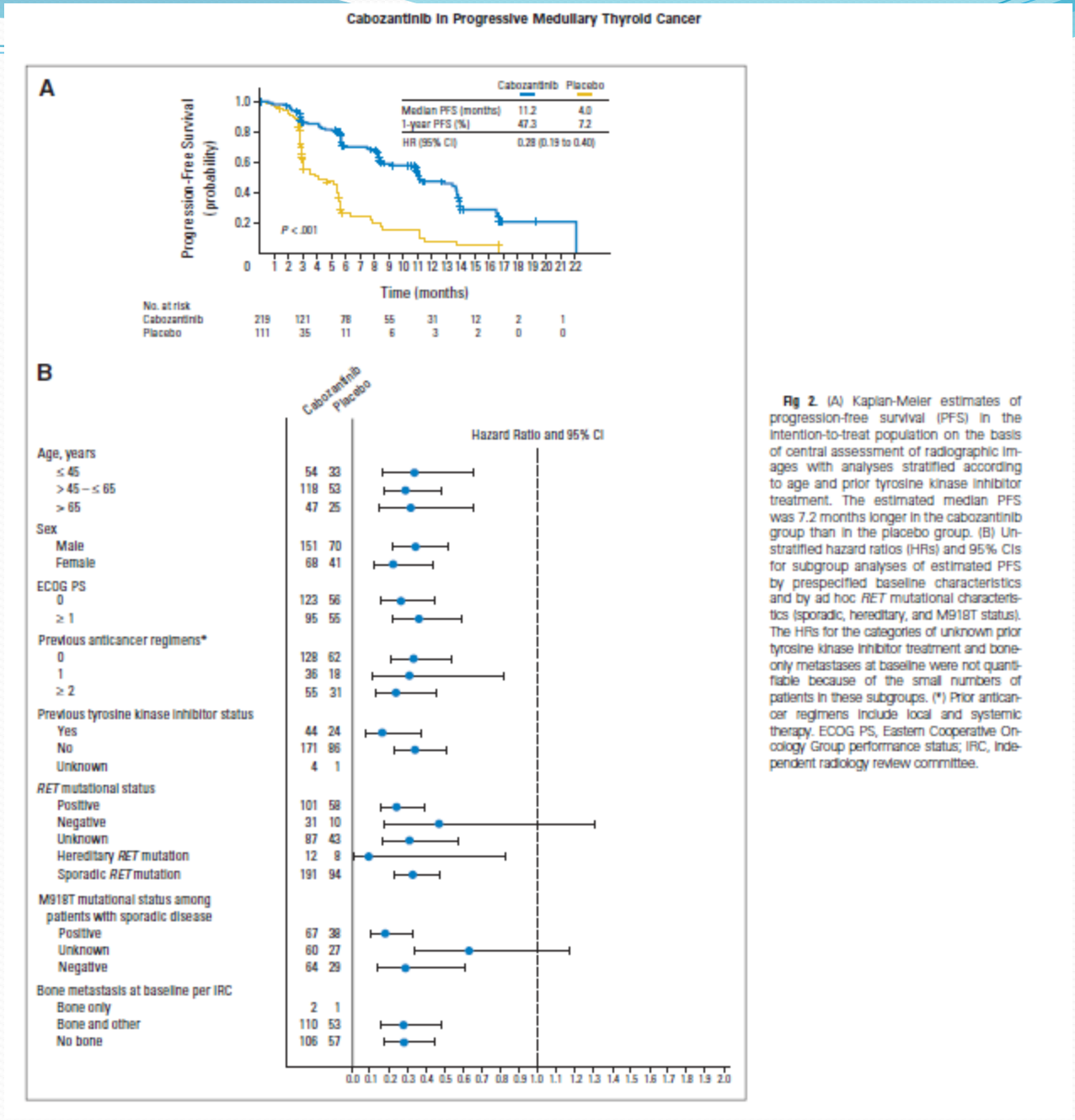
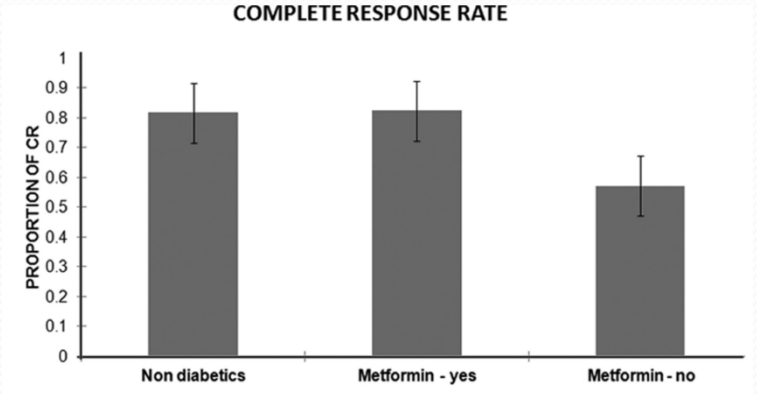


Fig 2. (A) Kaplan-Meier estimates of progression-free survival (PFS) in the intention-to-treat population on the basis of central assessment of radiographic images with analyses stratified according to age and prior tyrosine kinase inhibitor treatment. The estimated median PFS was 7.2 months longer in the cabozantinib group than in the placebo group. (B) Unstratified hazard ratios (HRs) and 95% CIs for subgroup analyses of estimated PFS by prespecified baseline characteristics and by ad hoc *RET* mutational characteristics (sporadic, hereditary, and M918T status). The HRs for the categories of unknown prior tyrosine kinase inhibitor treatment and bone-only metastases at baseline were not quantifiable because of the small numbers of patients in these subgroups. (*) Prior anticancer regimens include local and systemic therapy. ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, Independent radiology review committee.

Elisei R, et al. JCO Epub ahead of print Sept 2013

Thyroid Cancer Treatment

- Retrospective study: 34 pts with diabetes and thyroid cancer on metformin v. 21 diabetics with thyroid cancer not on metformin v. 185 non-diabetics with thyroid cancer
- Those NOT treated with metformin had larger tumors and decreased likelihood of complete response
- In vitro data supportive of findings



Group	Proportion of CR (%)	SD	P value (vs metformin	P value (vs non-metformin)	Overall p value
Non-diabetics	81.6%	38.8%	0.921	0.009	
Metformin	82.4%	38.7%	-	0.044	
No metformin	57.1%	50.7%	0.044	-	0.029

Klubo-Gwiedzinska et al JCEM 2013;98:3269-3279

Summary of Studies on Thyroid Cancer Treatment

- Recent Developments: Certain patient groups, such as older patients, have increased risks for guideline discordance.

- Future Challenges: Optimal treatment of thyroid cancer is a moving target.

- Future Challenges: We need more treatment options for high risk thyroid cancer patients.

Thyroid Cancer Follow-up

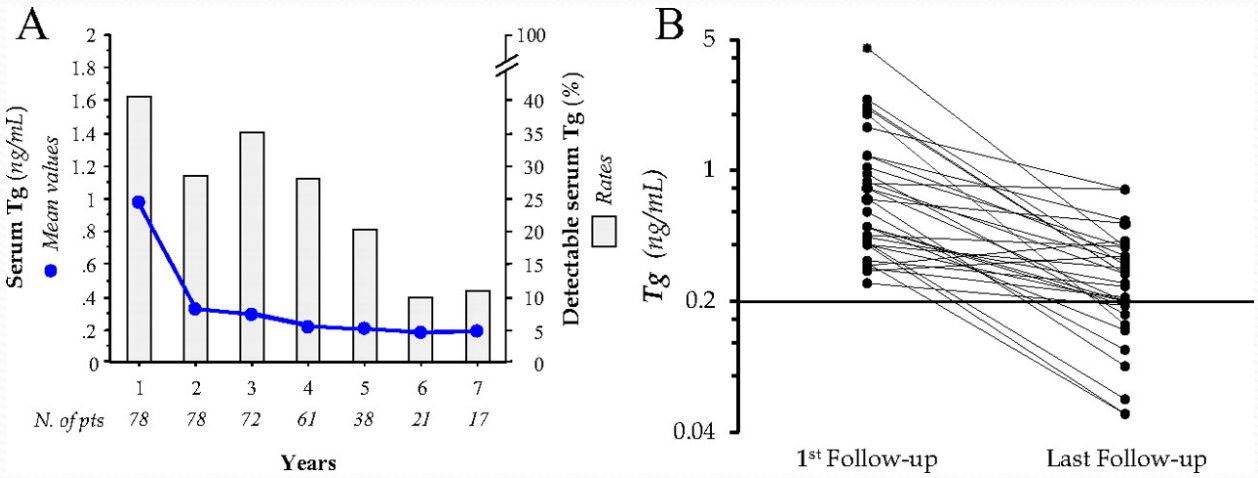
Thyroid Cancer Follow-up: Tg if no RAI

- 290 pts. with no lymph node mets followed w/o RAI post surg
- 495 control patients who received RAI post surg
- Median 5 yr f/u: 95% with undetectable tg if no RAI v. 99% if RAI. One tg + pt. with visible recurrence.

Durante C, et al. JCEM 2012; 97:2748-2753

- 86 pts. with no RAI post surgery
- 96% with no antibodies with tg < 2 ng/ml two years post op. One patient with tg = 11 ng/ml and recurrence. 10 pts with + antibodies and antibodies decreased or became undetectable in 6/7 pts followed.

Nascimento C, et al. EJE epub ahead of print Aug 12, 2013

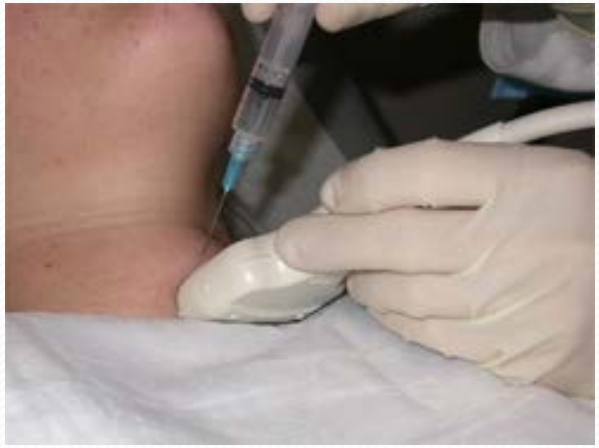


Thyroid Cancer Follow-up: Recurrence

- 948 pts. from 8 hospitals with no evidence of disease
- Follow-up was a median of 10 years
- 1.4% with recurrence in cervical lymph nodes
- All recurrence occurred within 8 years post diagnosis
- Recurrence was unrelated to RAI use

Durante C, et al. JCEM 2013;98:636-642

Thyroid Cancer Follow-up: Lymph node FNA



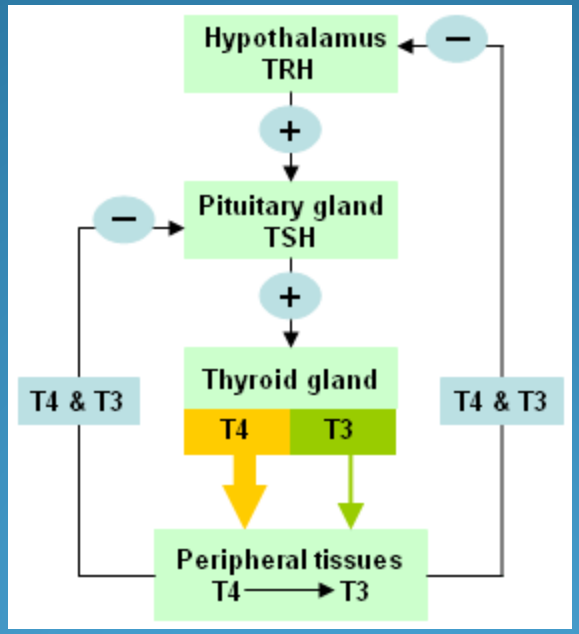
- Retrospective study of 528 cases of FNA-tg measurements
- Area under curve showed optimal cutoff value of FNA-tg = 1.0 ng/ml
- FNA-tg + cytopathology read had the best diagnostic power (98% sensitivity, 94% specificity)

Moon JH, et al. JCEM 2013;98:1061-8

Summary of Thyroid Cancer Follow-up

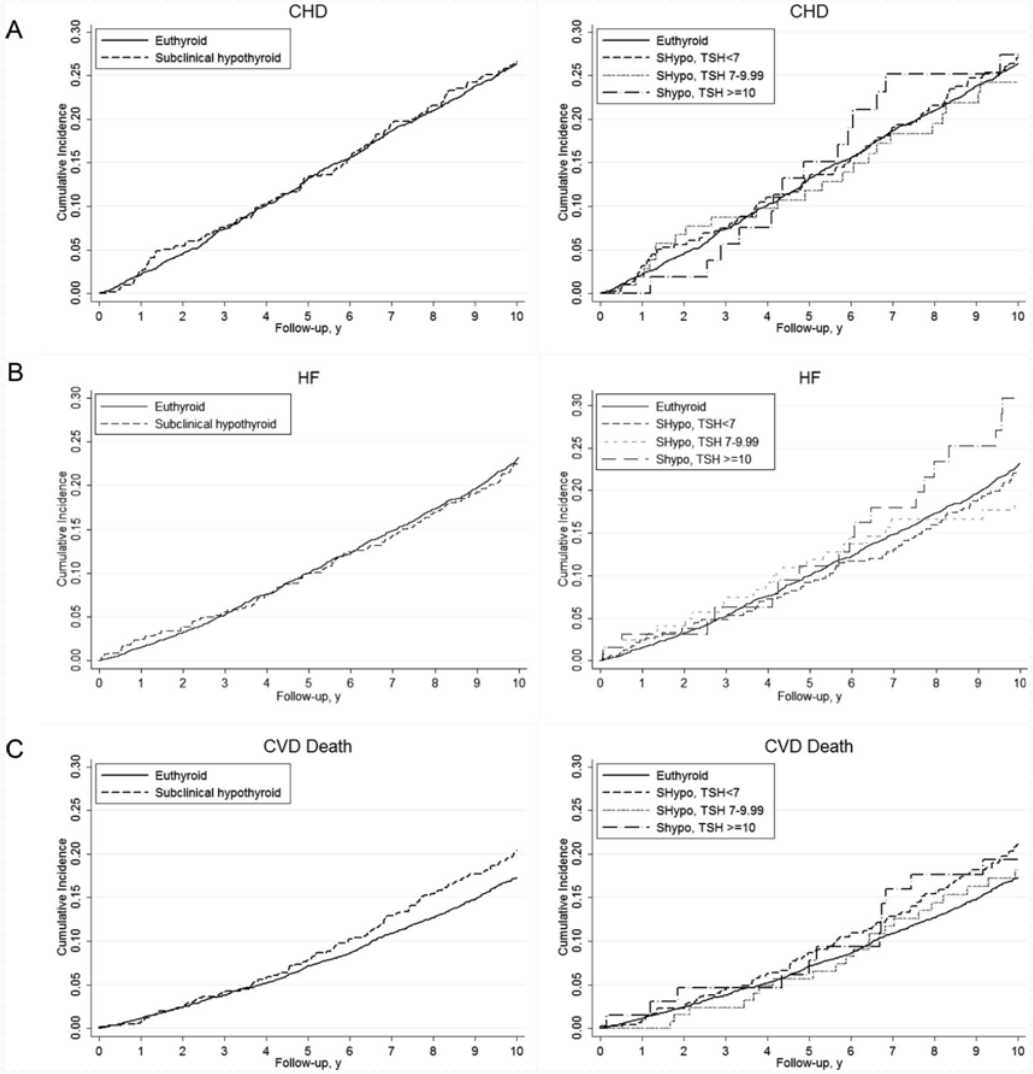
- Recent Developments: Thyroglobulin is low or undetectable in most low risk patients who do not receive RAI. It also decreases over time.
- Recent Developments: Few patients without evidence of persistent disease post initial treatment will have recurrence.
- Recent Developments: Cytopathology plus thyroglobulin wash-out (tg <1.0 ng/ml) is optimal.
- Future Challenges: Studies involving long-term thyroid cancer follow-up will help confirm appropriate management.

Thyroid Function



Thyroid Function: Older Adults

No increased risk of death (CHD, HF, CV)in older adults with subclinical hypothyroidism



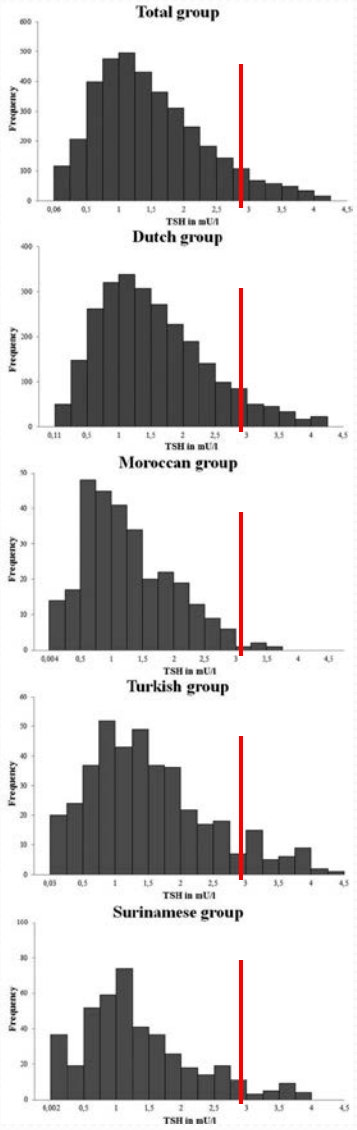
Hyland KA, et al. JCEM 2013;98:533-40

Thyroid Function: Older Adults

- 843 pts in the Cardiovascular Health Study All Stars Study (mean age 85 yr)
- Over 13 years the oldest of old had an increase in TSH, slight increase in fT4 and decrease in TT3
- TSH level did not affect mortality
- Higher fT4 was associated with death
- Conclusion: mild elevations in TSH in older adult pts may not need treatment

Waring AC, et al. JCEM 2012; 97:3944-50.

Thyroid Function: Pregnancy



- Upper TSH range in first trimester is 2.5 mIU/L and second and third trimester is 3.0 mIU/L with the total population reference range
- 3944 women (2765 Dutch, 308 Moroccan, 421 Turkish, 450 Surinamese)
- 279 women found to have abnormal thyroid function tests with the population based reference range (normal= 2.5-97.5%). 18% were reclassified when ethnic specific reference ranges were used (44 normal, 7 a different disease)

Korevaar T I M, et al. JCEM 2013;98:3678-3686

Thyroid Function: Pregnancy

- 4039 children with information on autistic symptoms at age 6 and with a maternal fT4 level measured.
- Severe maternal hypothyroxinemia = 3.4% of population (N=136) with fT4 < 10.99 pmol/L (<5%)
- 80 children with probable autism. Odds of autism (adjusted OR 3.89 (1.83-8.2) when mother had severe hypothyroxinemia in early pregnancy.

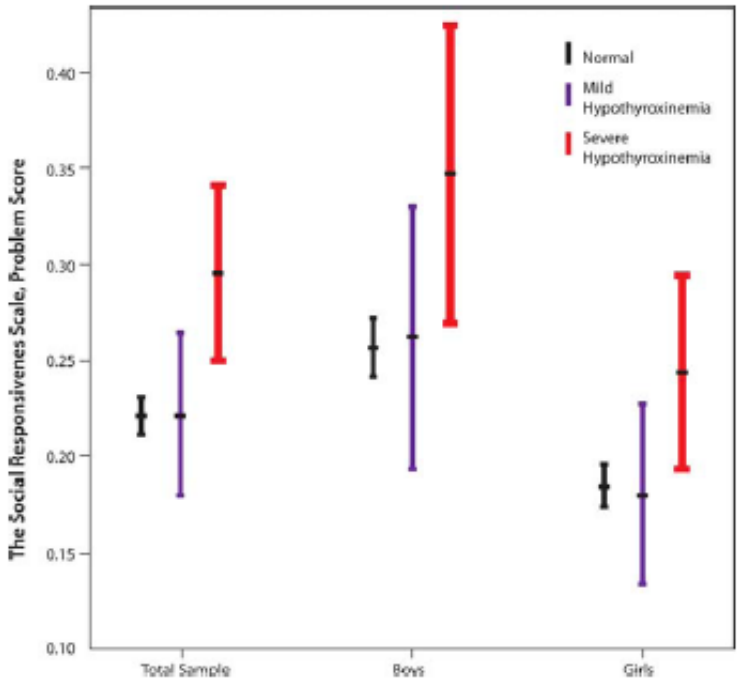


FIGURE 2: Maternal hypothyroxinemia in early pregnancy and autistic symptoms in the children at age 6 years.

Roman GC, et al. Ann Neurol Epub ahead of print Aug 2013

Summary of Thyroid Function

- Recent Developments: Mild elevations of TSH in older adults may not need treatment.
- Recent Developments: There may be ethnic differences in TSH reference ranges during pregnancy. Low fT4 in pregnancy may be related to neurocognitive conditions, such as autism.
- Future Challenges: Are there clinical implications if we apply population based goal TSH parameters to different ethnic/age groups? If low fT4 is associated with neurocognitive problems, will raising fT4 result in improved outcomes?

Thank you

- Thank you to the program chairs for the invitation to present "Recent Developments and Future Challenges in Thyroidology: Clinical Endocrine Review".
- Thank you to the thyroid research community for the rich, broad clinical research in the past year.