Old and New Tools in Clinical Practice

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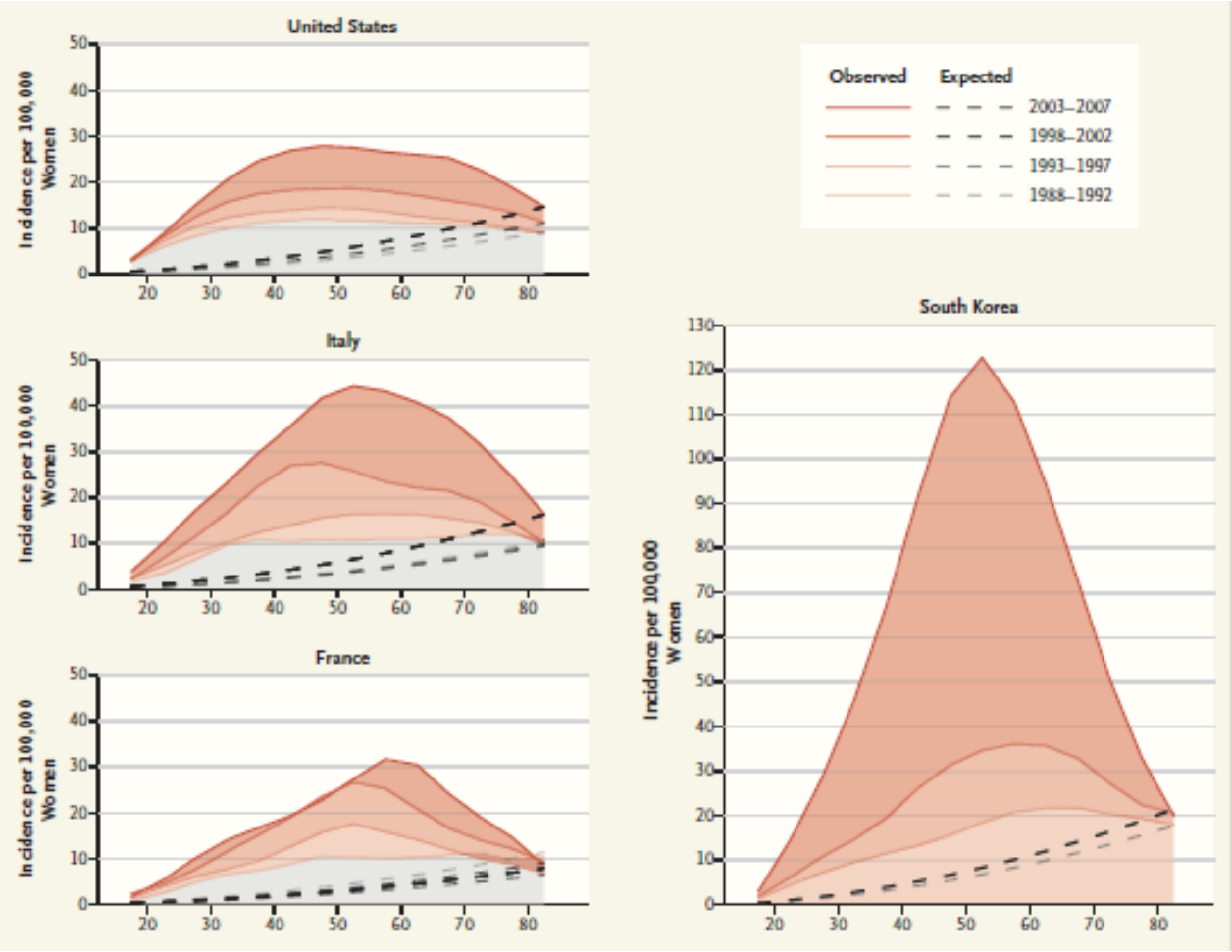
Disclosure of interests

None

Overall prevalence of Thyroid nodules

China	49%
USA	67%
Germany	68%
Finland	27%
Turkey	51%
Italy	33%

Worldwide Thyroid-Cancer Epidemic? The Increasing Impact of Overdiagnosis



We know everything about the problem of microPTC overdiagnosis and overtreatment…

Vaccarella et al., N Engl J M ed 375;7 , 2016

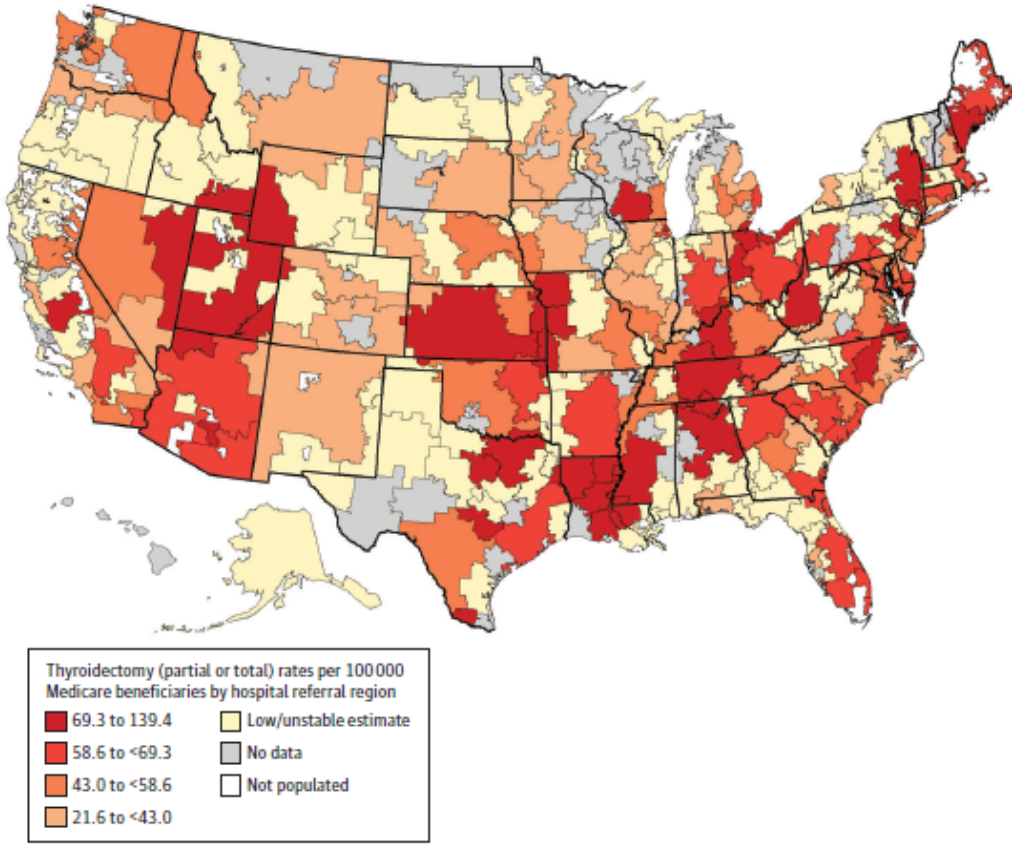
When we come to the overwhelming number of benign nodules…

Too many Thyroidectomies

- **Over 37.000** Thyroidectomies in 2014
- **Less than 10.000** due to malignancy

- About **60,000** Thyroidectomies and hemithyroidectomies yearly performed
- **Nontoxic nodular goiter** is the indication in **36 %** of cases

Nationwide Variation in Rates of Thyroidectomy



- A 6.2-fold difference in Tx rates across US suggests widely divergent practice patterns in the management of thyroid nodules and cancer .
- Rates are unrelated to health care availability, regional socioeconomic status, or surgeons per capita.

Francis et al. JAMA Otolaryngol Head Neck Surg. 2017;143(11):1122-1125.

Outline

- **State of the art**
- **A two-step approach** in the management of benign thyroid nodules
- **Totem und Tabu** in the management of thyroid nodules
- How to **choose the right treatment**
- **THMs**

A Two-step approach

1°Turning point:
Does our patient need a treatment for his/her thyroid nodule(s)?

2°Turning point:
Which treatment best suits our patient and his/her nodule?

The 3 major factors treatment for benign thyroid nodules

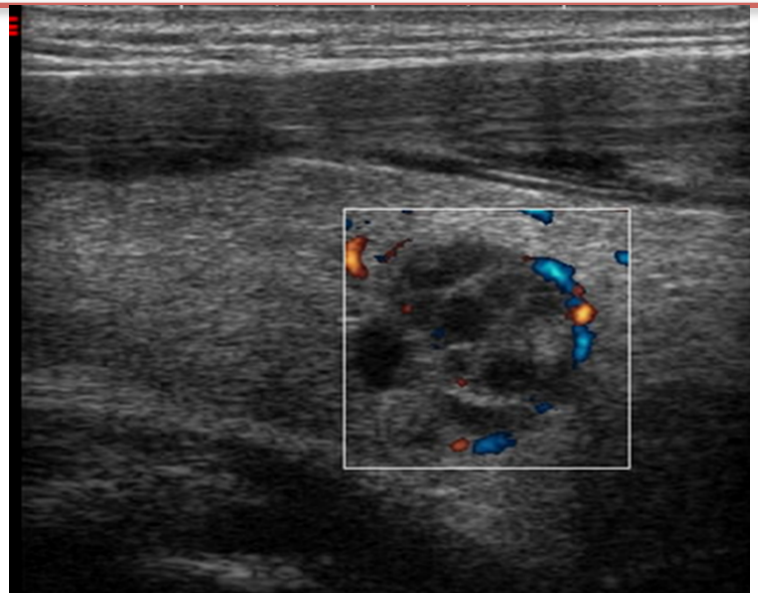
- **Enlargement causing symptoms**
- **Risk of Malignancy**
- (Subclinical) Hyperfunction

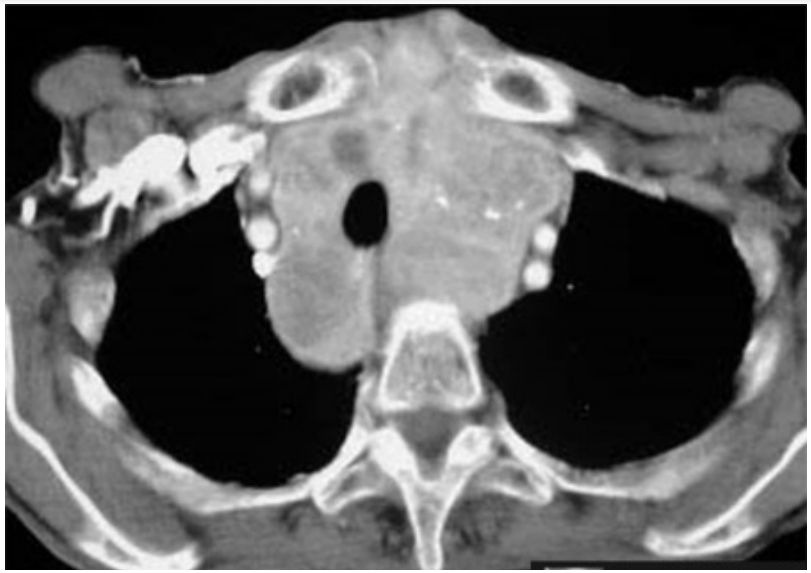
Symptoms are frequent in large goiters

	≤200 gr (600 pts)	200-400 gr (108 pts)	400-600gr (36 pts)	> 600 gr (9pts)
Gland weight (gr)	73.5 ± 51.3	275 ± 4.8	492.7 ± 63.4	1027.6 ± 417
Compressive symptoms (%)	14.4	36.1	52.8	44.4
Dysphagia (%)	7.9	21.3	27.8	22.2
Hoarseness (%)	7.3	22.2	25	22.2
Respiratory distress (%)	10.5	37.0	50.0	44.4
Severe respiratory distress (%)	2.0	10.2	25.0	33.3
Tracheal compression (%)	2.9	24.1	55.6	88.9
Tracheal deviation (%)	36.1	63.0	97.2	100
Tracheomalacia (%)	2.1	10.2	27.8	77.8

Agarwal et al. World J Surg (2012) 36:755–760

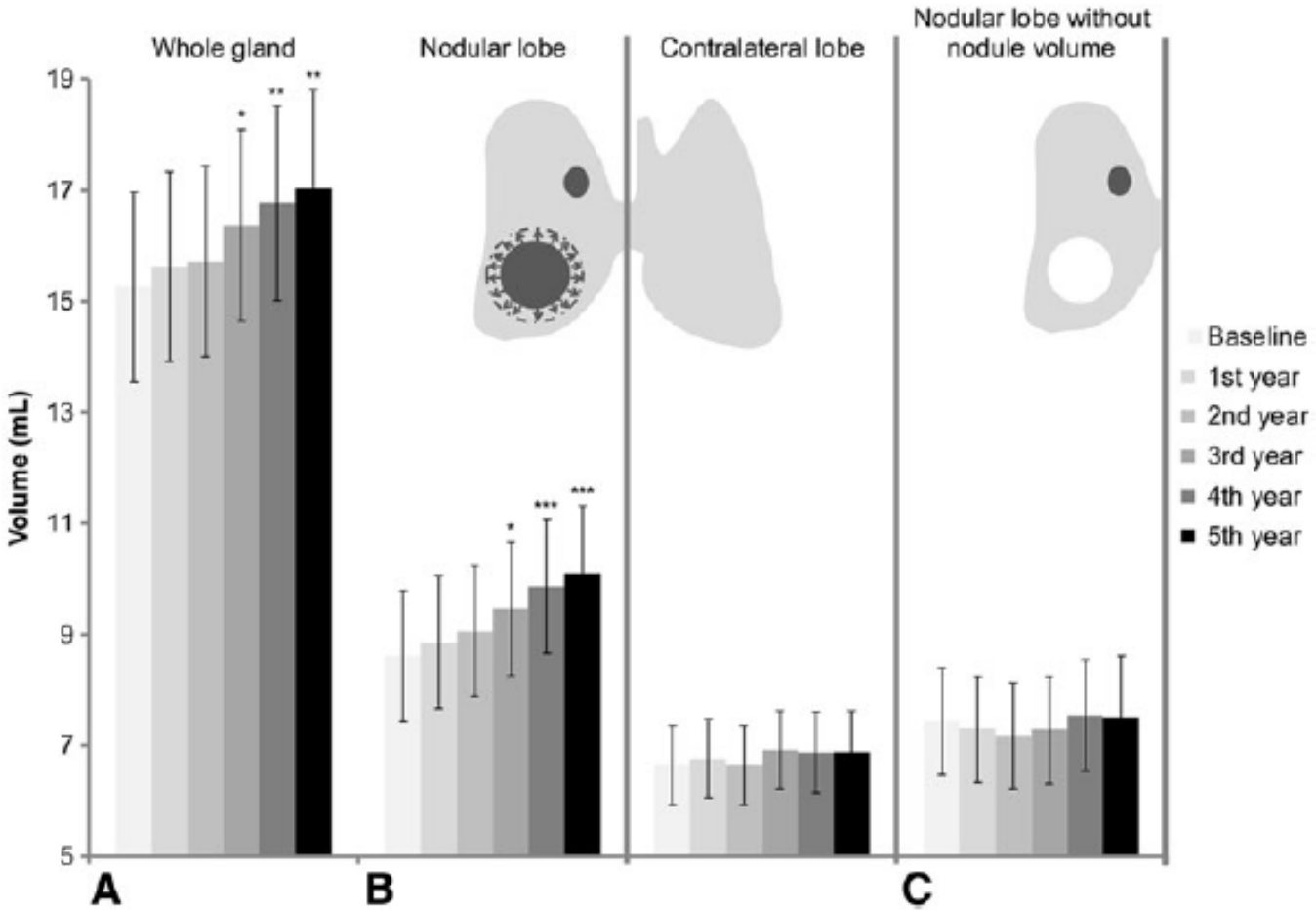
NTS vs. MNG: Definitions do matter!





- A thyroid gland of normal size showing single or multiple nodules should be defined as **Nodular Thyroid disease (NTD) or Uni/multinodular Thyroid gland**
- The definition of **Multinodular goiter (MNG**) indicates a structurally and functionally heterogeneous thyroid enlargement

Temporal Changes in Thyroid Nodule Volume



Grani et al. THYROID Volume 27, Number 11, 2017

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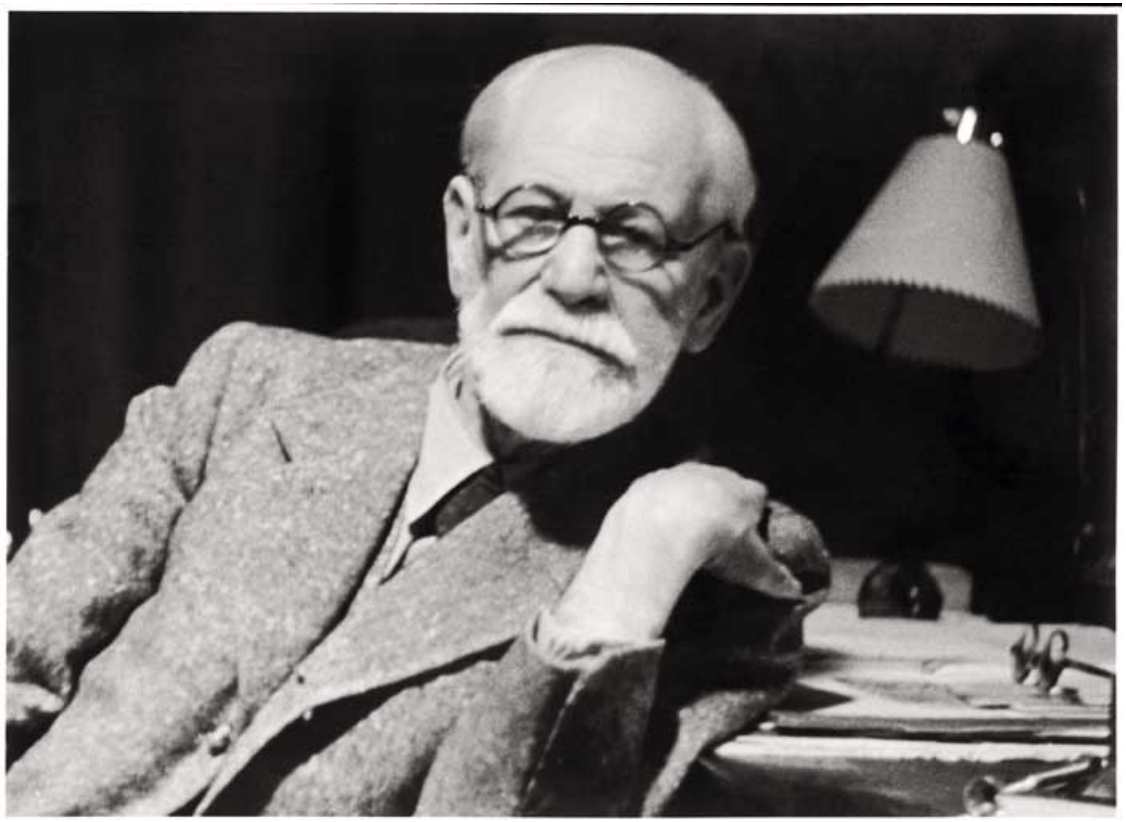


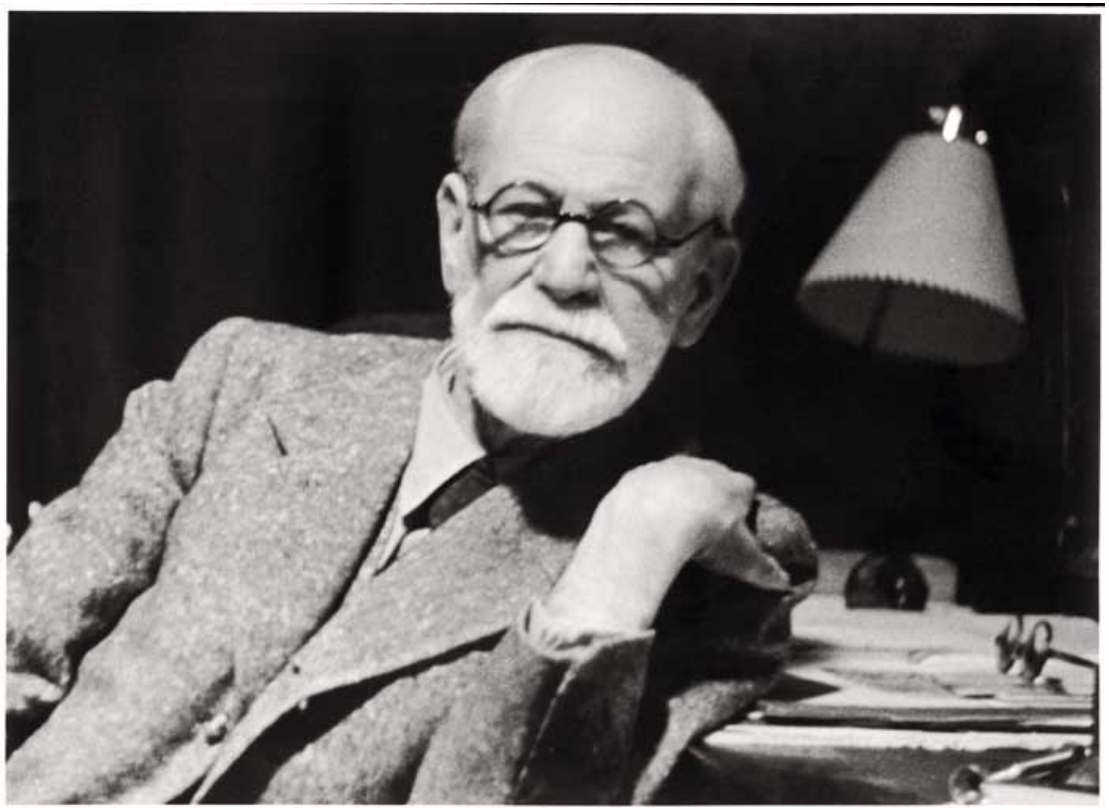
Totem und Tabu 1.

Soon or after, all thyroid nodules will grow…

Long-term follow-up of benign nodules

- **Nodule growth** occurred in **11.1%** (174/1567) nodules, 15.4% (153/992) patients
- Mean diameter increase = **4.9 mm** (13.2-18.1 mm)
- **75.8%** (1188) nodules remained **stable** (655 pts = 66.0%)
- **13.1%** (205) nodules **shrank** (184 pts =18.5%)

Durante et al., JAMA. 2015;313(9):926-935



Totem und Tabu 2.
Thyroid nodules which grow are more likely to be malignant…

Is an Increase in Thyroid Nodule Volume a Risk Factor for Malignancy?

196 Growing FNAC-diagnosed benign nodules

→ **2** malignancies (1%).

346 Operated for reasons other than nodular growth

→ **16** malignancies (4.6%).

Nodule growth itself is not a risk factor for malignancy.

Nakamura et al., THYROID Volume 25, Number 7, 2015

What Is the Appropriate Follow-Up Strategy for Benign thyroid nodules?

- 263 patients
- 48 patients underwent surgery
- 215 patients were followed with annual US
- 89 (41.3%) nodules underwent repeat FNA

Significant numbers of benign thyroid nodules enlarge more than 5 mm over 3 years, triggering repeat FNA or thyroidectomy. Larger diameter nodules and more rapidly growing nodules were not predictive of malignancy.

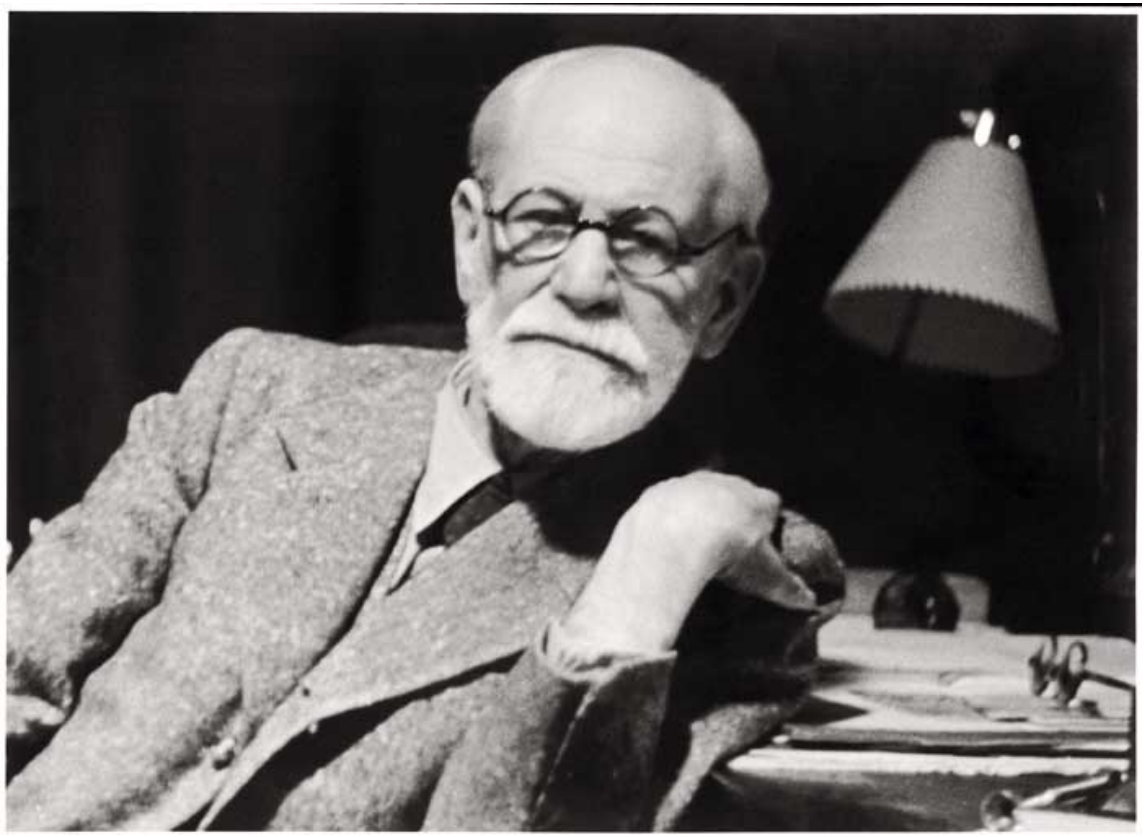
Ajmal et al. J Am Coll Surg 2015, 220:987-992.

Thyroid Nodule Size and Prediction of Cancer

Nodule Size	No. of Nodules	No. Cancerous (%)	*P*
1.0–1.9 cm	3621	383 (11)	<.01
≥2.0 cm	3727	544 (15)	
2.0–2.9 cm	1956	265 (14)	
3.0–3.9 cm	998	163 (16)	.14
≥4.0 cm	773	116 (15)	

5000 patients with over 7000 thyroid nodules

Kamran et al., J Clin Endocrinol Metab. 2013;98(2):564-570



Totem und Tabu 3.

To what extent a benign FNA result is reliable in the long term…?

Repeat FNA: is it worthwile?

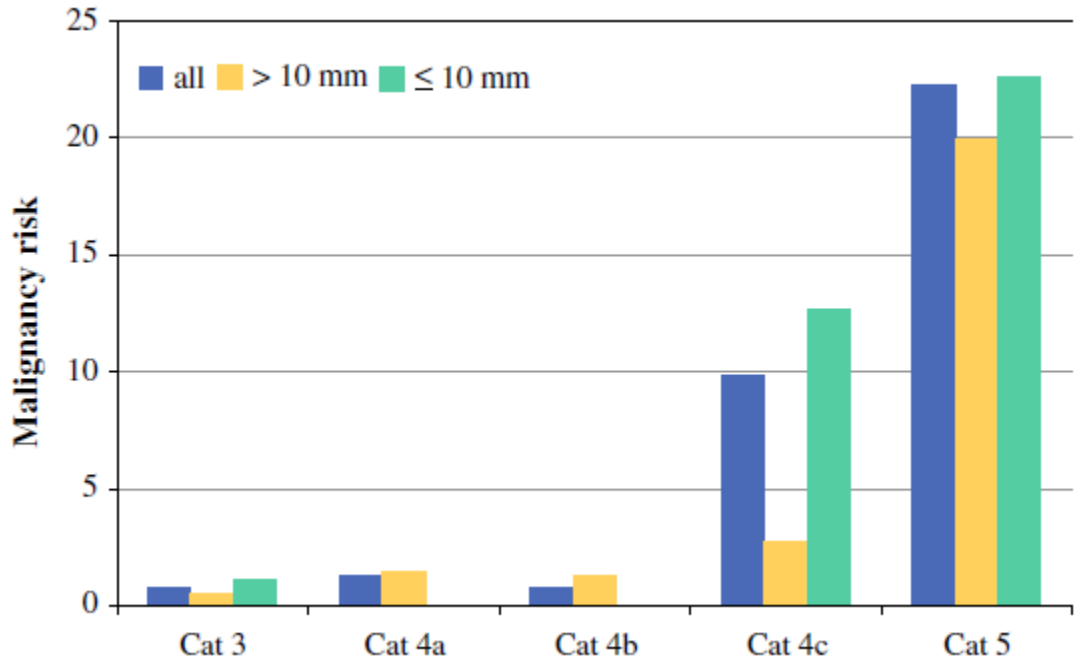
	Thy 2	THY 3	THY 4	THY 5	Total
N.	**4353**	**236**	**29**	**60**	**4678**
%	**93.0**	**5.0**	**0.6**	**1.2**	

2000-2015 = 31469 patients submitted to FNA
26157 patients with benign FNA results (Thy2)
4678 (= 17.8%) at least 2 FNA
4353 confirmed Thy2 result
325 (= 6.8%) Thy 3-4-5 result

Chance of a worrisome "second" FNA result in a large population of patients with cytologically benign thyroid nodules

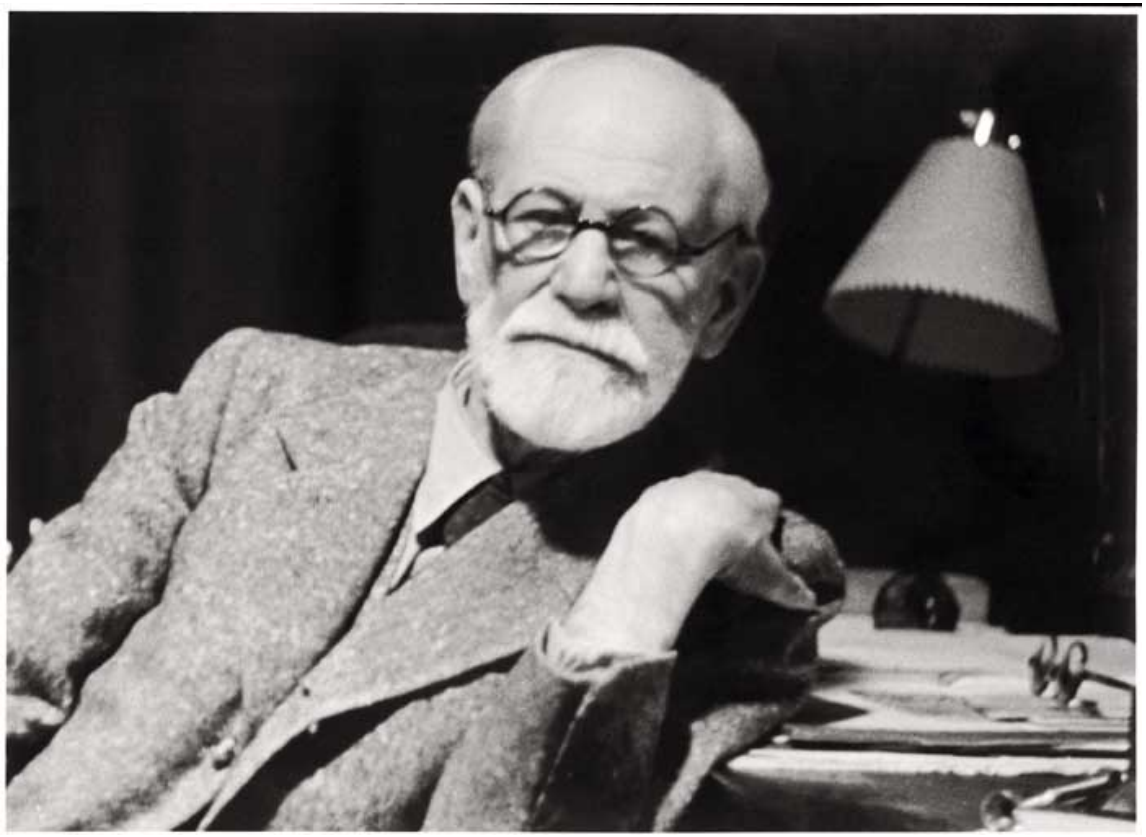
~ 1.0%

Malignancy Risk Stratification in Thyroid Nodules with Benign FNA



Overall malignancy risk = 3.1 % (43/1398 thyroid nodules),.
Low-risk US categories (3-4a-4b): 0.7, 1.2 , and 0.7 (4b) %
High-risk US categories (4c -5): 9.8 and 22.2 %

Moon et al. Ann Surg Oncol (2014) 21:1898–1903



Totem und Tabu 4.

Large thyroid nodules may be malignant, irrespectively of a benign FNA…

False negative FNA rates in large size thyroid nodules

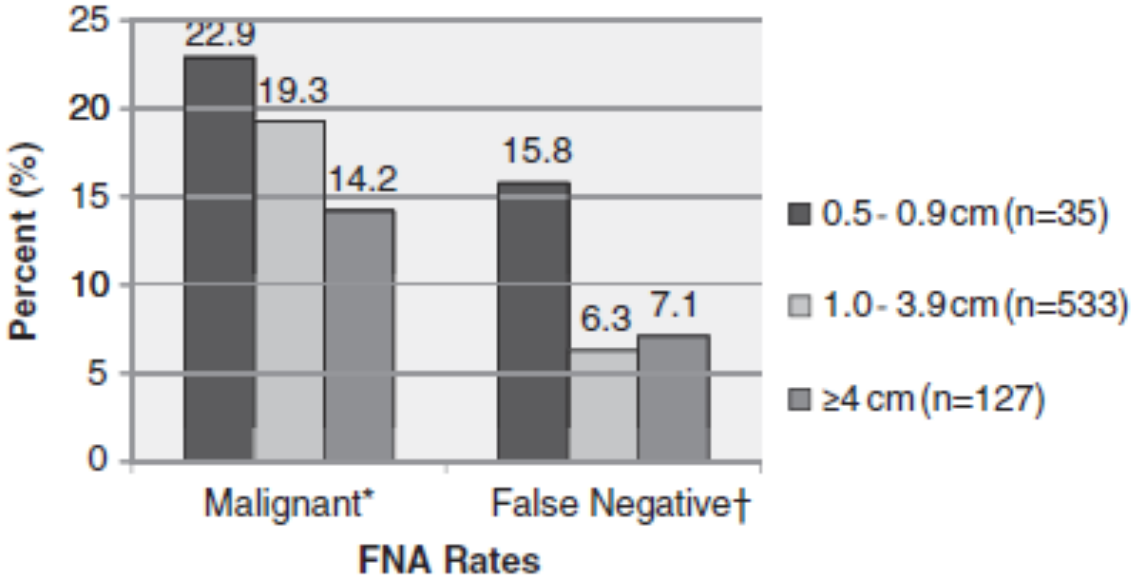
Author (Ref. No.)	Year	Size criteria	Number of nodules with benign FNA*	Number of nodules with malignancy	False-negative rate (%)	Recommendation
Meko and Norton (19)	1995	≥3	16	4	25.0	Surgery
Carrillo (10)	2000	≥4	35	7	20.0	Close follow up or repeat FNA
		<4	39	2	5.1	
McCoy (11)	2007	≥4	71	9	12.7	Surgery
Giles (13)	2015	≥3	240	28	11.7	Surgery
		≥4	146	16	11.0	
Wharry (25)	2014	≥4	125	13	10.4	Surgery
Pinchot (9)	2009	≥4	52	4	7.7	Surgery
Albuja-Cruz (8)	2013	≥4	113	17	15	Not indication for surgery
		<4	209	25	12	
Mehanna (12)	2013	≥3	55	6	10.9	Not indication for surgery
		<3	33	2	6.1	
Shrestha (23)	2012	≥4	98	7	7.1	Not indication for surgery
		<4	319	22	6.9	
Kuru (21)	2010	≥4	98	4	4.3	N/A†
		<4	319	4	1.3	
Rosario (20)	2009	≥4	84	3	3.6	Not indication for surgery
Yoon (26)	2011	≥3	112 (558[a])	2	1.8 (0.4[b])	Not indication for surgery
Raj (24)	2012	≥4	118	1	0.8	Not indication for surgery
Porterfield (22)	2008	≥3	145 (694[a])	1	0.7 (0.1[b])	Not indication for surgery
Present study		≥3	164 (632[a])	22	13.4 (3.6[b])	Surgery considering US features

*FNA, fine-needle aspiration

†N/A not applicable

Nam et al., PLOS ONE October 12, 2017

The Impact of Thyroid Nodule Size on the Risk of Malignancy and Accuracy of FNA



- Nodule size ≥ 4 cm is neither associated with an increased risk of false-negative results nor an increased overall risk of malignancy.

- Large nodule size should not prompt automatic referral for thyroidectomy.

Shresta et al., THYROID : vol 22, Number 12, 2012

False-negative FNA in large nodules?

	1.0-1.9 cm	2.0-2.9 cm	3.0-3.9 cm	≥ 4 cm
False negative FNA	1.1%	0.7%	1.5%	1.3%

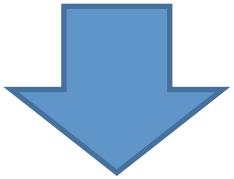
A large nodule (even if cytologically benign) may require resection based on cosmetic, symptomatic, or clinical concerns alone. This approach remains reasonable, although such a recommendation given to a patient with a nonmalignant, low-risk lesion must be weighed against the small but not inconsequential risk of surgical complications

Kamran et al., JCE&M Volume 98, Issue 2, 1 February 2013

False-negative FNA in large nodules?

Limitations	Point of strenght
Retrospective study Single Institution Small number pts (85)	Systematic (all patients operated on regardless of FNA results)

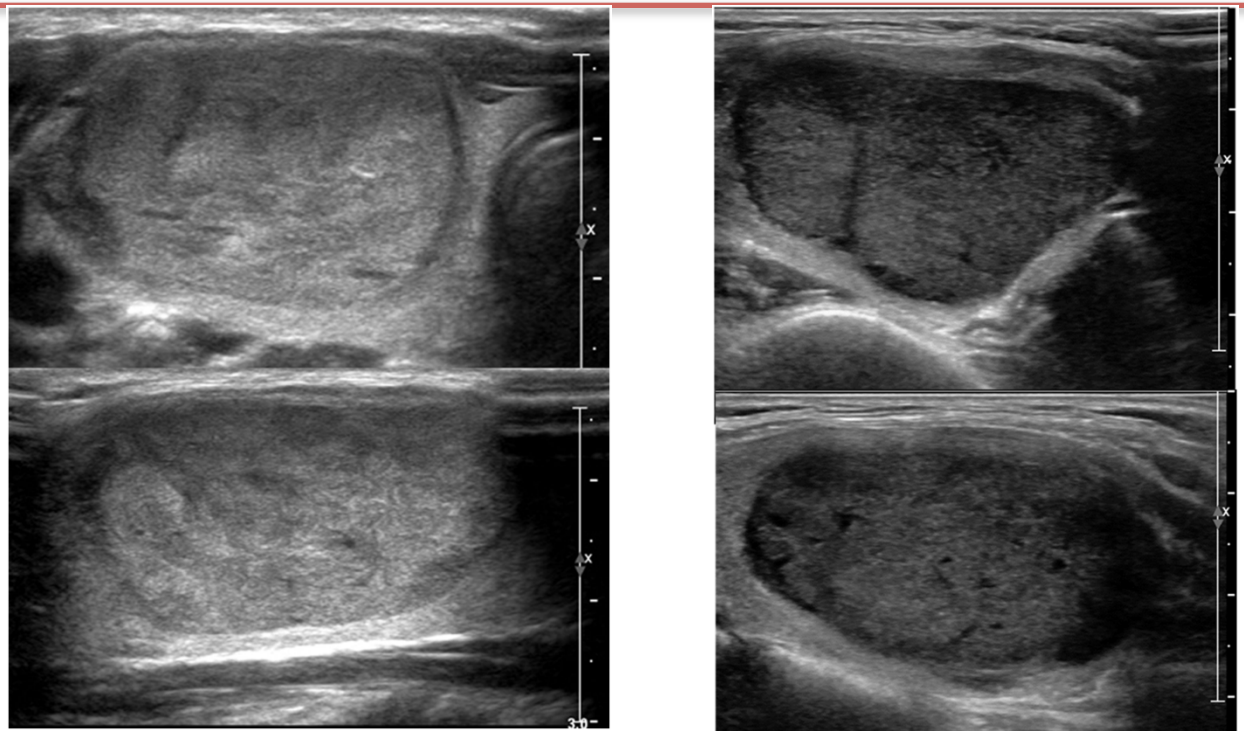
1. FNAC false negative rate of 0%, a NPV of 100%,
2. Post-test probability of malignancy for nodules ≥4 cm with benign FNAC = 0%



Patients with thyroid nodules ≥4 cm and benign FNAC should not automatically undergo thyroidectomy

Megwalu UC et al. Endocrinol Metab . 2017 Mar;32(1):77-82.

TIRADS helps predicting false negative cytology in large nodules



632 thyroid nodules ≥ 3 cm; 23 (3.6%) malignant (Minimally invasive FTC 15/23; PTC follicular variant 6/23). The malignancy risks of US categories 3, 4a, 4b, and 4c nodules were 0.9%, 4.6%, 10.0%, and 11.8%, respectively

Nam et al., PLOS ONE October 12, 2017

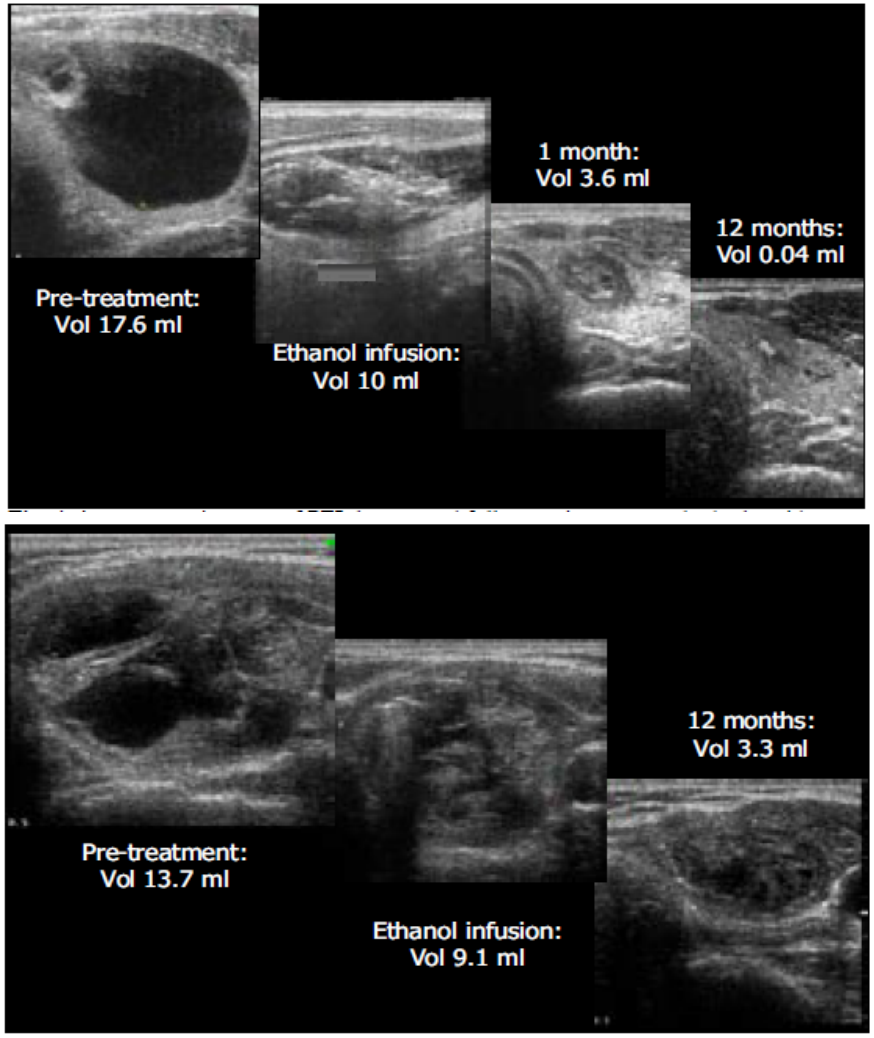
2° Turning point

Which treatment best suits our patient and his/her nodule?

Factors to be taken into account:

- **Patient's values, expectations (and fears)**
- **Patient's age and clinical history**
- **Local expertise**
- **Thyroid nodule size and texture**
- **US risk of malignancy**
- **Thyroid function**

PEI results in "pure" cysts and in "mixed" thyroid nodules

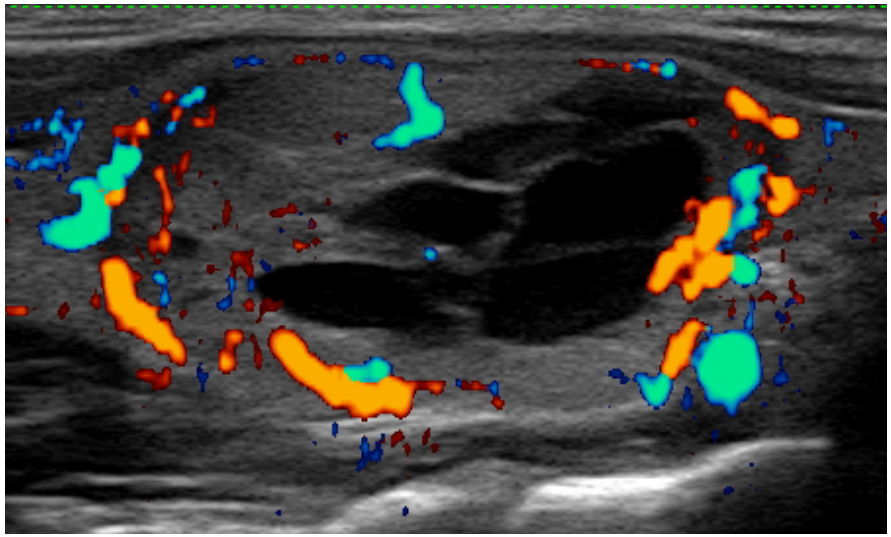


Median nodule volume reduction after PEI

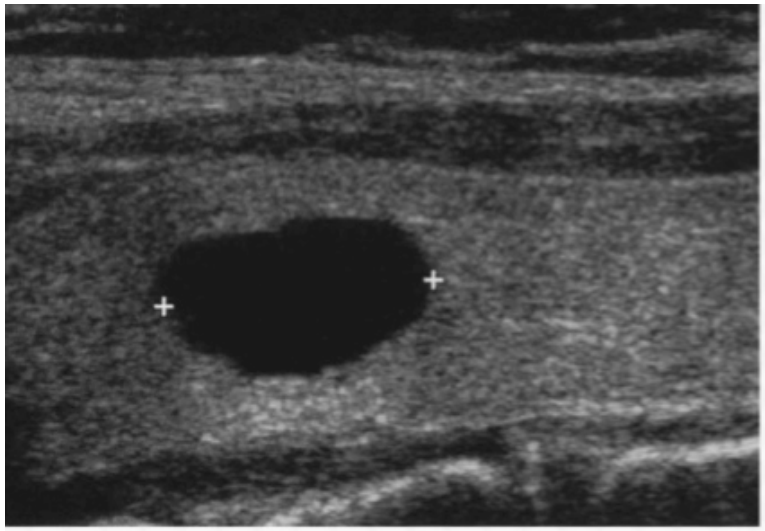
88.8% empty body cysts

65.8% mixed nodules

Valcavi, Endocr Pract. 2004;10(No. 3)



A



B

Would you consider PEI for these nodules?

No

Only for nodule A

Only for nodule B

Yes , for both nodules

Comparative Efficacy of Radiofrequency and Laser Ablation

Pooled percentage and absolute mean volume changes (95% confidence interval) reported

RFA	**77.8% (67.7–88.0)**	**9.2 mL (5.8–11.9)**
LA	**49.5% (26.7–72.4)**	**5.3 mL (2.1–8.5)**

No major complications after either RFA or LA.
RFA appears to be superior to LA in reducing benign solid thyroid nodule volume, despite the smaller number of treatment sessions without major side effects.

Ha et al. J Clin Endocrinol Metab. 2015 100(5):1903-11

Laser vs. RF ablation for the treatment of benign thyroid nodules

601 nodules treated at 8 centres (May 2009 – Dec 2014)
LA 449 (309 females, age 57 ± 14 years)
RF 152 (107 females, age 57 ± 14 years)
A matched cohort composed of 138 patients from each group was selected after adjustment with propensity score matching.

	6 months (%)	12 months
LA	-67 ± 19	-70 ± 19
RF	-57± 21	-62± 22

Major complications occurred in 4 cases in each group
LA and RFA showed nearly similar outcome but LA was slightly more effective than RFA in large nodules

Pacella et al., Int J Hyperthermia. 2017 Dec;33(8):911-91

Indications for RF ablation in thyroid pathology: Italian Opinion Statement

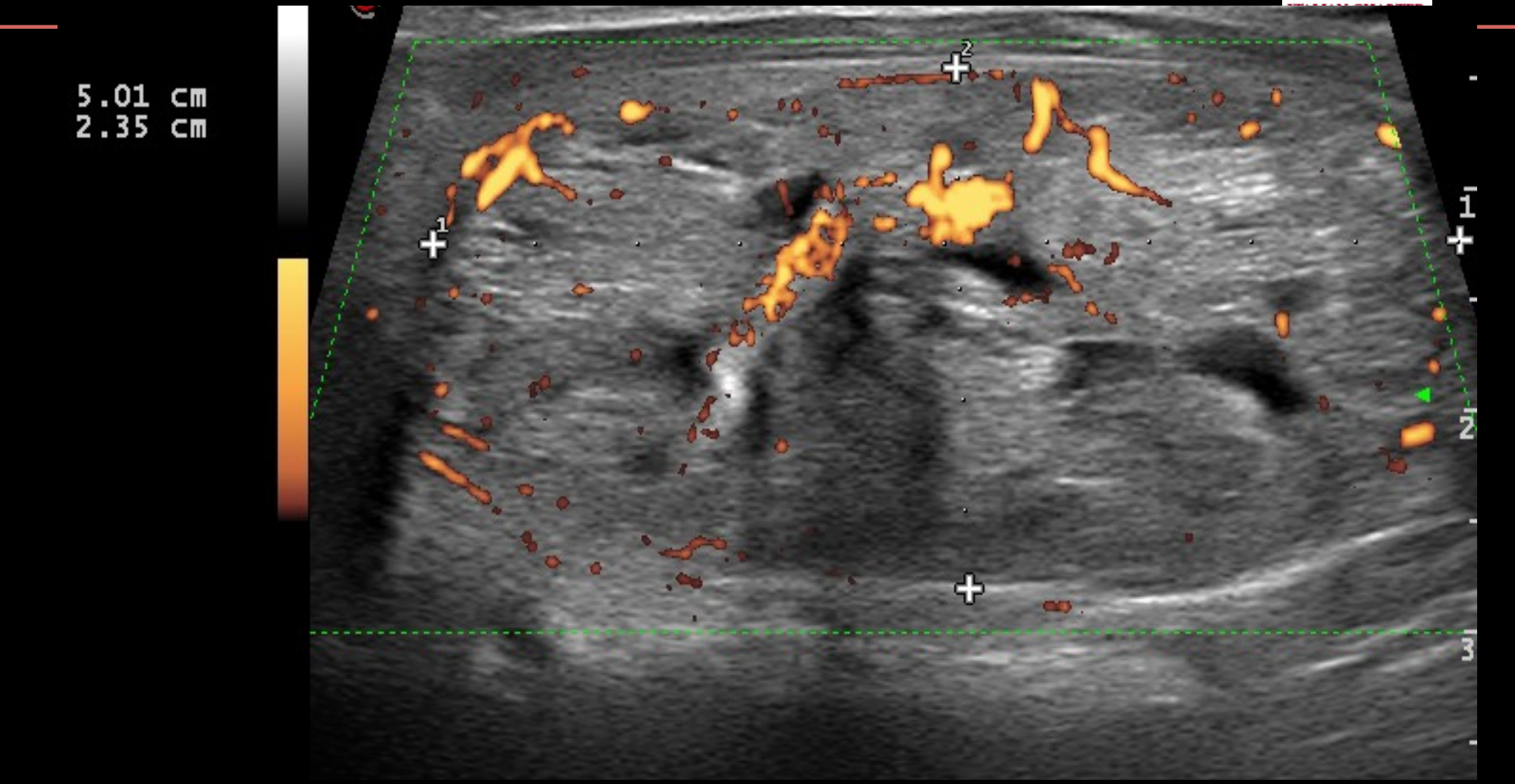
- Large (volume ≥20 ml), nonfunctioning, benign thyroid nodules in patients with local symptoms or cosmetic complaints when surgery is contraindicated or declined.
- Autonomously functioning thyroid nodules (AFTN), hot/warm at scintiscan, either toxic or pretoxic, when surgery and radioiodine are contraindicated or declined.
- Palliative therapy for recurrent thyroid cancers in the neck when surgery is contraindicated and radioiodine is ineffective

Garberoglio et al., J Ultrasound (2015) 18:423–430

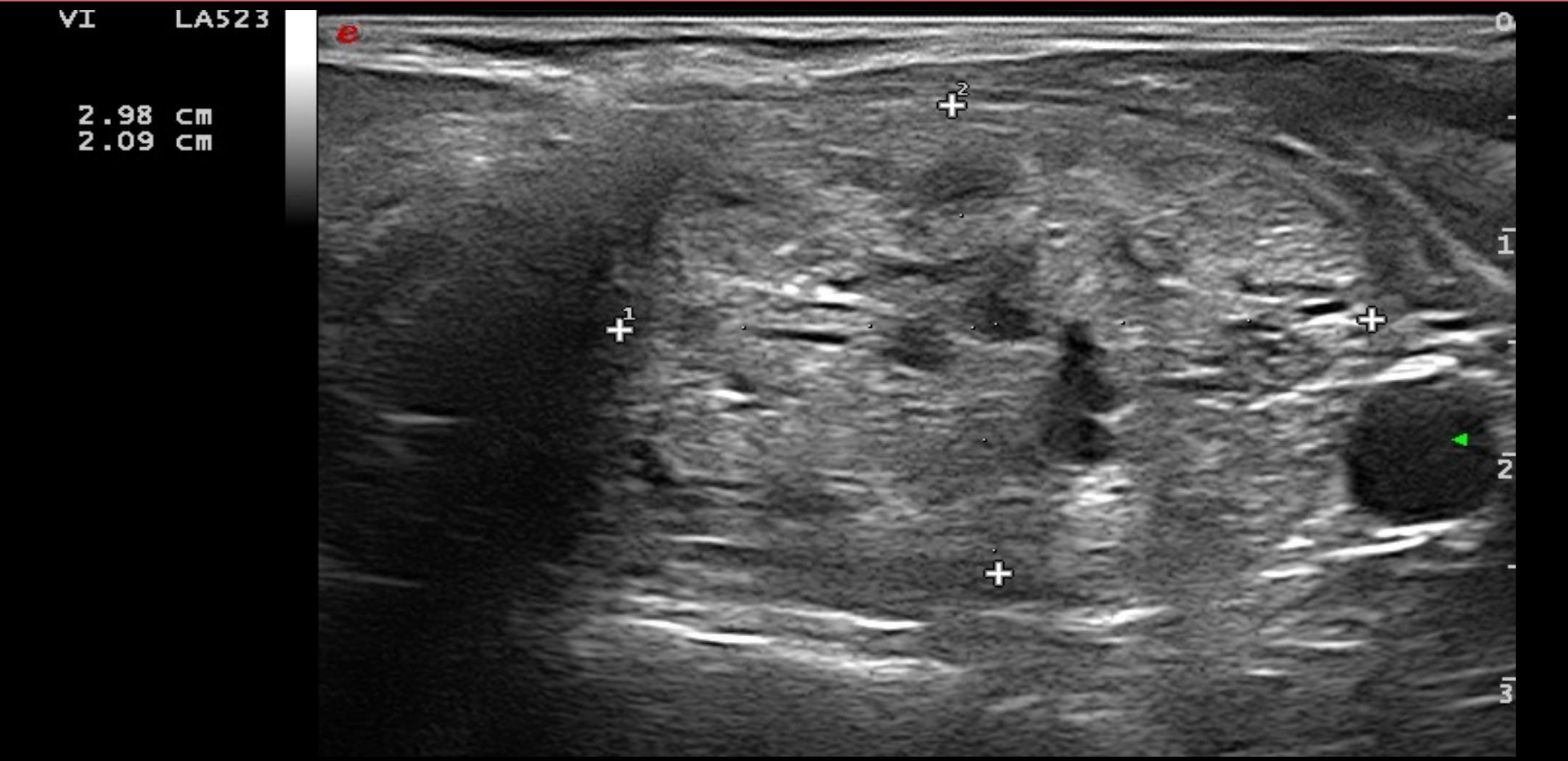
Other indications

- Symptomatic goiter in a elderly and/or fragile patients at high surgical risk
- Large AFTNs in the frame of a multimodal treatment
- Thyroid neoplasms in pazients at high surgical risk
- Neck recurrences of thyroid cancer not amenable to other treatments

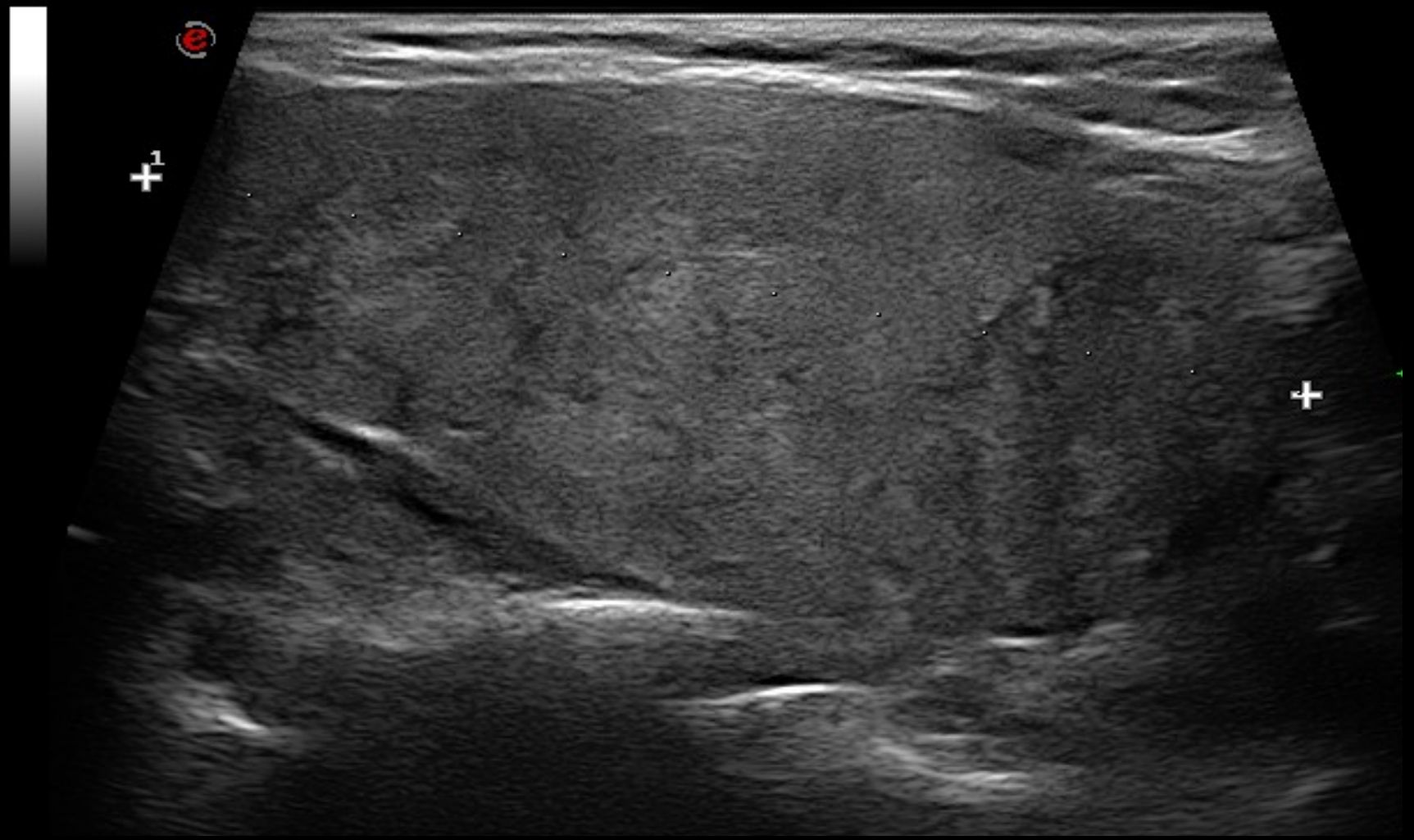
The spongiform nodule ♥ ♥ ♥ ♥



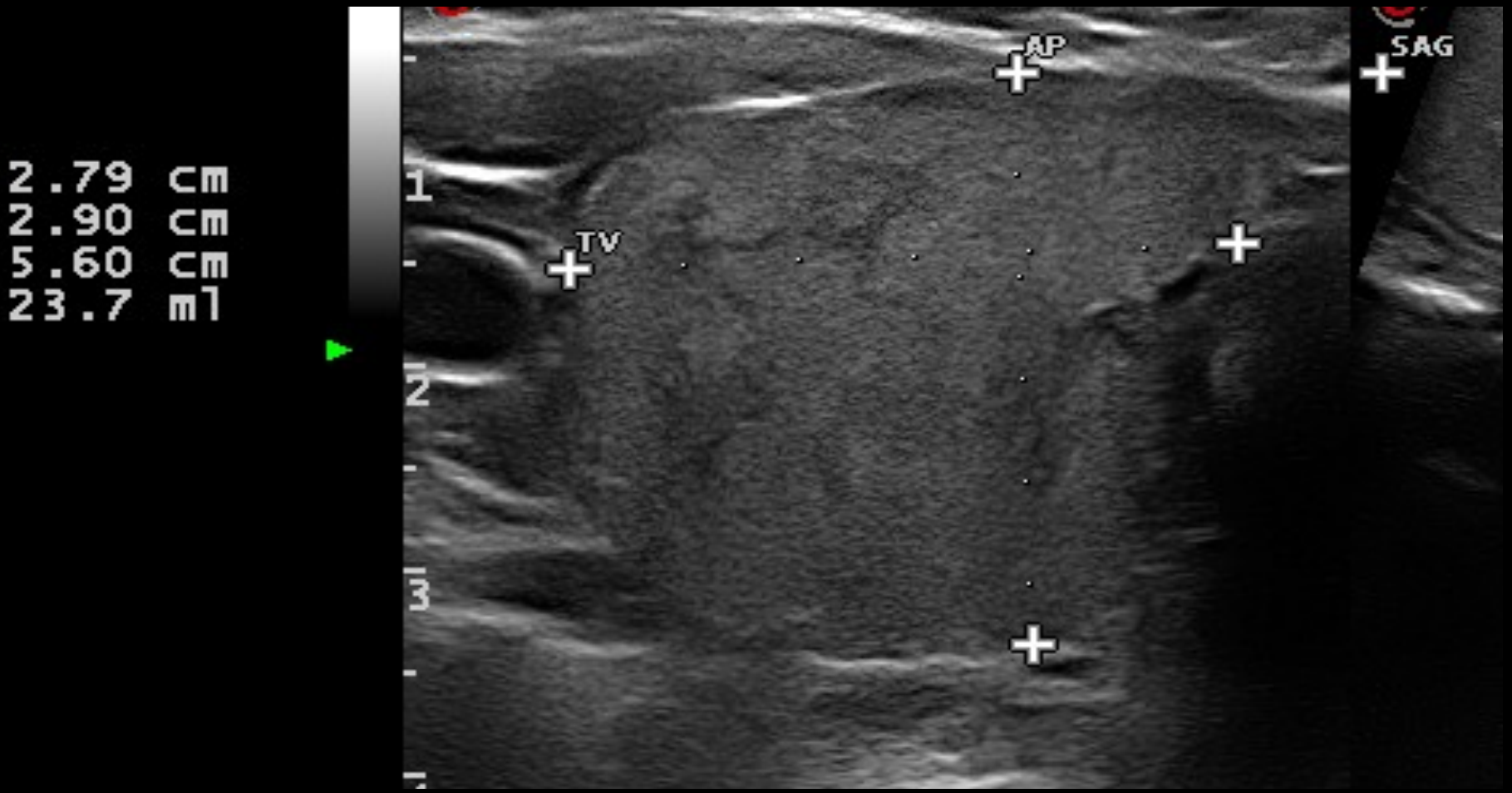
The spongiform nodule ♥ ♥ ♥ ♥



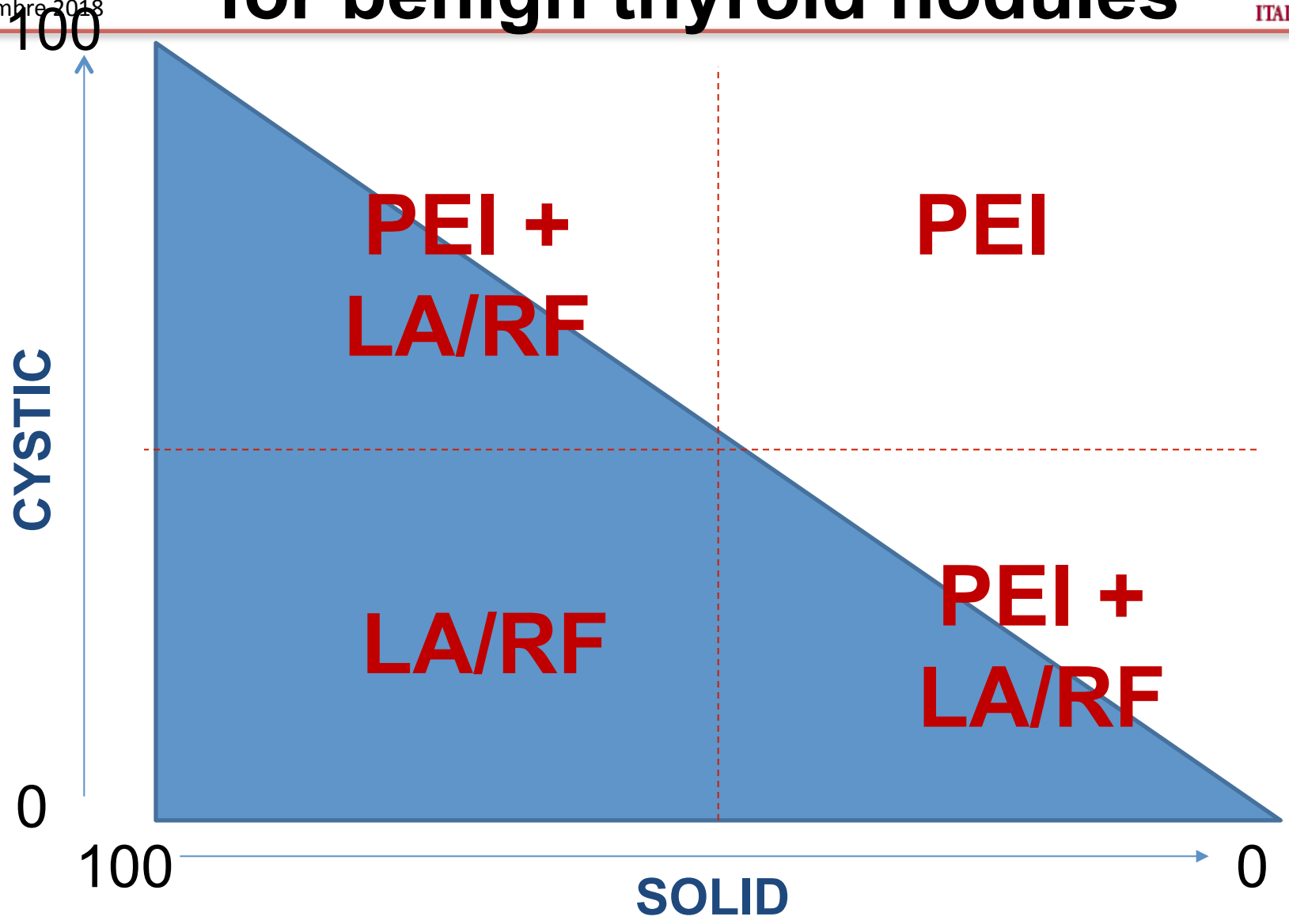
The adenomatous nodule ♥ ♥



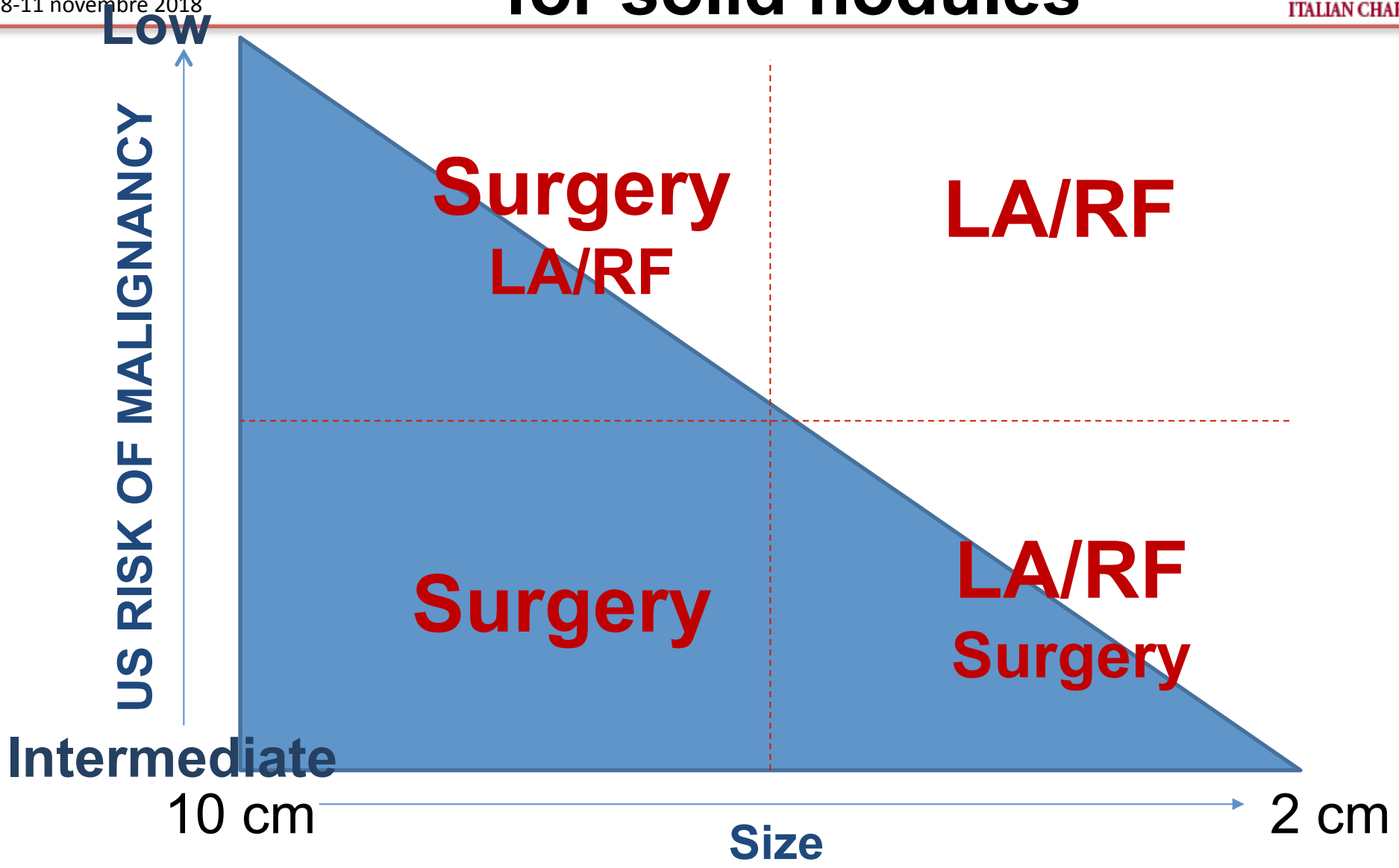
The adenomatous nodule ♥ ♥



Choosing the right treatment for benign thyroid nodules



Choosing the right treatment for solid nodules



Contraindications to Thermal ablation procedures

Patient-focused

1. Low compliance to US-guided procedure
2. (Too) great expectations

Nodule-focused

1. Incomplete visualization of the target
2. “Hard” parenchymatous nodule
3. MNG

Thermal ablation: issues which should be thoroughly discussed with the patient

- Describe possible complications
- Explain the reduction rate and timing
- Make clear that the nodule does not disappear
- Describe the possibility of an additional session of treatment if there is significant regrowth (or insufficient reduction)
- Describe the possibility of future surgery if needed

Modified from Cesareo et al., Clinical Endocrinology 2017.

THMs

- The majority of benign nodules exhibited no significant size change with time: they simply need a loose follow-up strategy
- Large benign thyroid nodules are neither synonymous of malignancy nor do they automatically cause compressive symptoms (usually associated with MNG)
- When treatment seems the right choice, US-interventional techniques should be considered as a valuable option: in experienced hands, they have proved to be quite effective, and safe
- In the next future, molecular markers will probably be more and more useful to refine our strategy in everyday's clinical practice

Thank you for your attention!