Nodulo tiroideo

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Thyroid nodule and DTC: Epidemiology

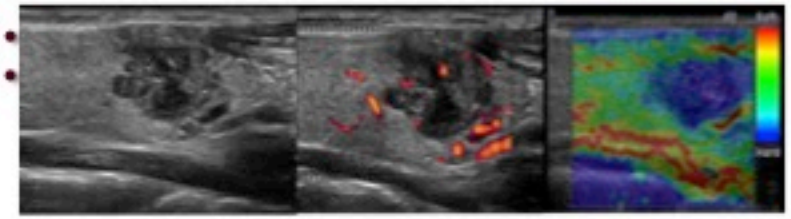
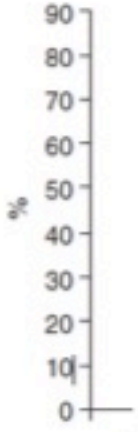


Table 1 Incidence of thyroid carcinoma in childhood thyroid nodules

Report	Number	%	References
1	69/138	50.0	Hayles *et al.* (1960)
2	9/44	20.4	Adams (1967)
3	9/38	23.7	Psarras *et al.* (1972)
4	12/30	40.0	Kirkland *et al.* (1973)
5	6/36	16.7	Scott & Crawford (1976)
6	10/49	20.4	Valentin *et al.* (1986)
7	12/58	20.7	Desjardins *et al.* (1987)
8	11/109	9.2	Belfiore *et al.* (1989)
9	7/32	21.9	Fowler *et. al.* (1989)
10	10/57	17.5	Raab *et al.* (1995)
11	41/148	27.7	Attie (1996)
12	17/52	32.7	Lafferty & Batch (1997)
13	26/71	36.6	Millman & Pellitteri (1997)
11	5/24	20.8	Lugo-Vicente *et al.* (1998)
12	15/93	16.1	Hung (1999)
13	7/60	11.7	Wasikowa *et al.* (1999)
14	3/31	9.7	Arda *et al.* (2001)
15	4/18	22.2	Blackburn *et al.* (2001)
16	37/155	23.9	Niedziela *et al.* (2004)
Overall	299/1134	26.4	

Figure 2 P
thyroids in



Eur J Clin. I
2362.2009.(
nodules de

Palpable nodules have been reported to occur in 5,3% of women and 0,8% of men.

Unexpected nodules have been demonstrated in up to 60% by US.

20-40% of pts with 1 palpable nodule are found to have additional nodes at US

DTC prevalence:5-15%

Thyroid nodules are uncommon in children before puberty (1,5% or less). Any nodule discovered in such an age group should be therefore viewed with suspicion

Thyroid Cancer: U.S. Trend, Incidence and Mortality

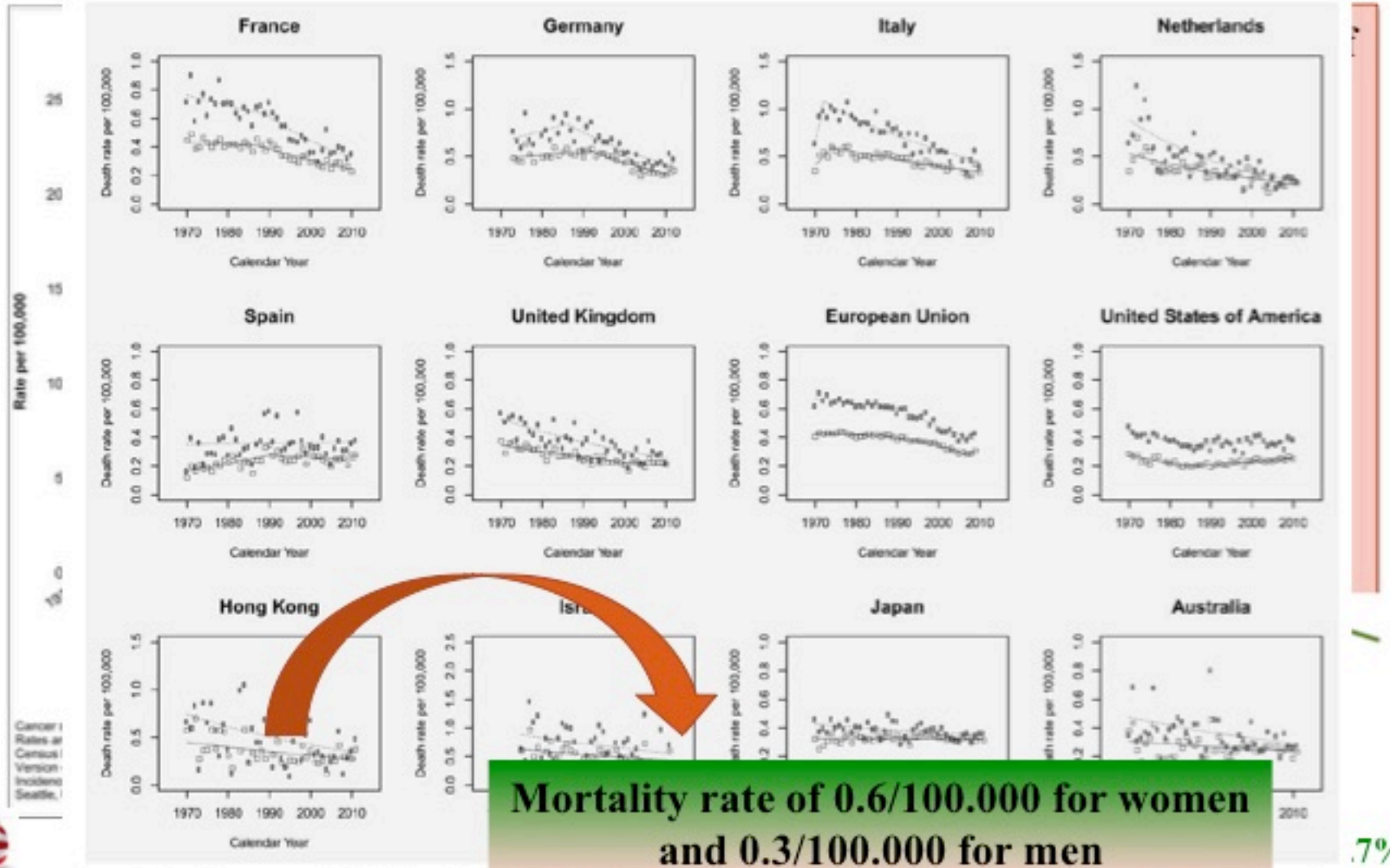


Figure 2. Trends in age-standardized (world population) death rates from thyroid cancer per 100,000 men (all ages and age 35–64 years) in selected countries worldwide, 1970–2012. All ages ——; truncated at 35–64 years ----

http://seer.cancer.gov/statfacts/html/thyro.html

La Vecchia et al IJC 2015

DTC Incidence trend: an overdiagnosis of an indolent disease (small PTC)

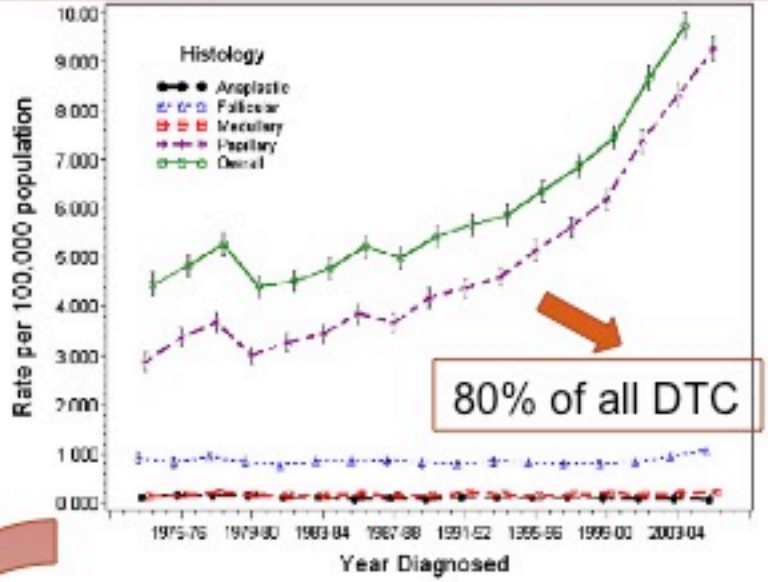


Fig 1. Trends in incidence of overall thyroid cancer cases (1973–2006). Data are age-adjusted to 2000 U.S. Census and stratified by histological subtype with 95% CI.

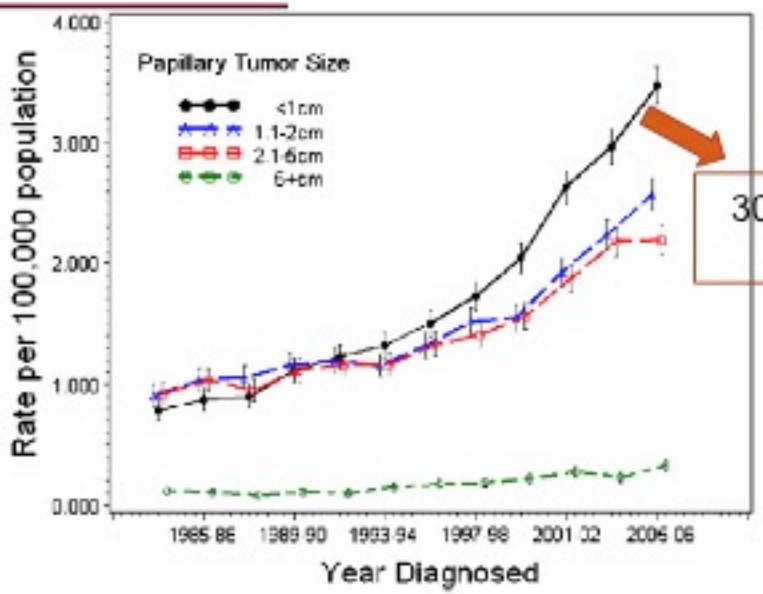


Fig 2. PTC incidence rates by tumor size (1983–2006). Data are age-adjusted to the 2000 U.S. Census with 95% CI.

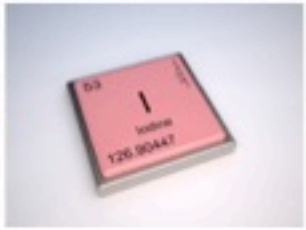
Results. *Thyroid cancer incidence increased 2.6-fold from 1973 to 2006. This change can be attributed primarily to an increase in papillary thyroid carcinoma, which increased 3.2-fold (P < .0001). The increase in papillary thyroid carcinoma also was examined based on tumor size. Tumors ≤1 cm increased the most at a total of 441% between 1983 and 2006 or by 19.2% per year, the incidence of papillary thyroid carcinoma also increased at 12.3%/year in 1.1–2-cm tumors, 10.3%/year in 2.1–5-cm tumors, and 12.0%/year for >5-cm tumors (all P < .0001 by Cochran–Armitage trend test). We also demonstrated a positive correlation between papillary thyroid carcinoma tumor size and stage of disease (Spearman, r = 0.285, P < .0001). Operative treatment for thyroid cancer also has shifted with total thyroidectomy replacing partial thyroidectomy as the most common surgical procedure.*

Conclusion. *Contrary to other studies, our data indicate that the increasing incidence of thyroid cancer cannot be accounted for fully by an increased detection of small neoplasms. Other possible explanations for the increase in clinically significant (>1 cm) well-differentiated thyroid carcinomas should be explored. (Surgery 2010;148:1147-53.)*

Cramer CL

Risk factors for DTCs

- **Previous radiation exposure (high)**
- **Iodine intake (less high)**



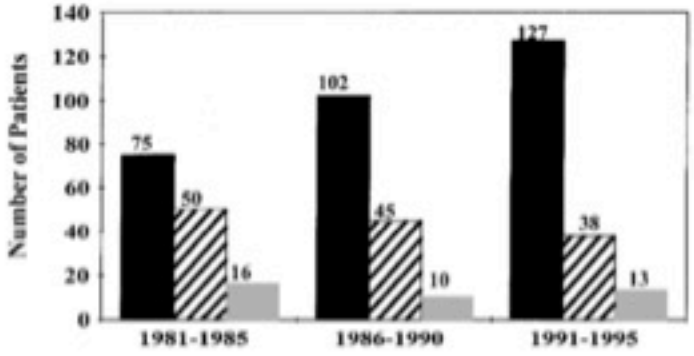
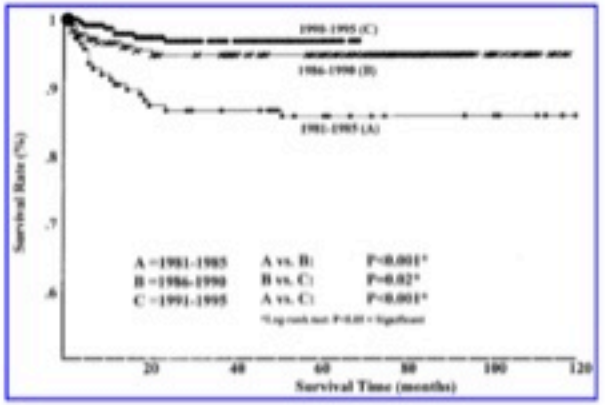


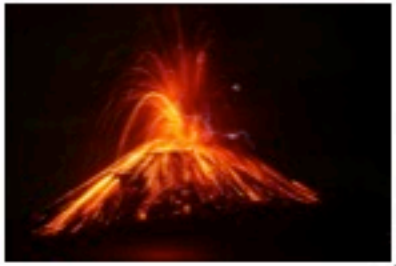
FIG. 2. Distribution of thyroid carcinoma diagnosed at the University of Wuerzburg between 1981–1995 with logical type (papillary: black columns; follicular: diagonal columns; anaplastic: grey columns) depicted in five

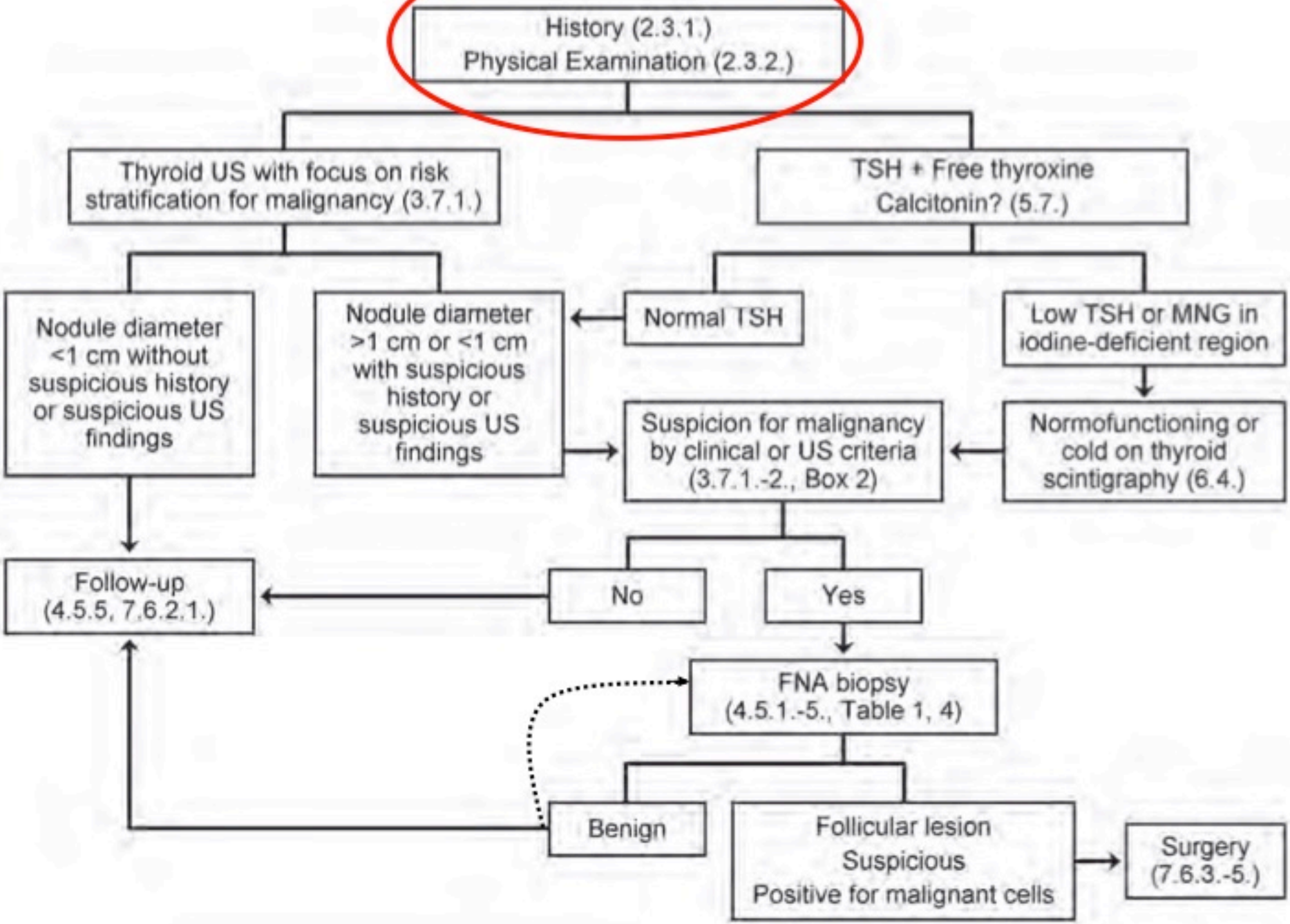


UIC: 4 ug/dl→ 4,6 ug/dl→ 7.2 ug/dl

Farahati et al Thyroid 2004

- **Thyroid disruptors (weak)**
- **Volcanos (weak)**

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TSH + Free thyroxine
Calcitonin? (5.7.)
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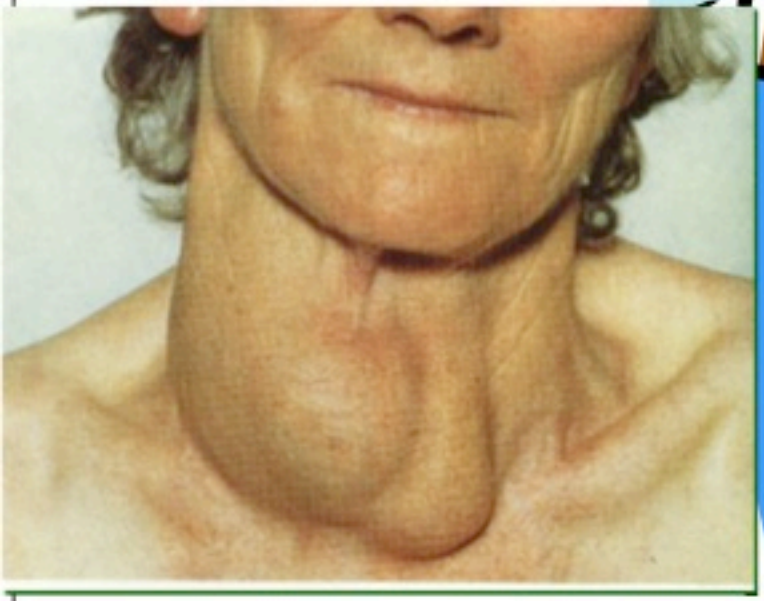
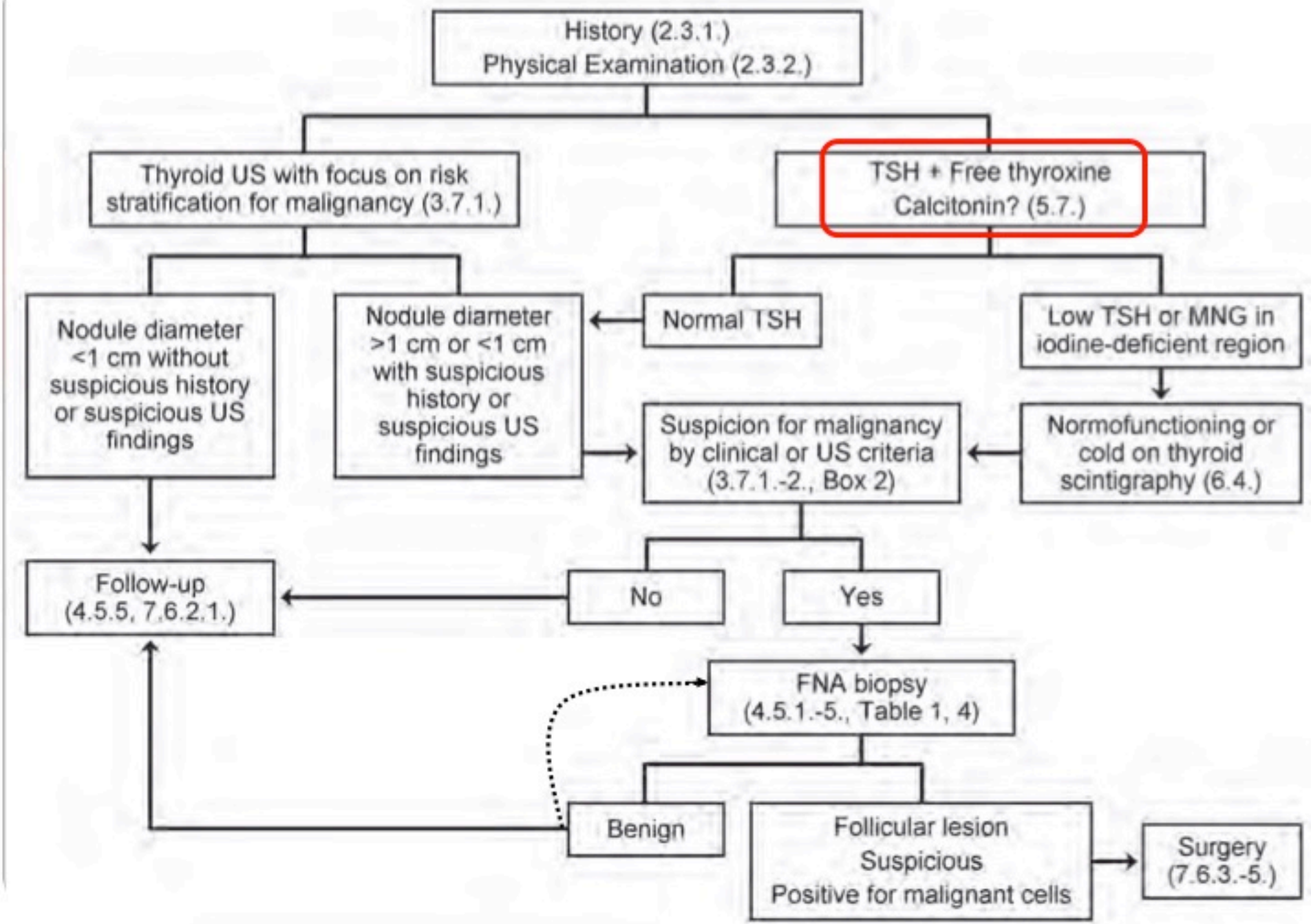
Nodule diameter >1 cm or <1 cm with suspicious history or suspicious US findings
Normal TSH
Low TSH or MNG in iodine-deficient region
Suspicion for malignancy by clinical or US criteria (3.7.1.-2., Box 2)
Normofunctioning or cold on thyroid scintigraphy (6.4.)
Follow-up (4.5.5, 7.6.2.1.)
No
Yes
FNA biopsy (4.5.1.-5., Table 1, 4)
Benign
Follicular lesion
Suspicious
Positive for malignant cells
Surgery (7.6.3.-5.)



FATTORI ANAMNESTICI-CLINICI SUGGESTIVI PER CARCINOMA TIROIDEO:

- Pregressa irradiazione capo-collo in età pediatrica
- Familiarità per MTC, MEN2A, PTC
- Età < 14 o > 70 anni
- Sesso maschile
- Sintomi da compressione (disfonia, disfagia, dispnea)
- Linfoadenopatia cervicale
- Nodo di consistenza dura, fisso
- Rapida insorgenza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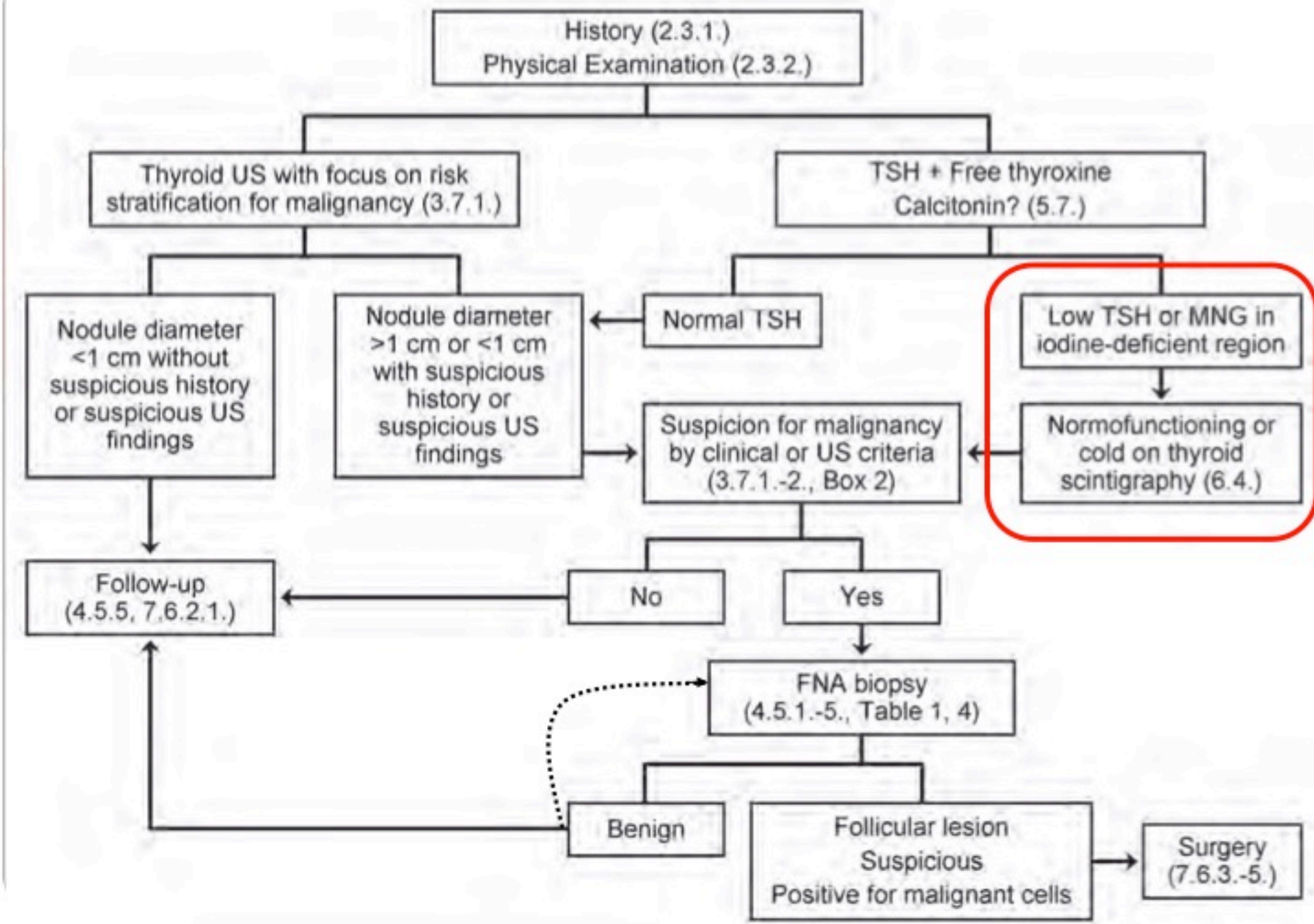
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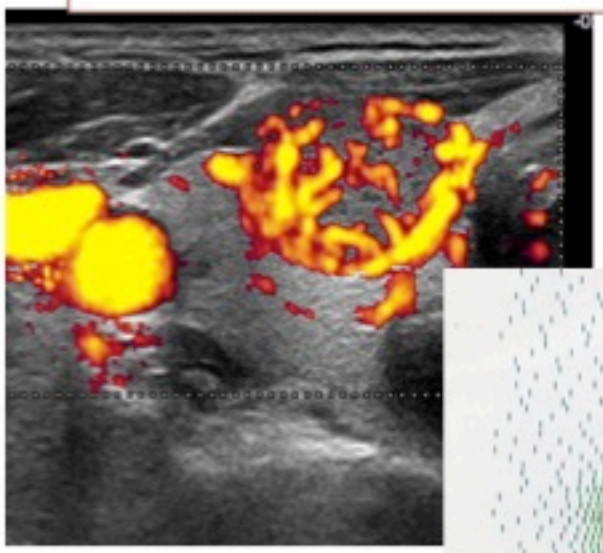
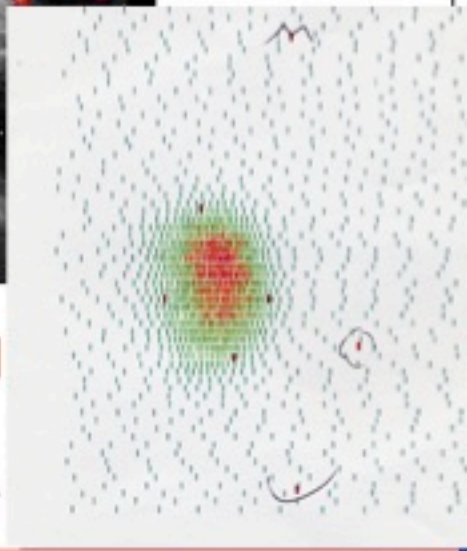
Follicular lesion
Suspicious
Positive for malignant cells
Surgery (7.6.3.-5.)

Che test di laboratorio eseguire? Il TSH e la Tg

- MISURARE IL **TSH** (**Grado A**; BEL3)
- SE IL TSH E' RIDOTTO MISURARE **FT4** E FT3; SE IL TSH E' AUMENTATO MISURARE FT4 E ANTI-TPO (Grado B; BEL3)
- ANTI-TIREOGLOBULINA NEI PAZIENTI CON SEGNI CLINICI ED ECOGRAFICI DI TIREOPATIA AUTOIMMUNE E ANTI-TPO NORMALI (Grado C; BEL3)
- IL DOSAGGIO DELLA **CT BASALE** PUO' ESSERE UTILE COME TEST DI SCREENING NELL' INQUADRAMENTO DEI PAZIENTI CON NODULI TIROIDEI (Grado B; BEL3)
- IL DOSAGGIO DELLA CALCITONINA E' RACCOMANDATO IN OGNI PAZIENTE CON NODULO TIROIDEO CANDIDATO ALLA CHIRURGIA (Grado B; BEL3)
- E' OBBLIGATORIO IN PAZIENTI CON STORIA O SOSPETTO CLINICO DI MTC E MEN2A (Grado A; BEL3)
- IL DOSAGGIO DELLA TIREOGLOBULINA PRIMA DELLA CHIRURGIA NON E' RACCOMANDATO (Grado C;BEL3)

TSH ai valori bassi o inibito





- In caso di nodo singolo o GMN se il TSH è al di sotto del limite inferiore del range di normalità (Grado B, BEL 3)
- In aree iodo-carenti per escludere autonomia funzionale in un nodulo, in un GMN anche se il TSH è normale (Grado B, BEL 3)

AACE/AME/ETA Thyroid Nodule Guidelines, *Endocr Pract.* 2010;16(Suppl

E' appropriato lo screening con il dosaggio della calcitonina in tutti i pazienti con nodulazione tiroidea?

CONSENSUS STATEMENT

European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium

Furio Pacini, Martin Schlumberger[1], Henning Dralle[2], Rossella Elisei[3], Johannes W A Smit[4], Wilmar Wiersinga[5] and the European Thyroid Cancer Taskforce

2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer

THYROID
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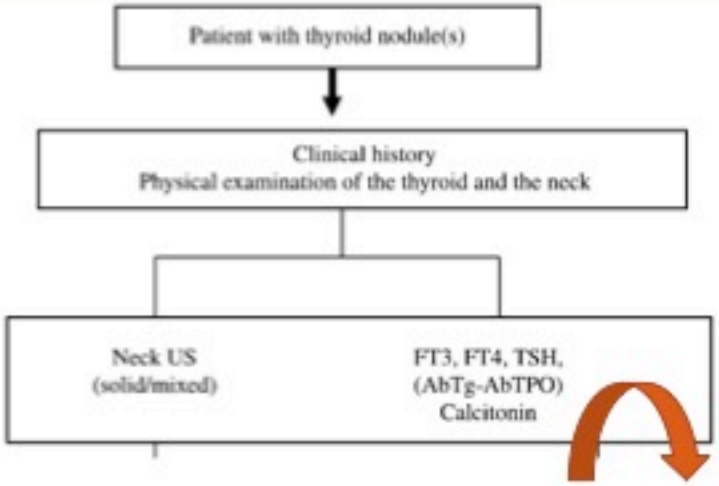

measurement of serum Ct allows the detection of unsuspected medullary thyroid carcinoma with a frequency of 1 in 200–300 thyroid nodules, with better sensitivity than FNAC, and that routine Ct screening improves the outcome. Thus, serum Ct measurement is recommended in the initial diagnostic evaluation of thyroid nodules (19–22).

- **RECOMMENDATION 4**

The panel cannot recommend either for or against routine measurement of serum calcitonin in patients with thyroid nodules.

(No recommendation, Insufficient evidence)

Insufficient

Evidence may be of such poor quality, conflicting, lacking (i.e., studies not done), or not externally generalizable to the target clinical population such that the estimate of the true effect of the test is uncertain and does not permit a reasonable conclusion to be made.

I **Recommends neither for nor against**
for or against providing the service
intervention improves important hea
conflicting. As a result, the balance

Che test di laboratorio eseguire? La Calcitonina

- MISURARE IL **TSH** (Grado A; BEL3)
- SE IL TSH E' RIDOTTO MISURARE **FT4** E FT3; SE IL TSH E' AUMENTATO MISURARE FT4 E ANTI-TPO (Grado B; BEL3)
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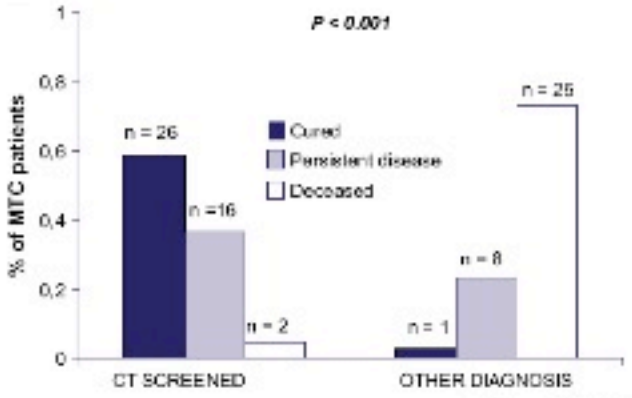
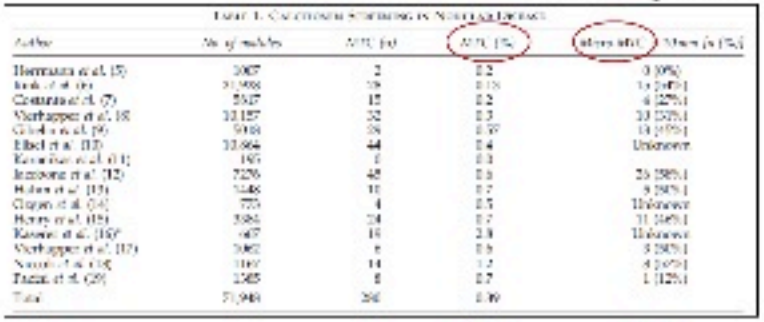
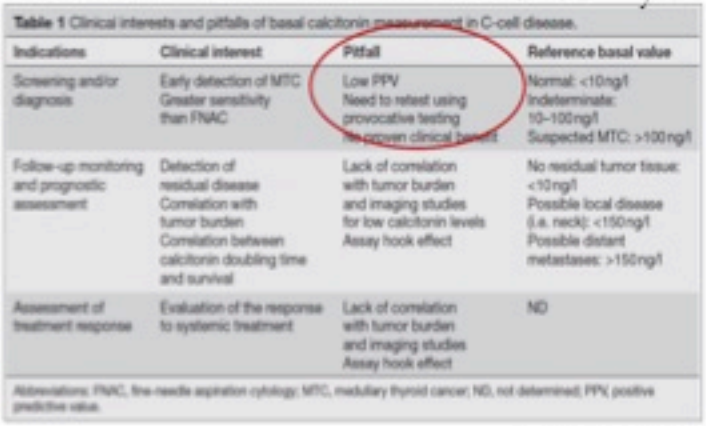


Elisei R JCEM2004



0.5% 50%

Daniels Thyroid 2011



Indications	Clinical interest	Pitfall	Reference basal value
Screening and/or diagnosis	Early detection of MTC Greater sensitivity than FNAC	Low PPV Need to retest using provocative testing No proven clinical benefit	Normal: <10ng/l Indeterminate: 10–100ng/l Suspected MTC: >100ng/l
Follow-up monitoring and prognostic assessment	Detection of residual disease Correlation with tumor burden Correlation between calcitonin doubling time and survival	Lack of correlation with tumor burden and imaging studies for low calcitonin levels Assay hook effect	No residual tumor tissue: <10ng/l Possible local disease (i.e. neck): <150ng/l Possible distant metastases: >150ng/l
Assessment of treatment response	Evaluation of the response to systemic treatment	Lack of correlation with tumor burden and imaging studies Assay hook effect	ND

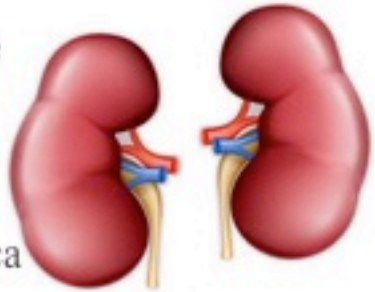
Abbreviations: FNAC, fine-needle aspiration cytology; MTC, medullary thyroid cancer; ND, not determined; PPV, positive predictive value.

Costante G 2009

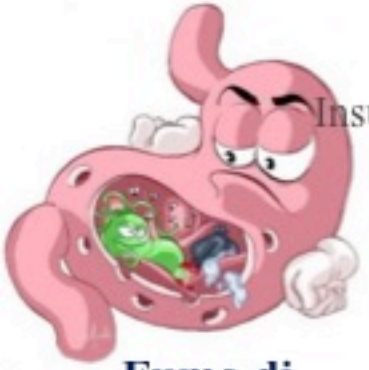
AACE/AME/ETA Thyroid Nodule Guidelines, *Endocr Pract.* 2010;16(Suppl 1) 7

Dosaggio della calcitonina e i «falsi positivi»:
le Ipercalcitoninemie secondarie e i problemi analitici

Malattie non tiroidee
Ipergastrinemia
Mastocitosi
Ipercalcemia
Insufficienza renale cronica

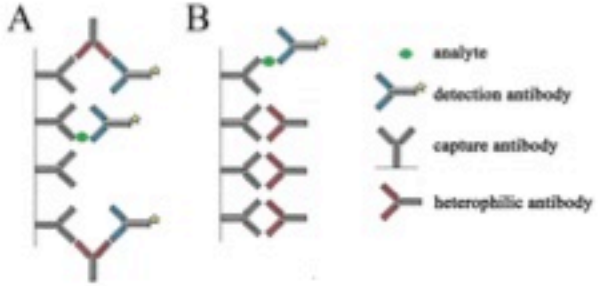


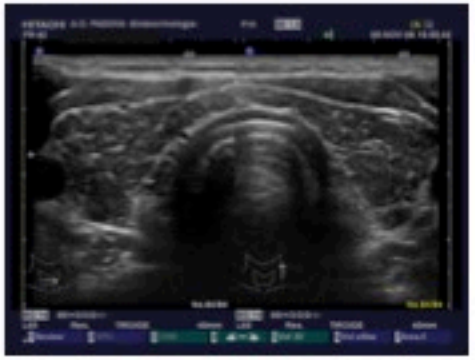
Tumori neuroendocrini



Fumo di sigaretta

Problemi Analitici
Interferenza da anticorpi eterofili
Dosaggi Competitivi
Macrocalcitoninemia





Malattie tiroidee
Tiroidite autoimmune
Carcinomi tiroidei differenziati

Farmaci
(PPI, betabloccanti, glucocorticoidi, glucagone)

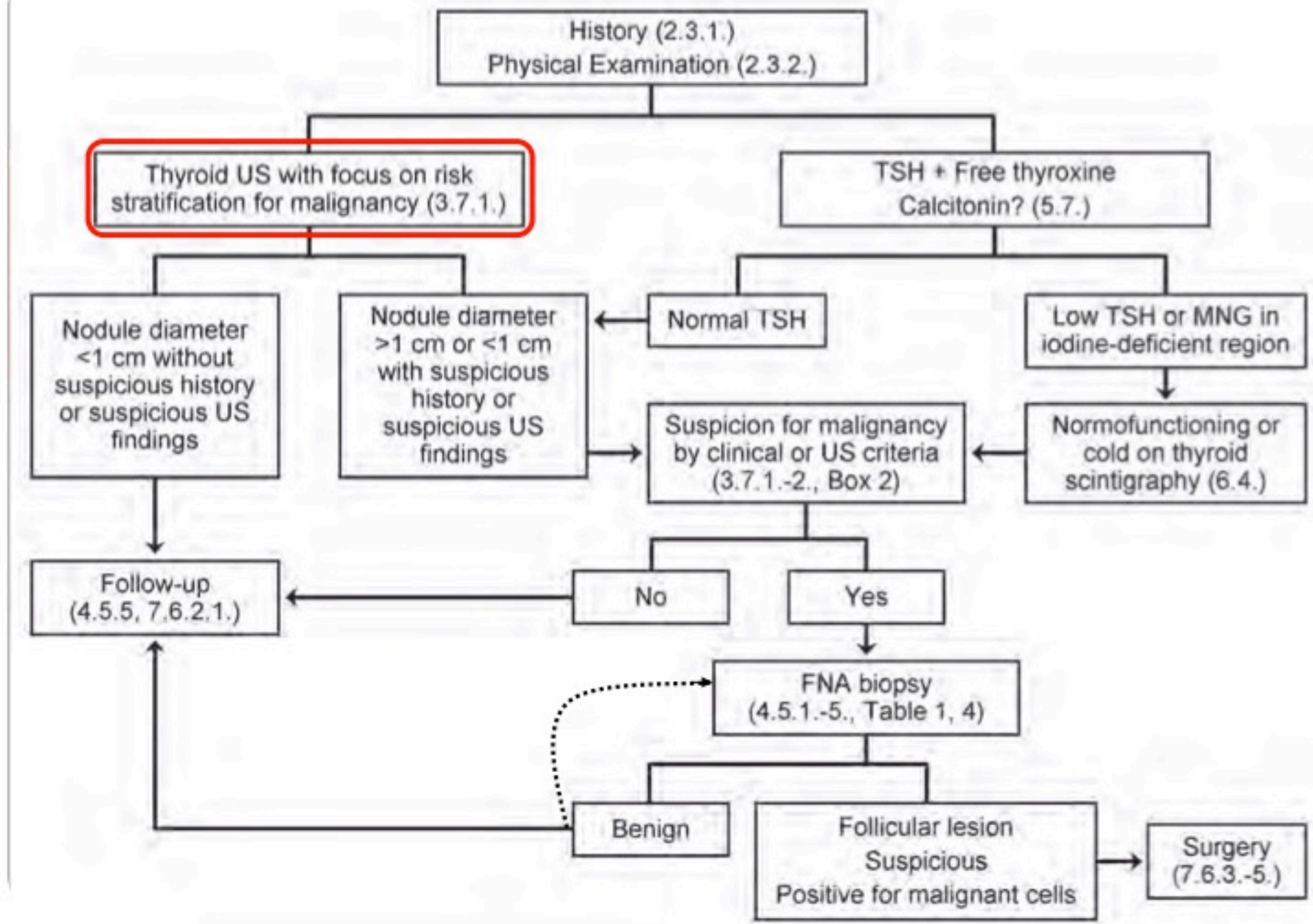
Censi S…Mian C Clin Chem Lab Med. 2016 May

Test di stimolo per la calcitonina: *perché stimolare?*

MTC versus Vs non-MTC conditions	Mian C, 2014 Ca-test	Machens A, 2009 Pg test
bCT females	**>26** Sens 81.8% Spec 97.9%	**>15** Sens 89% Spec 75%
bCT males	**>68** Sens 83.3% Spec 100%	**>80** Sens 13% Spec 100%
sCT females	**>78** Sens 100% Spec 76.6%	**>80** Sens 100% Spec 75%
sCT males	**>544** Sens77.8% Spec 85.4%	**>500** Sens 25% Spec 100%

- Per distinguere MTC da HCC: *individuazione del cutoff*
- Nel follow-up del paziente operato?

Mian C….Fugazzola L JCEM et al., 2014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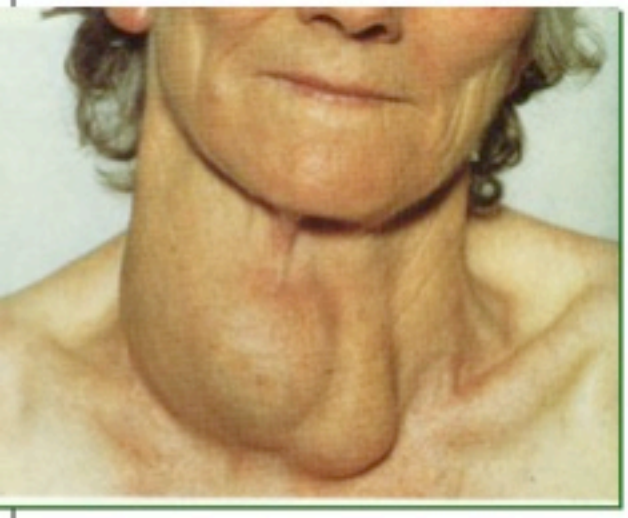
Follow-up (4.5.5, 7.6.2.1.)
No
Yes
FNA biopsy (4.5.1.-5., Table 1, 4)
Benign
Follicular lesion
Suspicious
Positive for malignant cells
Surgery (7.6.3.-5.)

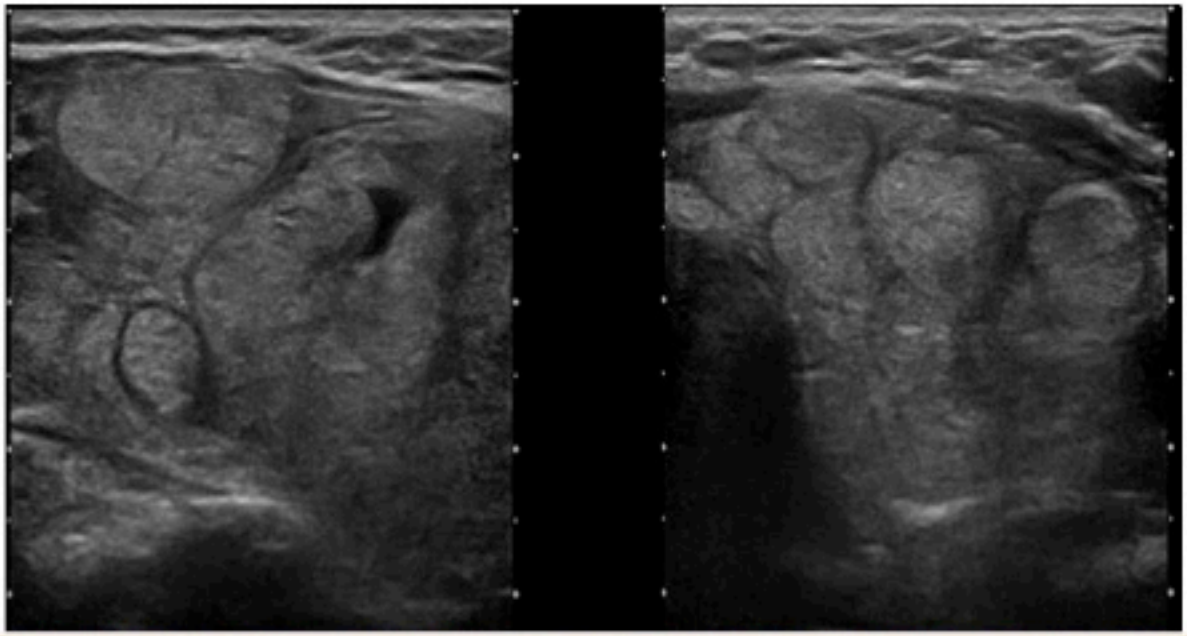
A quali domande deve rispondere l'ecografia?

- **E' un nodo vero o uno pseudonodulo?**
- **Quanto grande è?**
- **Ci sono delle caratteristiche di sospetto?**
- **C'è una linfoadenopatia satellite sospetta?**
- **La componente cistica, se presente, è maggiore del 50%?**
- **Il nodulo è localizzato in piani profondi?**

..Non ci comprenderemo mai fra noi finché non avremo ridotto la nostra lingua a non più di sette parole. (Khalil Gibran)

In linea di massima, se alla base della crescita del tessuto tiroideo vi sono condizioni esterne o intrinseche diffuse a tutta la ghiandola, si può giungere alla formazione di *"pseudonoduli"*

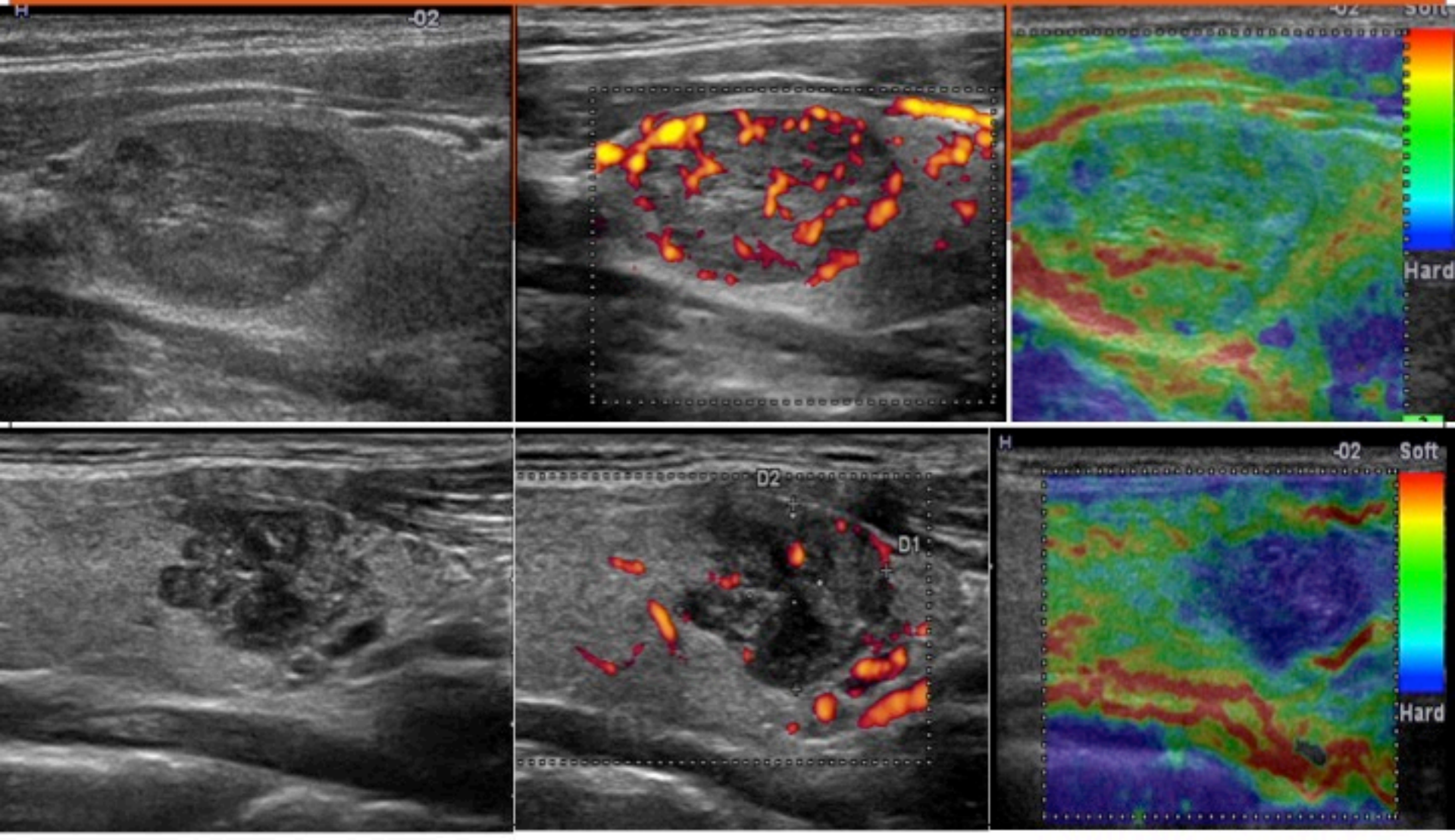


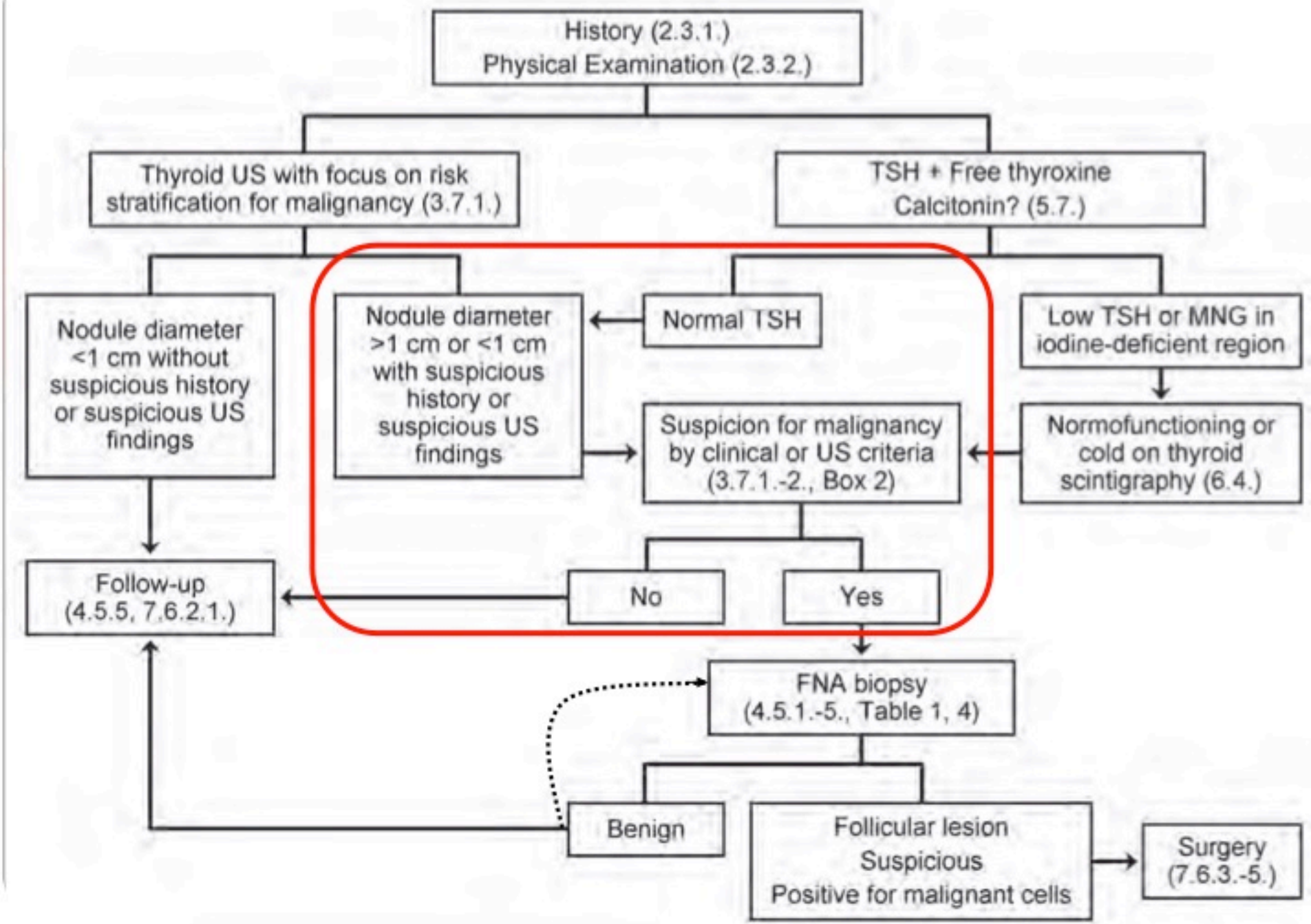


TSH, IGFI, Cause ambientali, etc. sono esempio di fattori esterni.
Deficit enzimatici in qualsiasi tappa dell'ormonogenesi tiroidea sono esempi di fattori intrinseci stimolanti direttamente o indirettamente la crescita.

Generalmente possiamo definire veri noduli quelli che derivano da un singolo clone cellulare:

ADENOMI O CARCINOMI

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Follow-up (4.5.5, 7.6.2.1.)
No
Yes
FNA biopsy (4.5.1.-5., Table 1, 4)
Benign
Follicular lesion
Suspicious
Positive for malignant cells
Surgery (7.6.3.-5.)

Quando eseguire l'esame citologico

- NEL **NODO MAGGIORE** DI **1 CENTIMETRO** SOLIDO E IPOECOGENO
- NEL NODO DI QUALSIASI DIMENSIONE CON SEGNI ECOGRAFICI DI

Table 4 Recommendations stated in the ten clinical practice guidelines

Recommendations	AACE/AME/ETA (2010)	ATA (2009)	BTA (2007)	ESMO (2012)	GAES (2013)	IKNL (2007)	LATS (2009)	NCCN (2013)	NCN (2000)	SEOM (2011)
Diagnosis										
Indications of fine-needle aspiration (without suspicions)	n >1 cm	n >0.5 cm	n >0.5 cm	n >1 cm	All nodules	All nodules	N/A	n >1.5 cm	All nodules	n >1 cm
Routine serum calcitonin	Optional	NR	N/A	R	R	R	Optional	Optional	Optional	R
Thyroid scan	Low TSH	Follicular lesion with low TSH	N/A	Unclear	Before operation	NR	N/A	Follicular lesion with low TSH	Unclear	NR

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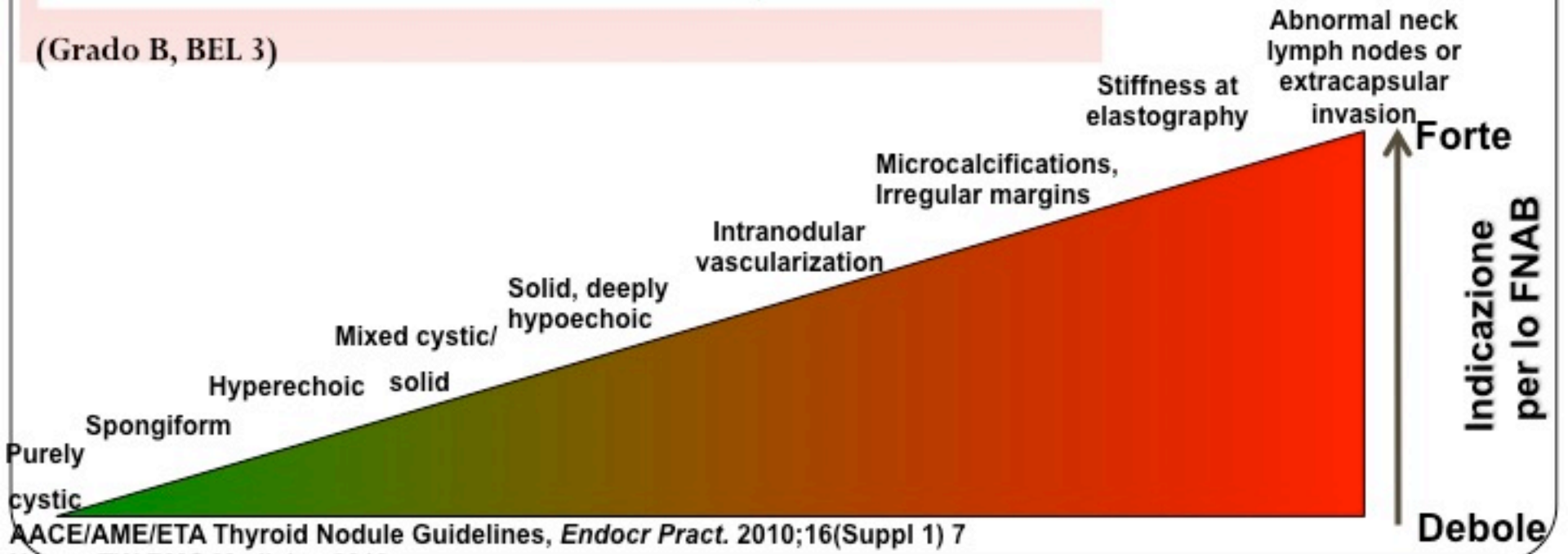
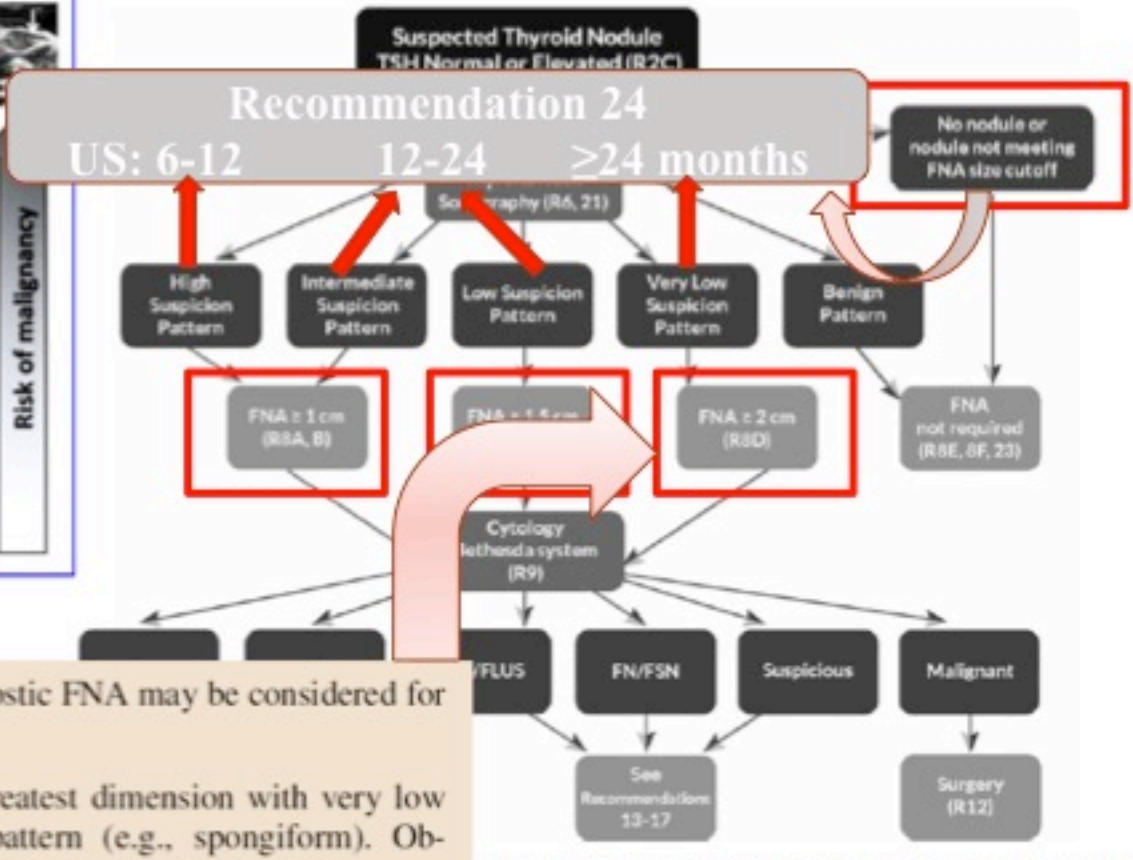
(Grado B, BEL 3)



AACE/AME/ETA Thyroid Nodule Guidelines, *Endocr Pract.* 2010;16(Suppl 1) 7
Huang TW BMC Medicine 2013

Criteri di esecuzione dell'agoaspirato secondo ATA 2015

Figure 2. ATA nodule sonographic patterns and risk of malignancy



ment of patients with thyroid nodules based on US pattern and

II. Thyroid nodule diagnostic FNA may be considered for (Fig. 2, Table 6):

(D) Nodules ≥2 cm in greatest dimension with very low suspicion sonographic pattern (e.g., spongiform). Observation without FNA is also a reasonable option.

(Weak recommendation, Moderate-quality evidence)

2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

1235 patients followed up to 19 years

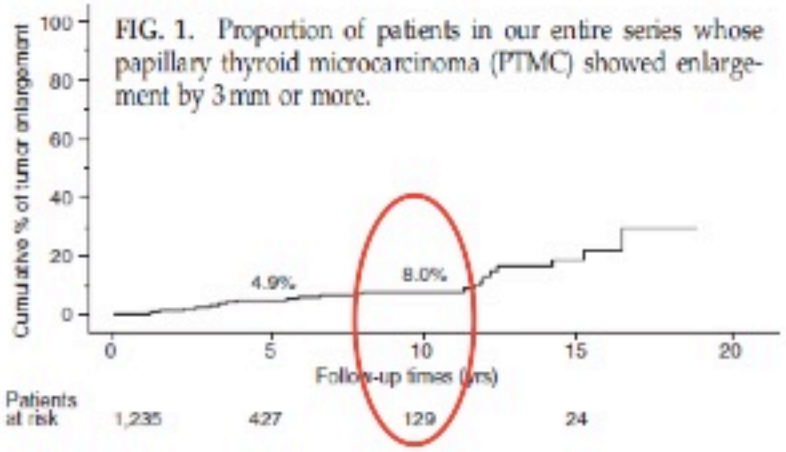


FIG. 1. Proportion of patients in our entire series whose papillary thyroid microcarcinoma (PTMC) showed enlargement by 3 mm or more.

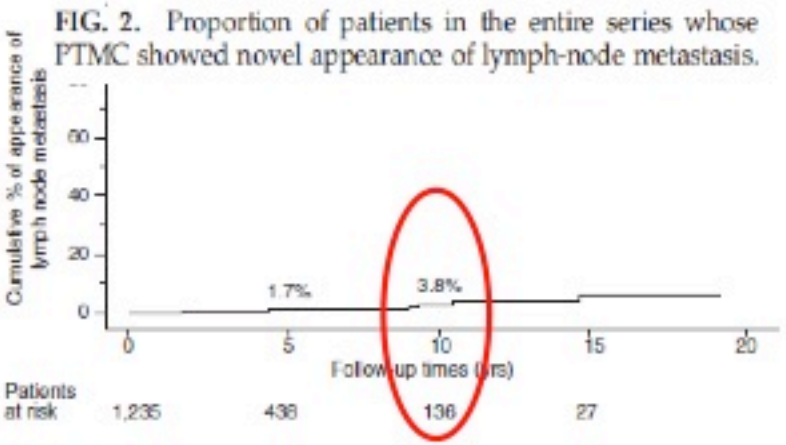


FIG. 2. Proportion of patients in the entire series whose PTMC showed novel appearance of lymph-node metastasis.

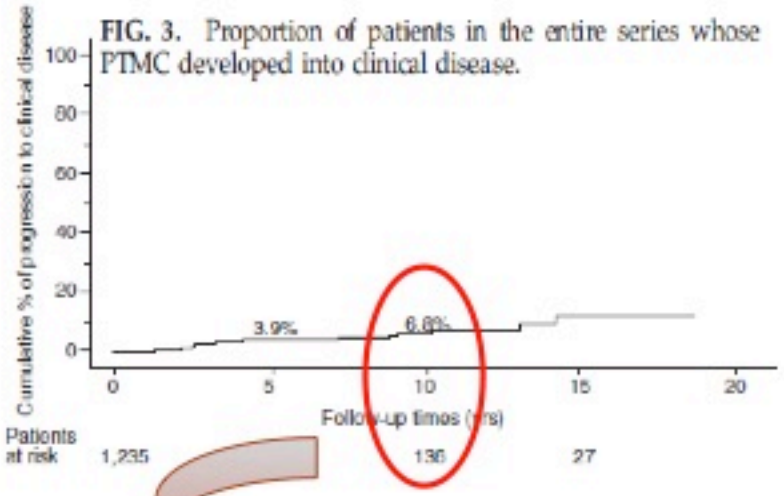
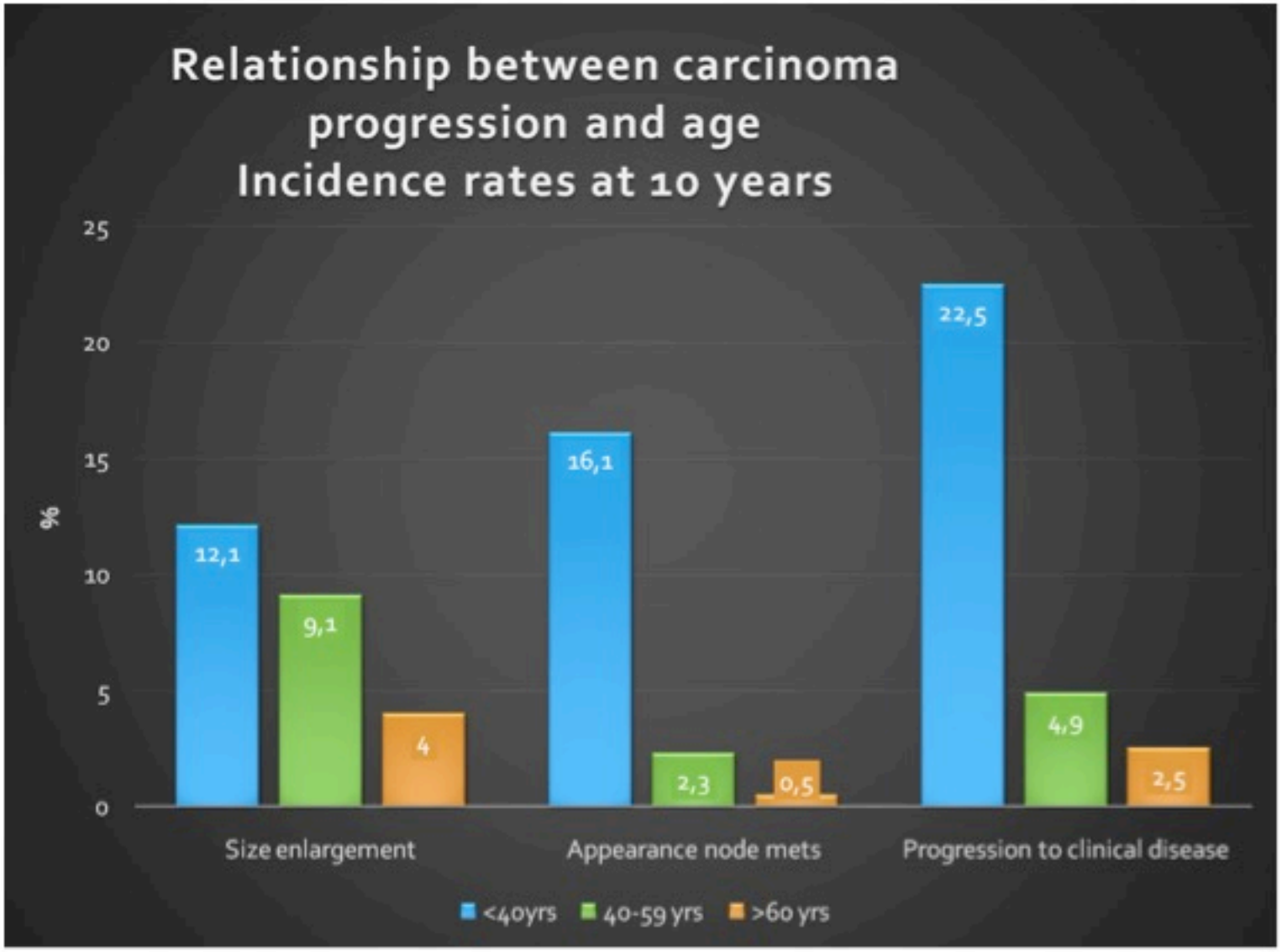


FIG. 3. Proportion of patients in the entire series whose PTMC developed into clinical disease.

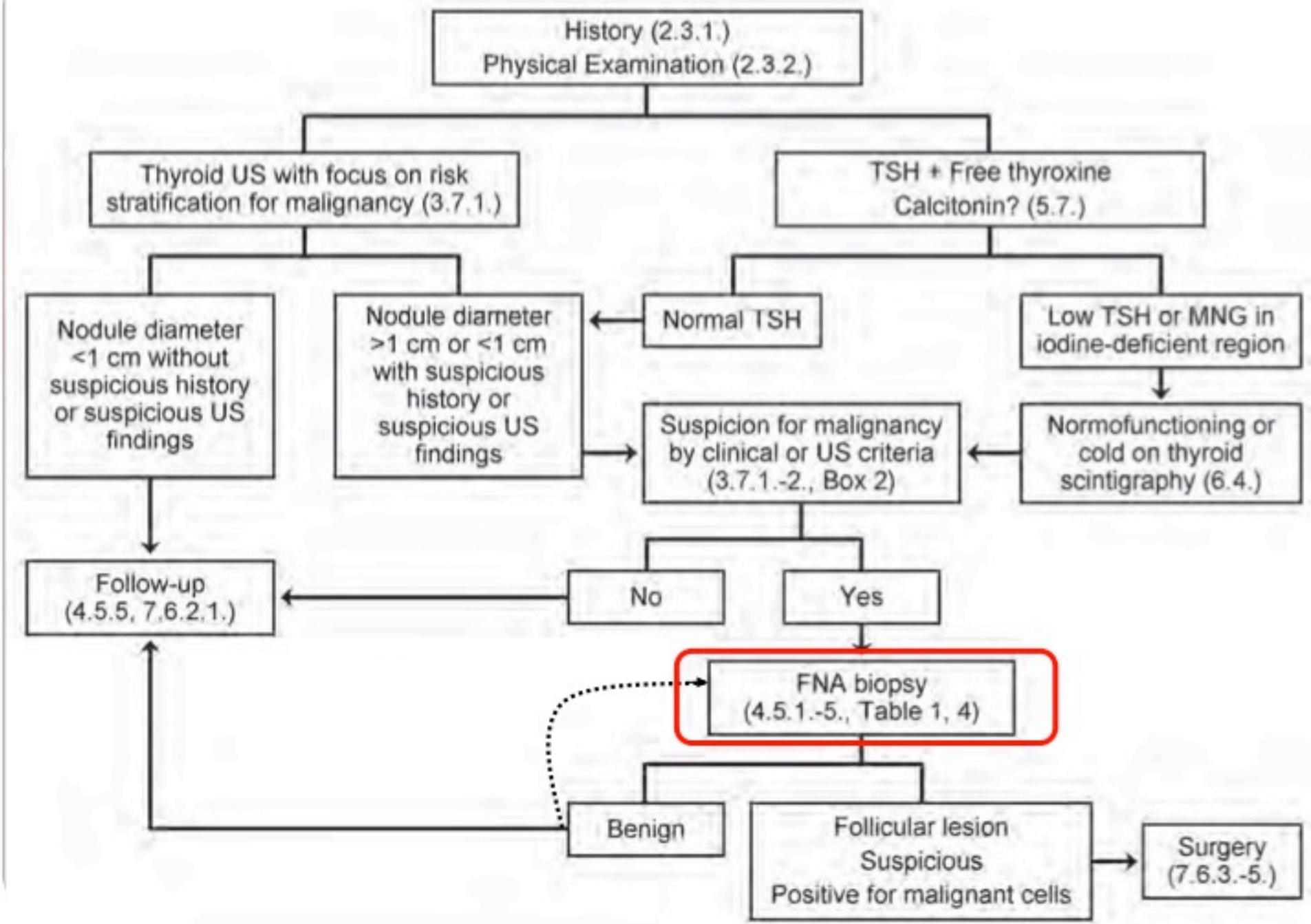
"We defined progression to clinical disease as the tumor size reaching 12mm or larger, or the novel appearance of lymph node metastasis"

ITO ET AL. THYROID Volume 24, Number 1, 2014

191 underwent surgical treatment: delayed surgery did not affect the outcome (follow-up:75 months)



ITO ET AL. THYROID Volume 24, Number 1, 2014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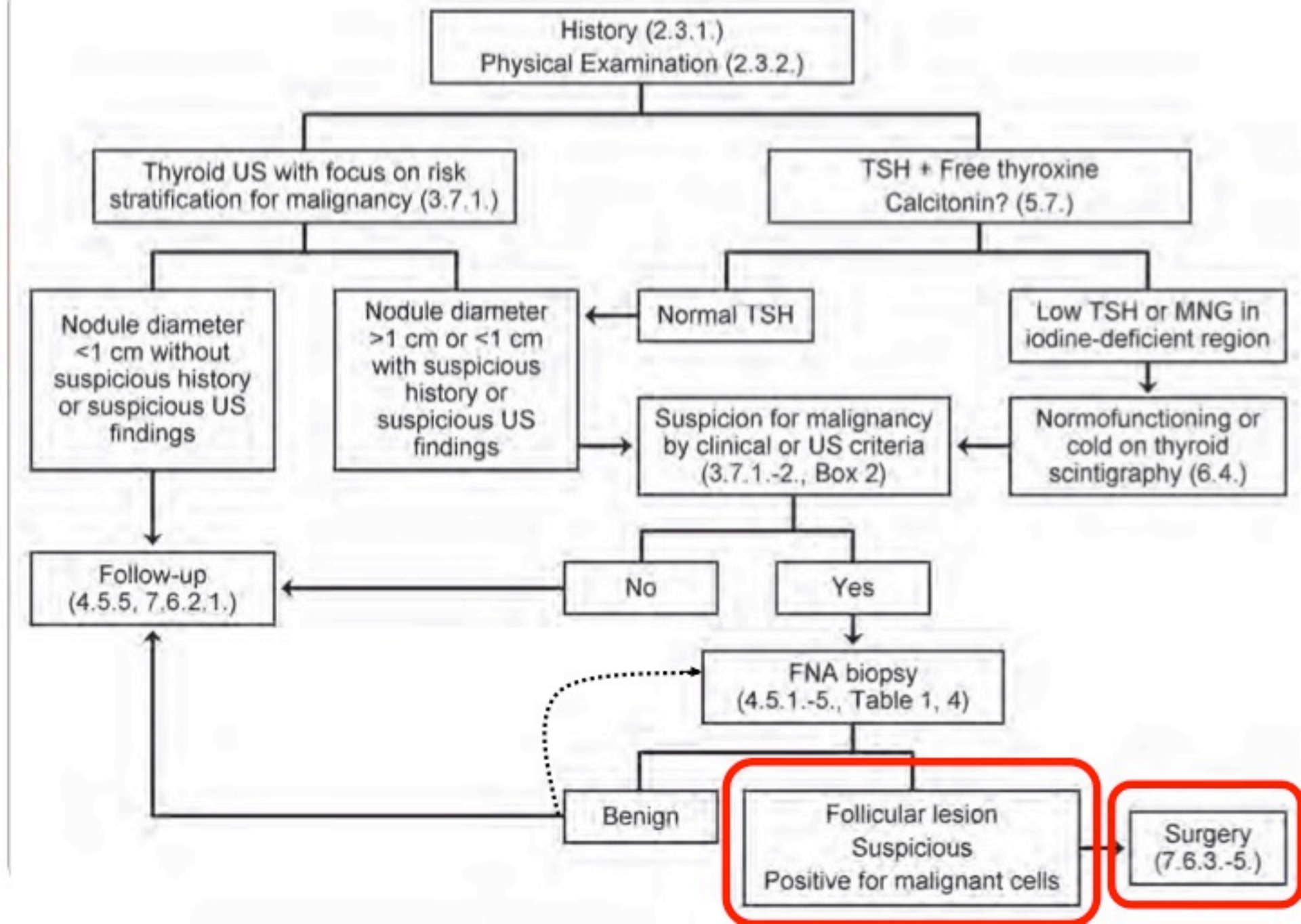
Benign
Follicular lesion
Suspicious
Positive for malignant cells
Surgery (7.6.3.-5.)

UK RCPath	SIAPEC-AIT 2013	USA BETHESDA
Diagnostic category		Terminology
Thy1/Thy1c Non-diagnostic for cytological diagnosis Unsatisfactory, consistent with cyst	**TIR 1** **TIR 1c** (cystic)	**I.** Non-diagnostic Cystic fluid only
Thy2/Thy2c Non-neoplastic	**TIR 2**	**II.** Benign
Thy 3a Neoplasm possible – atypia/non-diagnostic	**TIR 3A**	**III.** Atypia of undetermined significance or follicular lesion u.s. AUS/FLUS
Thy 3f Neoplasm possible - suggesting follicular neoplasm	**TIR 3B**	**IV.** Follicular neoplasm or suspicious for a follicular neoplasm
Thy 4 Suspicious of malignancy	**TIR 4**	**V.** Suspicious of malignancy
Thy5 Malignant	**TIR 5**	**VI.** Malignant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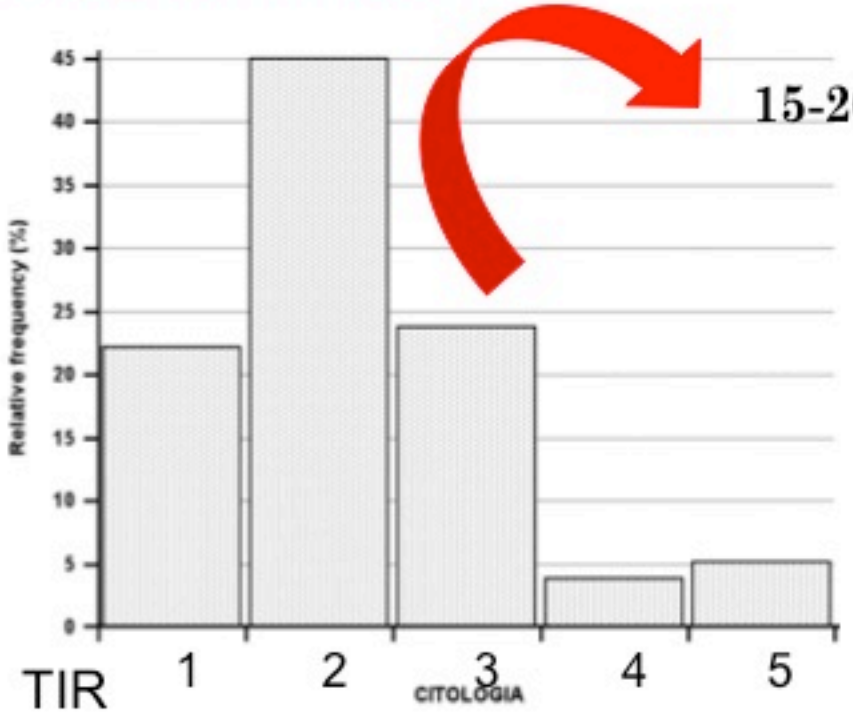
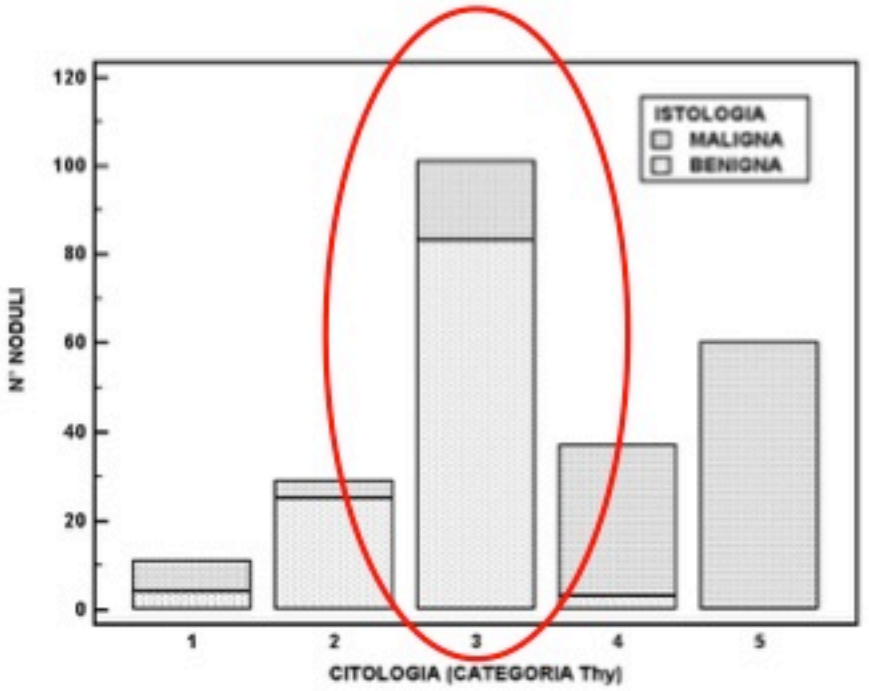
FNA biopsy (4.5.1.-5., Table 1, 4)
Benign
Follicular lesion
Suspicious
Positive for malignant cells
Surgery (7.6.3.-5.)

Quale follow-up nel nodo a citologia indeterminata?



15-20% di tutte le citologie

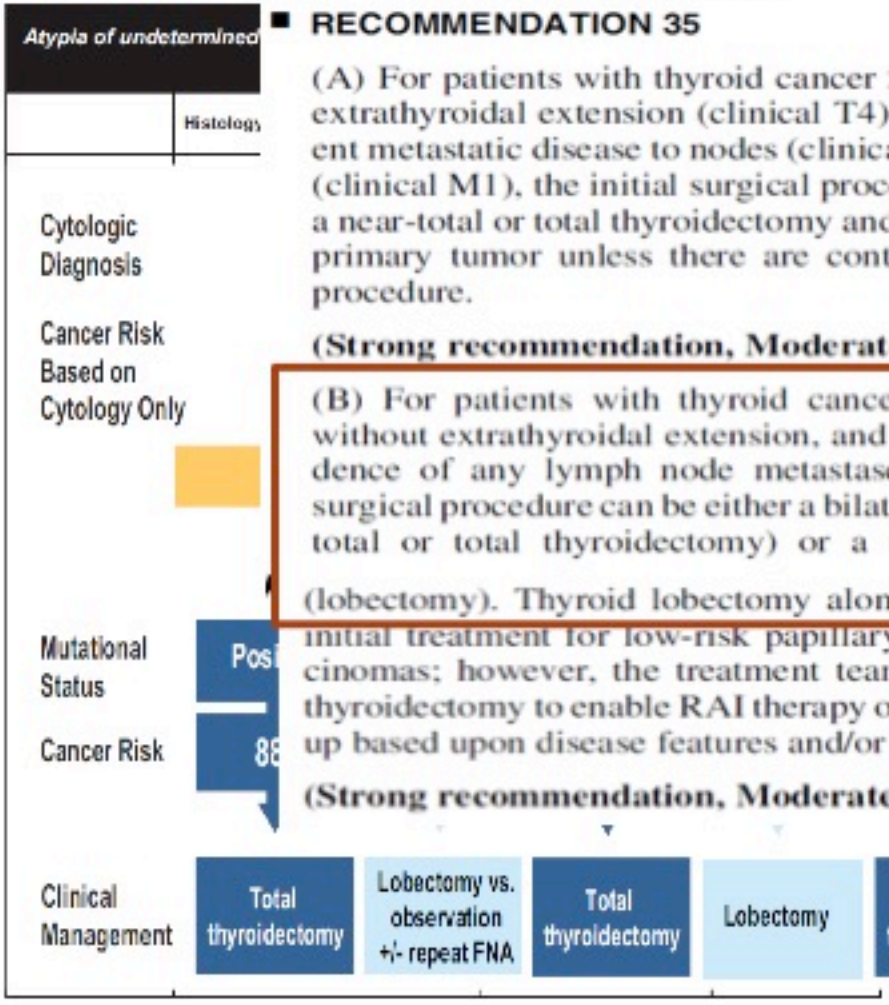


I nodi a citologia indeterminata nascondono un 15-30% di malignità

Mian C Own data

Impact of Mutational Testing on the Diagnosis and Management of Patients with Cytc Indeterminate Thyroid Nodules: A Analysis of 1056 FNA Samples

Yuri E. Nikiforov, N. Paul Ohori, Steven P. Hodak, S
Shane O. LeBeau, Robert L. Ferris, Linwah Yip, Raja
Mitchell E. Tublin, Michael T. Stang, Christopher Co
Andrew F. Stewart, and Marina N. Nikiforova



■ **RECOMMENDATION 35**

(A) For patients with thyroid cancer >4 cm, or with gross extrathyroidal extension (clinical T4), or clinically apparent metastatic disease to nodes (clinical N1) or distant sites (clinical M1), the initial surgical procedure should include a near-total or total thyroidectomy and gross removal of all primary tumor unless there are contraindications to this procedure.

(Strong recommendation, Moderate-quality evidence)

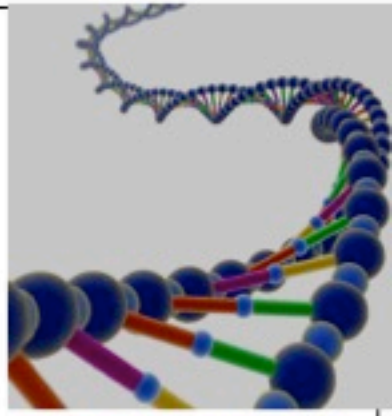
(B) For patients with thyroid cancer >1 cm and <4 cm without extrathyroidal extension, and without clinical evidence of any lymph node metastases (cN0), the initial surgical procedure can be either a bilateral procedure (near-total or total thyroidectomy) or a unilateral procedure (lobectomy). Thyroid lobectomy alone may be sufficient initial treatment for low-risk papillary and follicular carcinomas; however, the treatment team may choose total thyroidectomy to enable RAI therapy or to enhance follow-up based upon disease features and/or patient preferences.

(Strong recommendation, Moderate-quality evidence)

tico monocentrico su 513
nodi:
PTC-CV; 64% PTC-FV
i maligni sono mutati
adenomi RAS-positivi

Metab. 2011 Nov;96(11):3390-7

Quale follow-up nel nodo a citologia indeterminata? L'analisi molecolare



AUS/FLUS

Follicular neoplasm/ suspicious for follicular neoplasm

- **RECOMMENDATION 15**

  (A) For nodules with AUS/FLUS cytology, after consideration of worrisome clinical and sonographic features, investigations such as repeat FNA or molecular testing may be used to supplement malignancy risk assessment in lieu of proceeding directly with a strategy of either surveillance or diagnostic surgery. Informed patient preference and feasibility should be considered in clinical decision-making.

  (Weak recommendation, Moderate-quality evidence)

  (B) If repeat FNA cytology, molecular testing, or both are not performed or inconclusive, either surveillance or diagnostic surgical excision may be performed for an AUS/FLUS thyroid nodule, depending on clinical risk factors, sonographic pattern, and patient preference.

- **RECOMMENDATION 16**

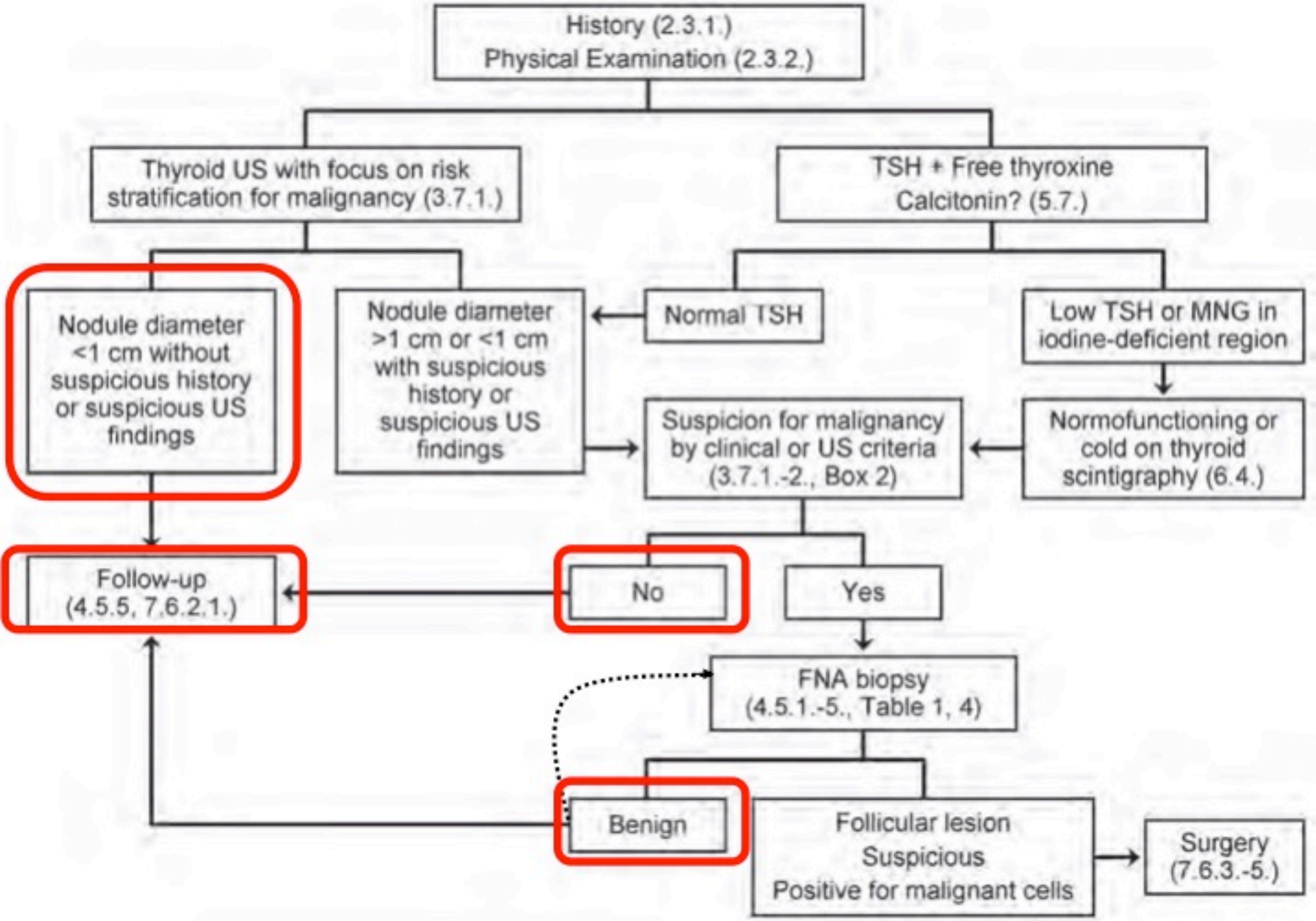
  (A) Diagnostic surgical excision is the long-established standard of care for the management of FN/SFN cytology nodules. However, after consideration of clinical and sonographic features, molecular testing may be used to supplement malignancy risk assessment data in lieu of proceeding directly with surgery. Informed patient preference and feasibility should be considered in clinical decision-making.

  (Weak recommendation, Moderate-quality evidence)

  (B) If molecular testing is either not performed or inconclusive, surgical excision may be considered for removal and definitive diagnosis of an FN/SFN thyroid nodule.

  (Strong recommendation, Low-quality evidence)

ATA 2016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No
Yes
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Benign
Follicular lesion
Suspicious
Positive for malignant cells
Surgery (7.6.3.-5.)

Quale follow-up nel nodo con citologia di benignità?

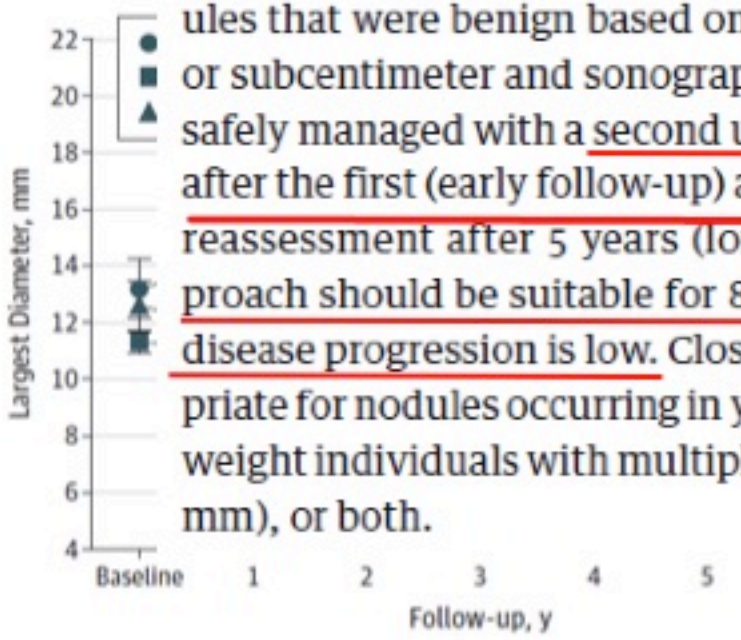
Original Investigation

The Natural History of Benign Thyroid Nodules

JAMA. 2015;313(9):926-935. doi:10.1001/jama.2015.0956

Cosimo Durante, MD, PhD; Giuseppe Costante, MD; Giuseppe Lucisano, MScStat; Rocco Bruno, MD; Domenico Meringolo, MD; Alessandra Paciaroni, MD; Efisio Puxeddu, MD, PhD; Massimo Torlontano, MD; Salvatore Tumino, MD; Marco Attard, MD; Livia Lamartina, MD; Antonio Nicolucci, MD; Sebastiano Filetti, MD

Figure 1. Changes in Thyrc
5 Years of Follow-up



Current guidelines suggest, based on expert opinion, repeating thyroid ultrasonography after 6 to 18 months and, if nodule size is stable, every 3 to 5 years.[7] The indolent behavior and limited growth observed in our study confirm that nodules that were benign based on initial fine-needle aspiration or subcentimeter and sonographically nonsuspicious can be safely managed with a second ultrasound examination 1 year after the first (early follow-up) and in the absence of changes, reassessment after 5 years (long-term follow-up). This approach should be suitable for 85% of patients, whose risk of disease progression is low. Closer surveillance may be appropriate for nodules occurring in younger patients or older overweight individuals with multiple nodules, large nodules (>7.5 mm), or both.

Risk factors OR
for growth

s)→ 3.2(3
9 (4 nodes)

1.7-4.9)

I 1.1-2.6

I 0.3-0.9)

Prevalence of thyroid cancer in original nodes : 0.3 % (5/1567). Only 2 had grown

Grazie per l'attenzione