CARCINOMA DIFFERENZIATO
DELLA TIROIDE:
DALLA DIAGNOSI
AL FOLLOW-UP

Le questioni aperte, le risposte possibili

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ASSOCIAZIONE MEDICI ENDOCRINOLOGI

Follow-up e persistenza di AbTg: cosa fare?

Enrico Graziano

Elevated Serum Thyroglobulin

A MARKER OF METASTASES IN DIFFERENTIATED THYROID CARCINOMAS

ANDRE J. VAN HERLE and ROBERT P. ULLER

From the Department of Medicine, Division of Endocrinology, Center for the Health Sciences, University of California at Los Angeles, School of Medicine, Los Angeles, California 90024

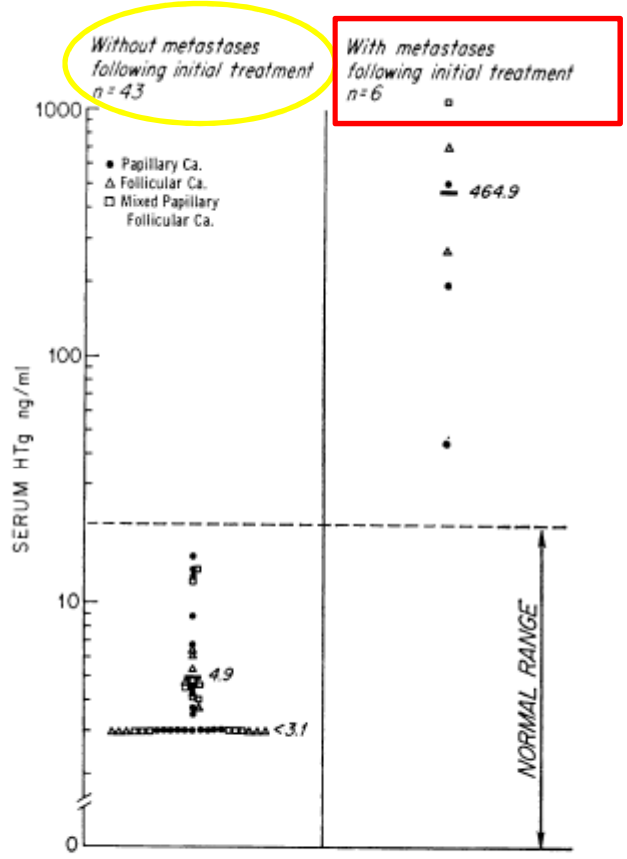
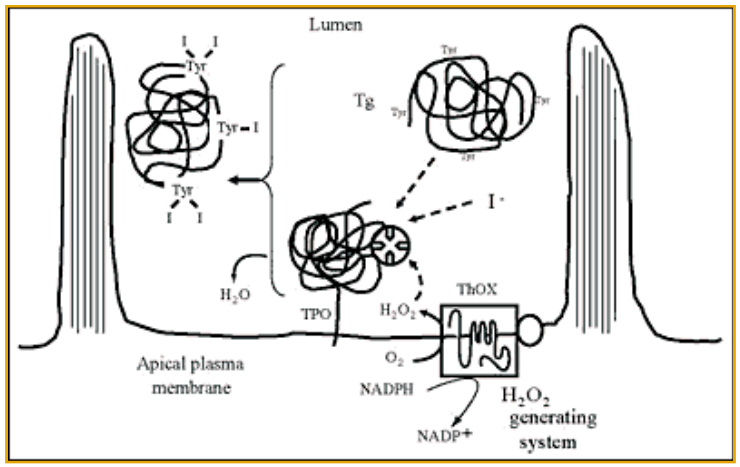


FIGURE 5 Serum HTg levels in patients with differentiated thyroid carcinoma after therapy is shown. The mean serum HTg concentration for patients without evidence of metastases (left panel) and with evidence of metastases (right panel) are indicated by the horizontal solid line. The upper limit of the normal range is indicated by the interrupted horizontal line.

Van Herle AJ 1975 , J Clin Invest 56: 272-277

Tireoglobulina

- glicoproteina globulare
- due subunità di 330 kD
- coefficiente di sedimentazione 19 S
- emivita di circa 65 ore
- substrato per la biosintesi degli ormoni tiroidei
- sintetizzata esclusivamente nel follicolo tiroideo

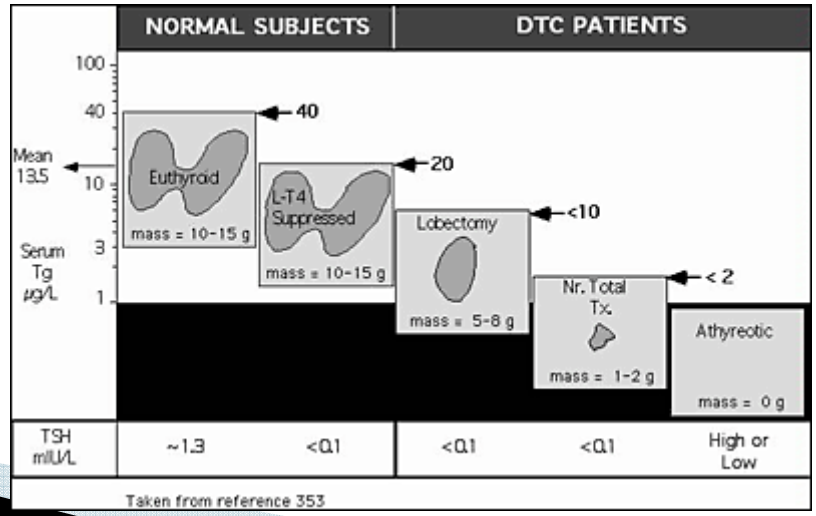


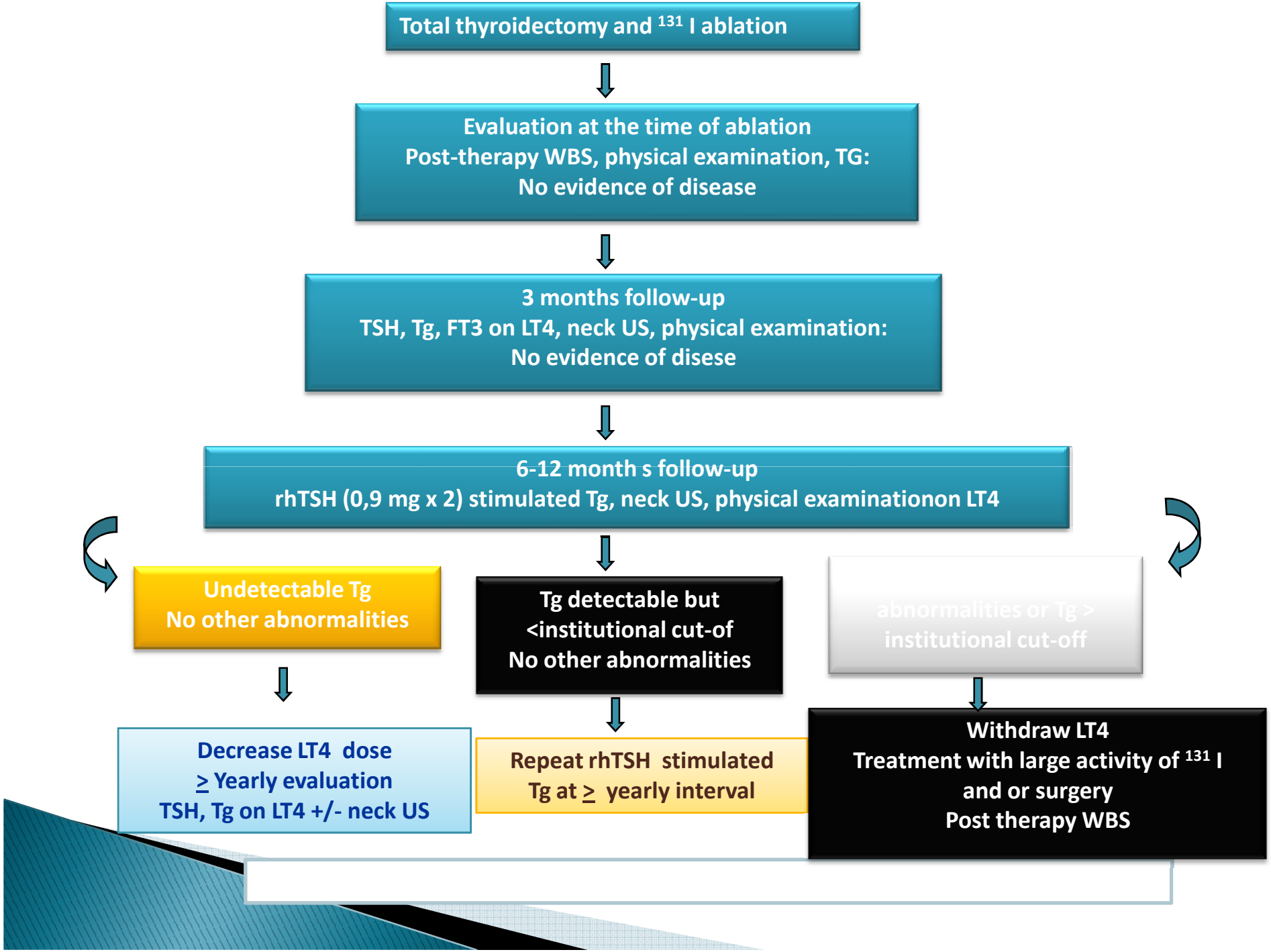
Tireoglobulina

La concentrazione della Tg nel siero dipende da:

- massa di tessuto tiroideo presente
- stimolazione del rTSH (TSH, rhTSH, HCG, Ab rTSH)
- traumi (FNA, ^{131}I) e infiammazione (tiroidite)

1 gr di tessuto normale produce → 1 ng/ml con TSH normale,
0,5 ng/ml con TSH < 0,1 mU/l

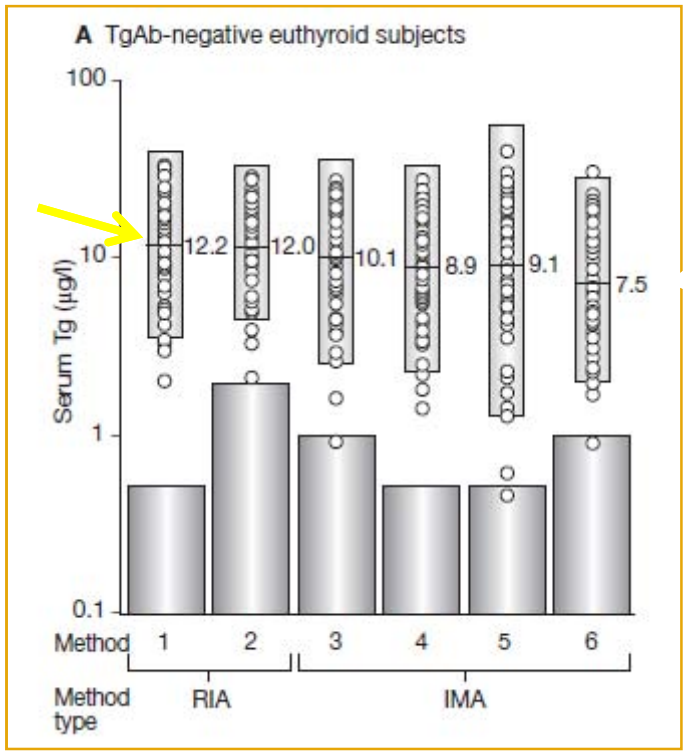



Total thyroidectomy and 131 I ablation
Evaluation at the time of ablation
Post-therapy WBS, physical examination, TG:
No evidence of disease
3 months follow-up
TSH, Tg, FT3 on LT4, neck US, physical examination:
No evidence of disese
6-12 month s follow-up
rhTSH (0,9 mg x 2) stimulated Tg, neck US, physical examinationon LT4
Undetectable Tg
No other abnormalities
Tg detectable but
<institutional cut-of
No other abnormalities
abnormalities or Tg >
institutional cut-off
Decrease LT4 dose
≥ Yearly evaluation
TSH, Tg on LT4 +/- neck US
Repeat rhTSH stimulated
Tg at ≥ yearly interval
Withdraw LT4
Treatment with large activity of 131 I
and or surgery
Post therapy WBS

Dosaggio della Tireoglobulina: tutto semplice?

Standardizzazione del dosaggio:

dopo l'introduzione dello standard CRM 457 variabilità tra metodi ridotta dal 42,9% al 28,85 (Feldt-Rasmussen U. 1994; Spencer C.A. 1996) ma non eliminata



Spencer CA, Lo Presti JS; 2008 Nat Clin Pract Endocrinol Metab

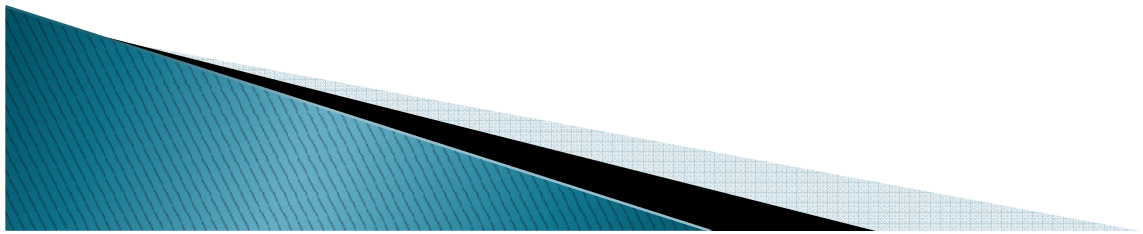
❑**Serum thyroglobulin should be measured every 6-12 months by an immunometric assay, ideally *in the same laboratory and using the same assay,* during the follow-up of patients with differentiated thyroid carcinoma who have undergone total or near-total thyroidectomy and thyroid remnant ablation.**

Recommendation A

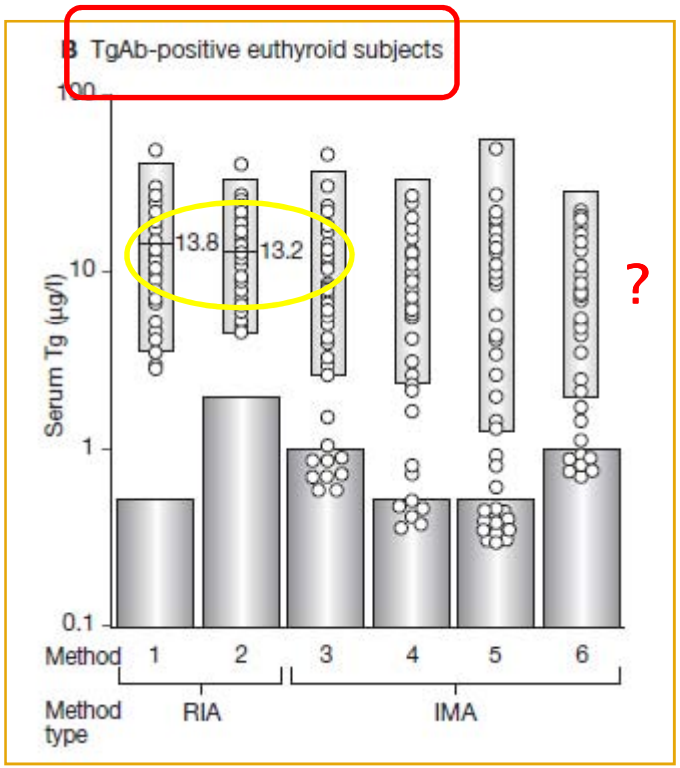
The American Thyroid Association Guidelines Taskforce-2006

❑**To ensure continuity in monitoring, clinicians should use *the same laboratory and Tg assay* on long-term basis. *Laboratories should not change methods without prior consultation with clinical users of the service* (IV, C)**

British Thyroid Association, Royal College of Physicians- 2007

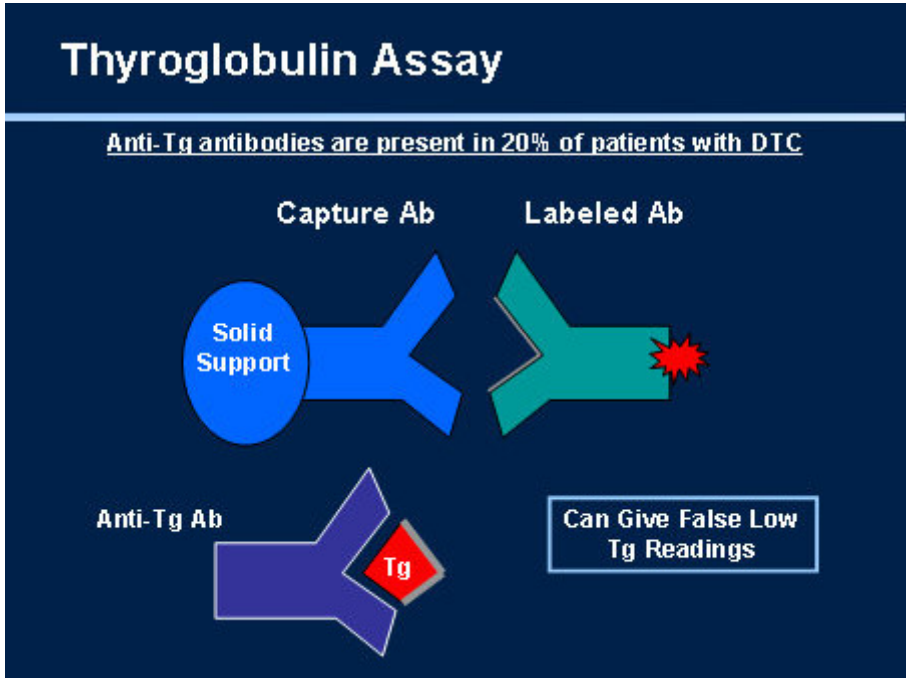


Dosaggio della Tireoglobulina: tutto semplice?



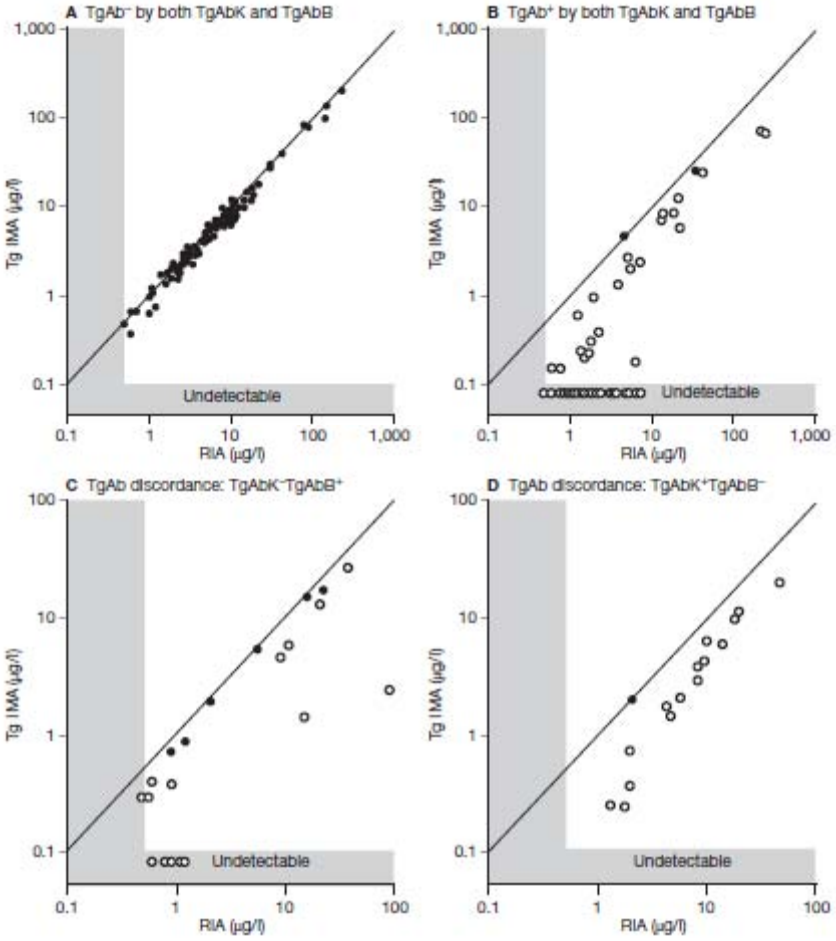
Spencer CA, Lo Presti JS; 2008 Nat Clin Pract Endocrinol Metab

Dosaggio della Tireoglobulina: tutto semplice?



Dosaggio della Tireoglobulina: tutto semplice?

AbTg negativi con A e B



AbTg positivi con A e B

AbTg negativi con A positivi con B

AbTg positivi con A negativi con B

Spencer CA, Lo Presti JS; 2008 Nat Clin Pract Endocrinol Metab

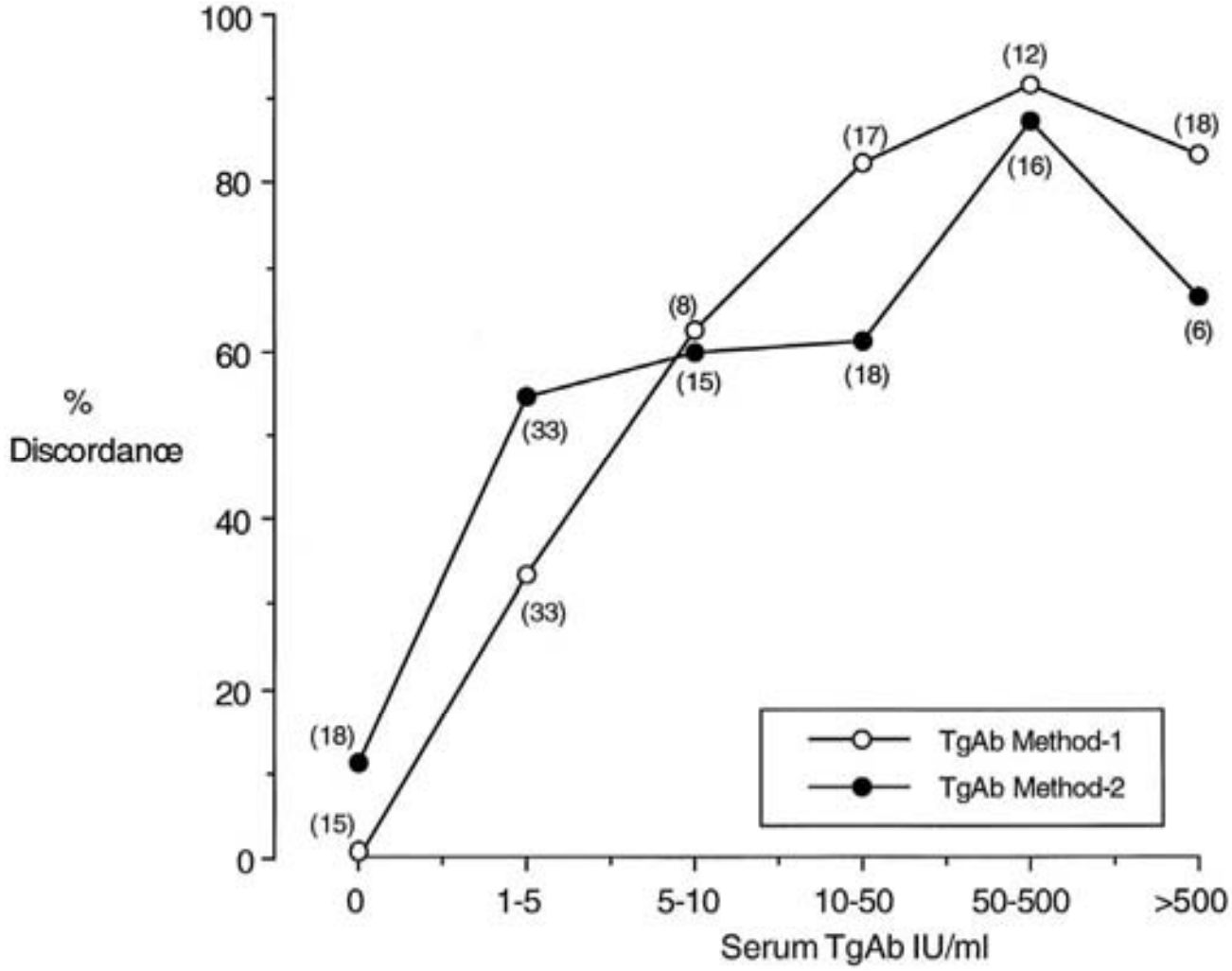
Il test di recupero può essere utilizzato per superare il problema dell'interferenza degli AbTg?

Recoveries of serum Tg (~10 ng/ml) from TgAb-positive sera

Tg method	Tg Conc. Mean ± SD (range)	Antibody status (n)	% Mean ±SD recovery of serum Tg	Range
RIA	6.6 ± 1.3 (2-12.7) 15.6 ± 3.7 (2.8-45)	TgAb NEG (10) TgAb POS (11)	99 ± 8 81 ± 19	89 – 109 48 - 106
IRMA-1	6.4 ± 1.2 (2.5-14.5) <0.3 (<0.3 to 1.1)	TgAb NEG (10) TgAb POS (11)	95 ± 8 73 ± 30	82 – 108 44 - 106
IRMA-2	6.4 ± 1.2 (2.5-14.5) <0.5 (<0.5 to 0.9)	TgAb NEG (10) TgAb POS (11)	95± 6 73 ± 38	89 – 109 0 - 100

Spencer C. A. et al. J Clin Endocrinol Metab 1998;83:1121-1127

Esiste un valore “soglia” del titolo degli AbTg che predice la comparsa dell’interferenza degli AbTg?



Spencer, C. A. et al. J Clin Endocrinol Metab 1998

Relationship between circulating TgAbs and measurable Tg values, TSH and amount of thyroid remnant tissue (^{131}-I 24-h uptake) prior initial radioiodine therapy

	Group I (TgAbs < 6 U/ml)	Group II (TgAbs >6 U/ml)	Group IIa (TgAbs 7–50 U/ml)	Group IIb (TgAbs >50 U/ml)
Number of patients	80	32	10	22
Percentage of Tg values <0.3 ng/ml	4%	59%	30%	73%
Tg levels (median of all samples)	5.0 ng/ml	<0.3 ng/ml	1.3 ng/ml	<0.3 ng/ml
Tg recovery (median of all samples)	100%	98%	97%	101%
TSH (median of all samples)	47 mU/l	57 mU/l	48 mU/l	59 mU/l
^{131}1 24-h uptake (median)	4.0%	4.4%	3.1	4.5%

Görges R et al, Eur J Endocrinol 2005;153:49-55

Anticorpi anti tireoglobulina

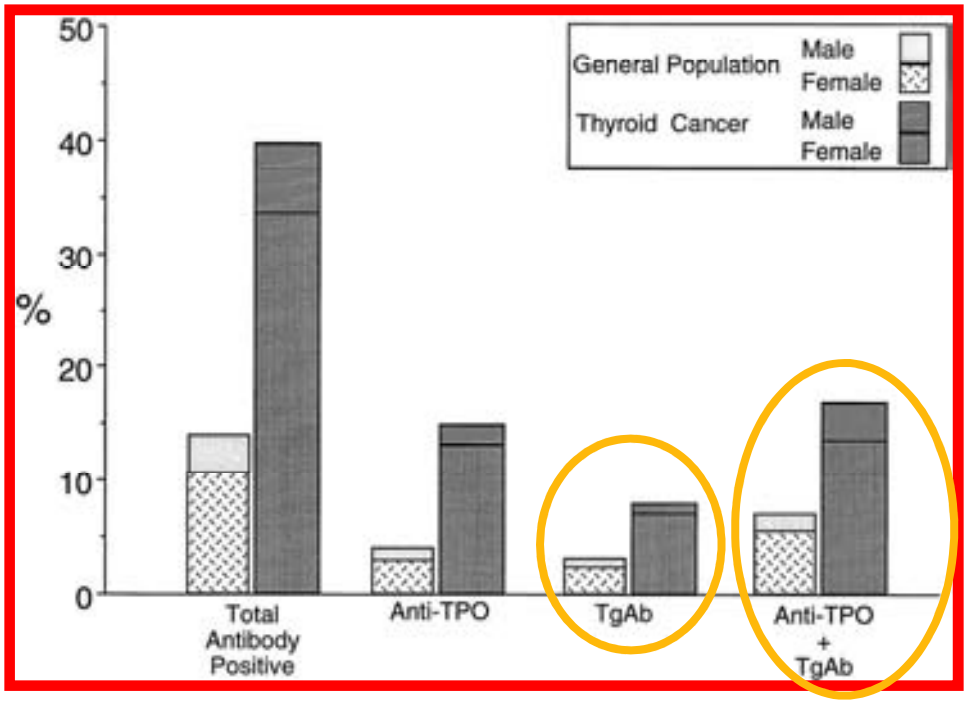
- Sono prodotti prevalentemente dai linfociti presenti nella tiroide, meno nei linfonodi cervicali e nel midollo osseo (Weetman AP, 1994, Endocr. Rev.), raramente dai linfociti circolanti (Mariotti S. 1984, JCEM)

- Sono policlonali, appartengono alla classe IgG, nei DTC prevale la classe IgG_2 (Caturegli AF 1994 Clin Exp Immunol)

Serum Thyroglobulin Autoantibodies: Prevalence, Influence on Serum Thyroglobulin Measurement and Prognostic Significance in Patients with Differentiated Thyroid Carcinoma

	213 DTC	⟷	4453 controls
• TgAb	24.9%		10.1%
• TgAb alone	8.0%		3.1%
• TgAb +TPOAb	16.9%		7.0%

- 3 TgAb methods:
- 1 agglutination, 1 ICMA,
- 1 RIA
- Serum Tg concentrations:
- 4 assay methods: 1 RIA,
- 2 IRMA, 1 ICMA



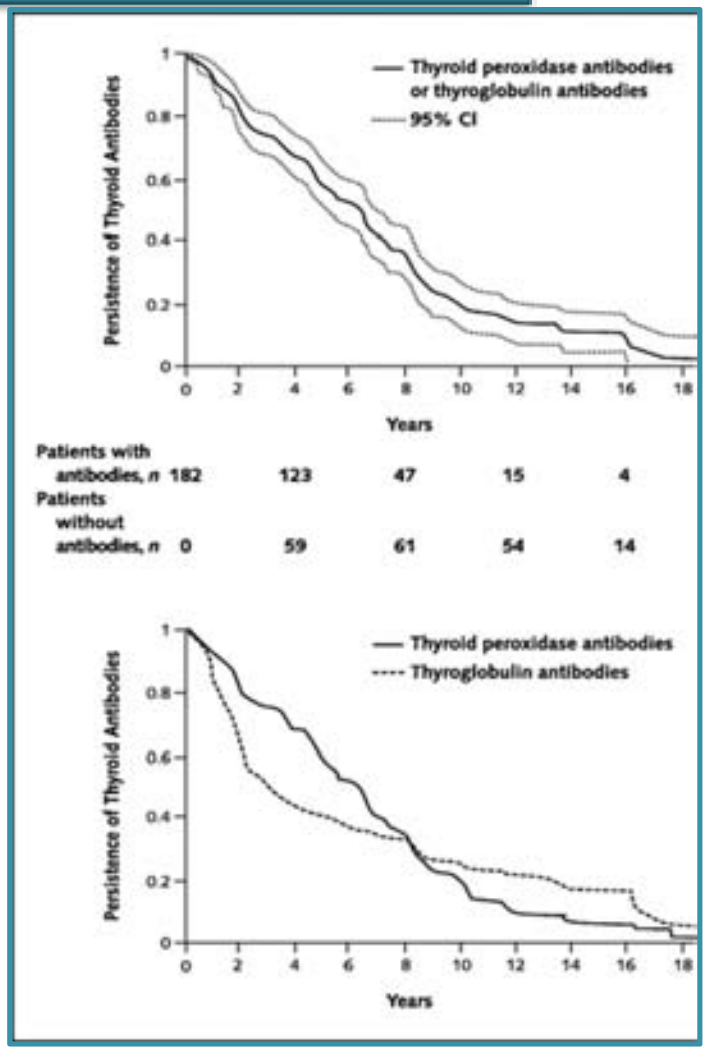
Spencer C. A. et al. J Clin Endocrinol Metab 1998

Disappearance of Humoral Thyroid Autoimmunity after Complete Removal of Thyroid Antigens
L.Chiovato, 2003, Ann Intern Med.

182 DTC, AbTg, AbTPO, AbTSH +
151 m., 31 f.
10 m. di Basedow, 34 tiroidite di Hashimoto
Età 6-81 a , media 39,7 +/-13,7 a
Follow-up 4-20 anni, media 10,1 +/- 4,1 a

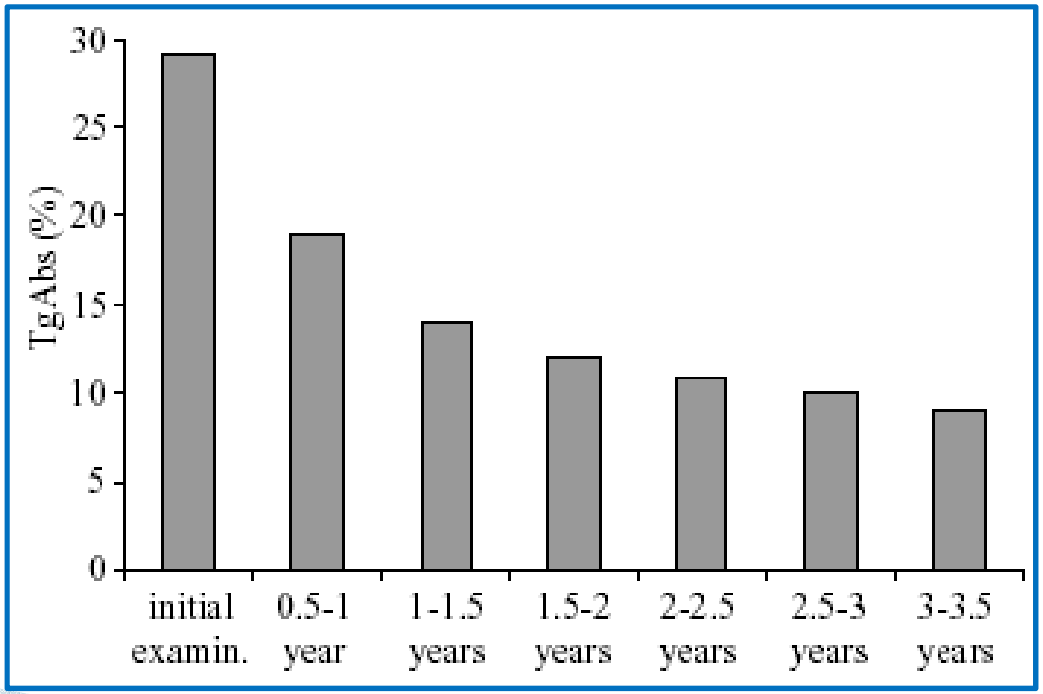
Table. Median Time to Disappearance of Thyroid Antibodies and Thyroid Tissue after Initial Treatment (Thyroidectomy and Iodine-131)

Variable	Median Time to Disappearance (95% CI), *y*
Thyroid peroxidase or thyroglobulin antibodies (*n* = 182)	6.4 (5.5–7.4)
Thyroid peroxidase antibodies (*n* = 172)	6.3 (5.3–7.2)
Thyroglobulin antibodies (*n* = 116)	3.0 (1.9–4.1)
Thyroid tissue (*n* = 182)	2.8 (2.4–3.2)



Clinical impact of TgAb in patients with differentiated thyroid carcinoma during the first 3 years after thyroidectomy

112 Pt, 81 f, 31m,
Mean age: 50 yr (range 17-78)
Mean follow-up: 33 ± 8 months
All Pt had been thyroidectomized and received radioiodine therapy

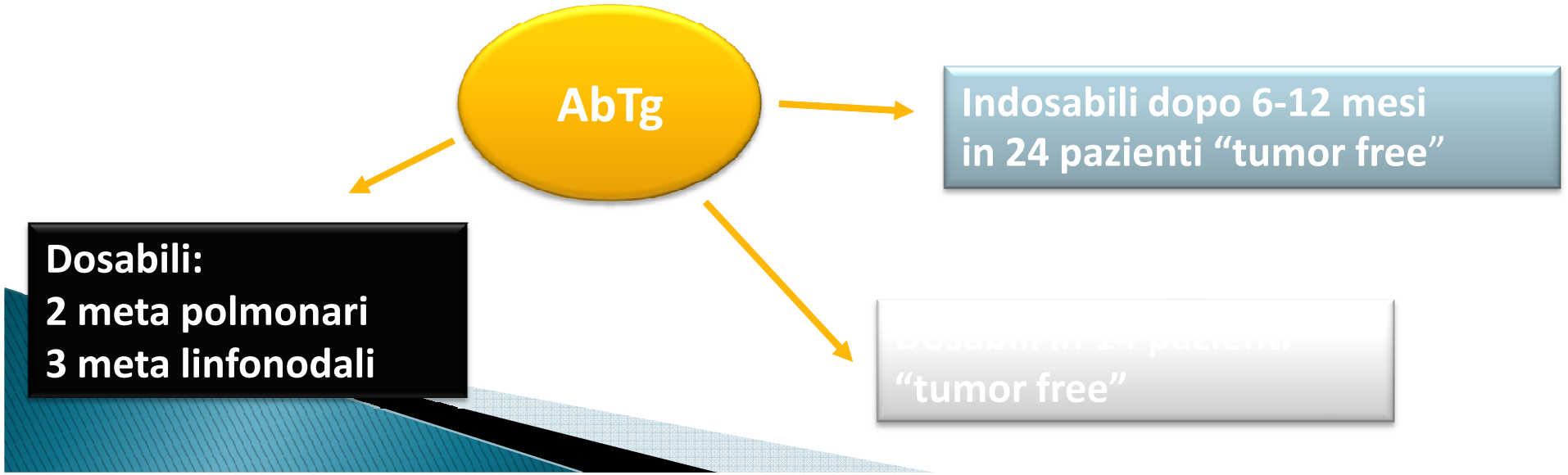


Görges R et al, Eur J Endocrinol 2005;153:49-55

Clinical Meaning of Circulating Anti-thyroglobulin Antibodies in Differentiated Thyrod Cancer: a Prospective Study
D.Rubello, J Nucl Med, 1992

43 pazienti con DTC
- 35 donne, 8 uomini
- 33 ca papillare, 10 ca follicolare
- AbTg+ prima dell'intervento chirurgico
- follow up di 2-5,4 anni
- Tg (IRMA) < 3 ng/ml, AbTg (RIA) < 50 U/ml

Nessuna correlazione tra valori preoperatori degli AbTg, estensione del tumore, decorso della malattia dopo la terapia



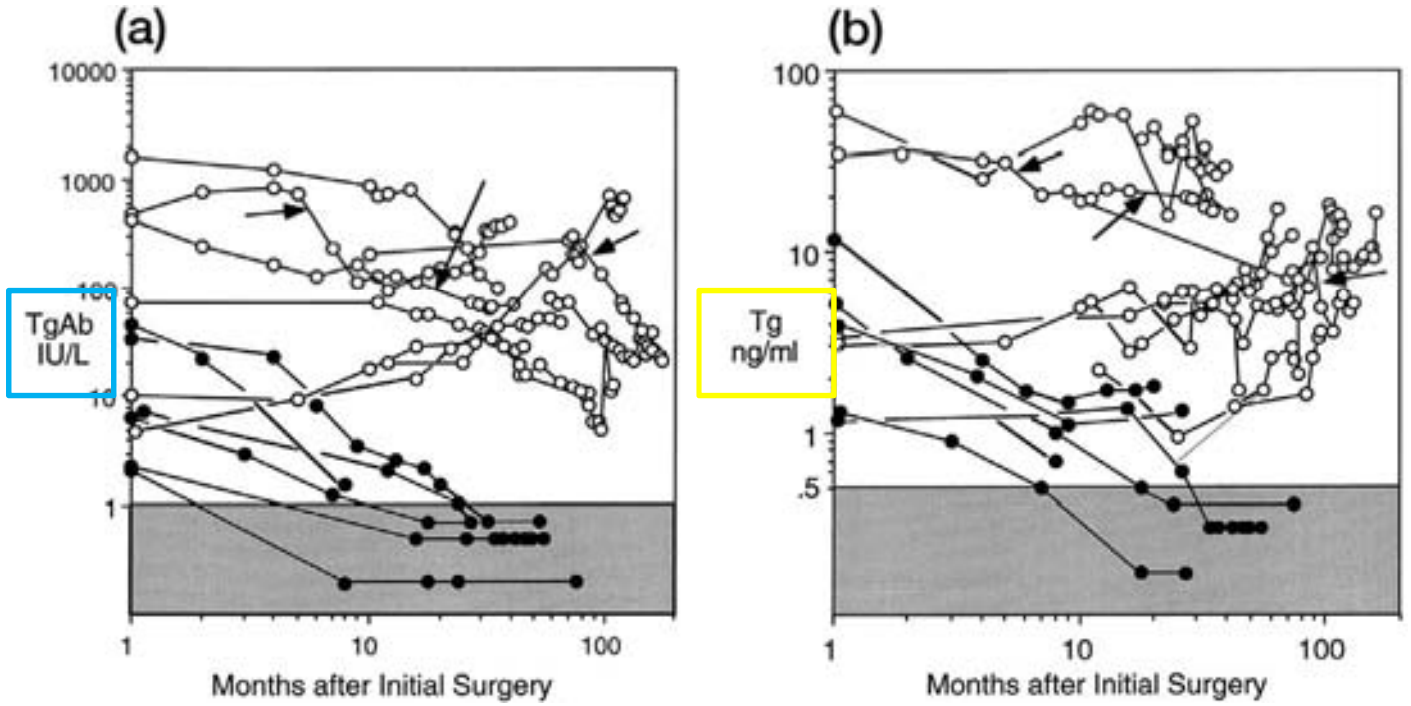
Clinical Meaning of Circulating Anti-thyroglobulin Antibodies in Differentiated Thyrod Cancer: a Prospective Study
D.Rubello, J Nucl Med, 1992

- La persistenza degli AbTg, soprattutto ad alto livello, può indicare di per sè la presenza di metastasi, tuttavia molti dei Pazienti con AbTg + erano considerati “tumor free”.

  Possibili spiegazioni: microfoci di tessuto metastatico, persistenza della memoria linfocitaria

- La scomparsa degli AbTg si associa a “guarigione”
- La persistenza degli AbTg nei pazienti “tumor free” consiglia attenta sorveglianza

Serum Thyroglobulin Autoantibodies: Prevalence, Influence on Serum Thyroglobulin Measurement and Prognostic Significance in Patients with Differentiated Thyroid Carcinoma



Spencer C. A. et al. J Clin Endocrinol Metab 1998;83:1121-1127

Clinical significance of elevated level of serum antithyroglobulin antibody in patients with differentiated thyroid cancer after thyroid ablation
J.K.Chung, 2002, Clinical Endocrinology

AbTg pos 51 ⇐ 226 DTC, Tg <1 ng/ml ⇒ AbTg neg 175

26 SEM (51%)

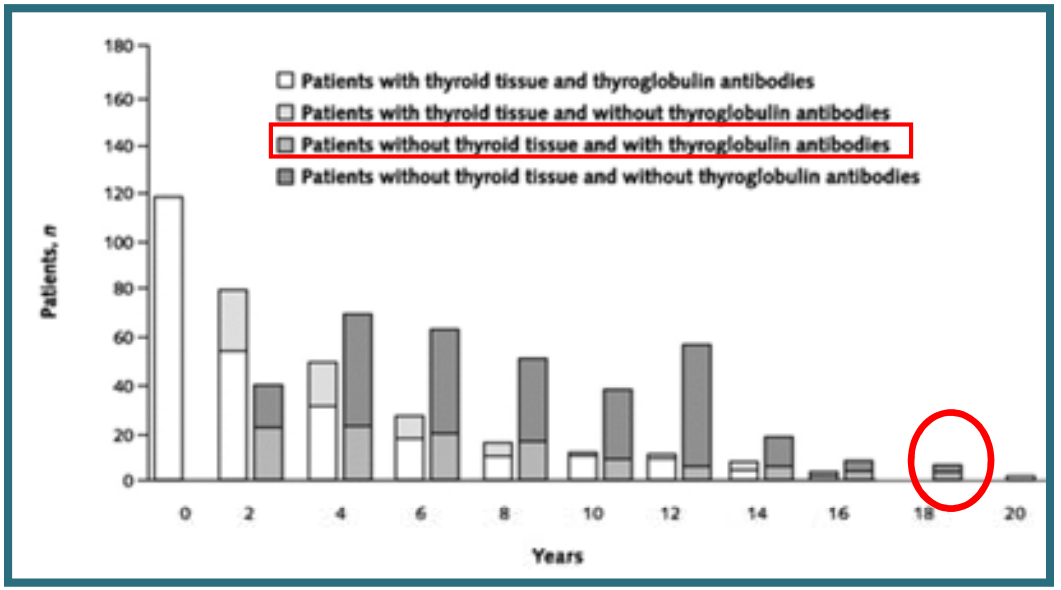
25 EM (49%)

AbTg:follow up 28,8 +/-12.3 mesi
19 riduzione o normalizzazione
4 aumento
3 immodificati

AbTg: dopo terapia
ridotti in 10, invariati
o aumentati in 4

6 recidive (3,4%)

Number of patients with persistent and ablated thyroid tissue at each 2-year time point



" at the end of individual follow-up 43 patients had persistent thyrod tissue"

0 → **metastatic lymphonode lesions**

10 → **distant metastatic lesions**

17 → **thyroid bed tissue**

10 → **detectable Tg despite negative imaging finding**

Chiovato L et al, Ann Intern Med 2003:153:49–55,

Serum thyroglobulin concentrations predict disease-free remission and death in differentiated thyroid carcinoma. Heemstra KA et al. Clin Endocrinol 2007

	Evaluable patients (*N*)*	Patients with positive TgAb (*N*, % of evaluable patients)
Pre-ablation	304	82 (27·0)
Six months after initial therapy, suppressed TSH	287	79 (27·5)
Six months after initial therapy, stimulated TSH	287	79 (27·5)
Two years after initial therapy, suppressed TSH	244	32 (13·1)
Five years after initial therapy, suppressed TSH	182	23 (12·6)

- **No significant differences in tumor presence between Pt TgAb + and TgAb –**
- **The presence of TgAb did not have a significant prognostic for disease-free remission or death**

Detection of circulating thyroid cells in peripheral blood.
Ditkoff B.A. 1996, Surgery

100 soggetti, 77 donne e 23 uomini
Tg mRNA con metodo RT-PCR

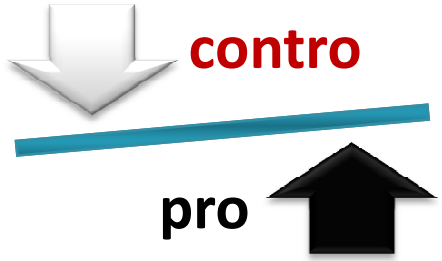
- **9/9 con carcinoma tiroideo metastatico**
- **7/78 ritenuti liberi da malattia**
- **0/6 operati per tireopatie benigne**
- **0/7 controlli sani**

Molecular Diagnosis of Residual and Recurrent Thyroid Cancer by Amplification of Thyroglobulin Messenger Ribonucleic Acid in Peripheral Blood
Ringel M.D., 1998 J Clin Endocrinol Metab

Tg mRNA is detectable in the blood of ***normal subjects*** as well as most patients with ***residual thyroid cancer*** who are taking thyroid hormone…

Detection of circulating thyroglobulin mRNA is more sensitive marker of residual thyroid tissue or cancer than immunoassay for serum Tg, particularly in patients treated with thyroid hormone or who have circulating antithyroglobulin antibodies.

Low Specificity of Blood Thyroglobulin Messenger Ribonucleic Acid Assay **Prevents Its Use** in the Follow-up of Differentiated Thyroid Cancer Patients
Elisei R., 2004 J Clin Endocrinol Metab



Sensibilità	82.3%
Specificità	24.2%
VPP	65.6%
VPN	43.7%

Detection of Thyrotropin-Receptor Messenger Ribonucleic Acid (mRNA) and Thyroglobulin mRNA Transcripts in Peripheral Blood of Patients with Thyroid Disease: Sensitive and Specific Markers for Thyroid Cancer
Chinnappa P.,2004 J Clin Endocrinol Metab

	TSHR mRNA	Tg mRNA	Serum Tg	131I WBS
Sensibilità	100	100	95	83
Specificità	98	92	96	100
PPV	95	83	90	100
NPV	100	100	96	94

Effectiveness of Peripheral Thyrotropyn Receptor mRNA In Follow-Up of Differentiated Thyroid Cancer
Milas M, Gupta M, Ann Surg Oncol 2009

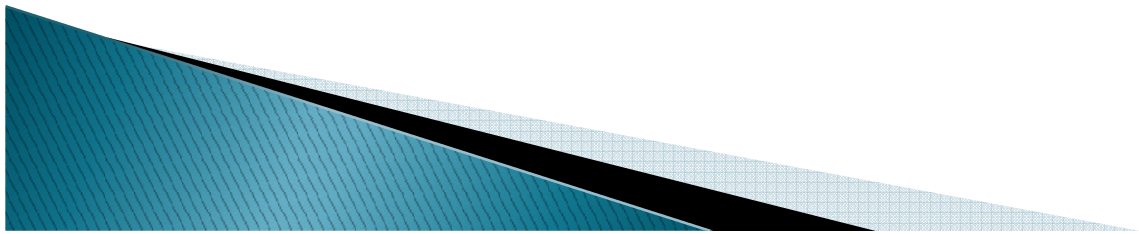
- 34 DTC patients
- median follow-up 20 ±14 m.
- TSHR mRNA by quantitative RT-PCR
- TSHR mRNA ≥1.02 ng/µg = cancer

TABLE 1 Summary of TSHR mRNA contributions to the assessment of disease status in 34 thyroid cancer patients during long-term follow-up

	Number of patients (%)
TSHR mRNA exhibited beneficial effects by	
Clear consensus with other clinical parameters	13 (38)
First indication of disease recurrence	2 (6)
In TgAb+ patients, reassurance of NED	5 (15)
Support of disease recurrence	2 (6)
First indication of recurrence	1 (3)
Total	23 (68)
TSHR mRNA exhibited negative effects by	
Missing gross disease	3 (9)
Missing occult disease	3 (9)
Discordance resolved only by future follow-up	5 (15)
Total	11 (32)

NCCN -Thyroid Carcinoma
Practice Guidelines in Oncology
v.1.2008

RNA based detection strategies (including the sodium –iodine symporter [NIS], TSH receptor, and Tg mRNAs) or DNA-based strategies to detect thyroid oncogenes in peripheral blood, represent current areas of active research that may improve the detection of residual cancer and the monitoring of these patients, especially during thyroxine treatment or when circulating anti-Tg antibodies are present.



Conclusioni 1

Tireoglobulina e AbTg

- La Tg deve essere dosata contemporaneamente al TSH (BTA, RCP IV,C)
- Ricercare sempre gli AbTg quando si dosa la Tg (BTA, RCP IV,C)
- Gli AbTg non sono sempre "riconosciuti" da tutti i metodi di dosaggio
- Tg indosabile con AbTg negativi non significa pertanto assenza certa di malattia
- I metodi IMA sottostimano la Tg, quindi rischio di diagnosi ritardate
- I metodi RIA in genere sovrastimano la TG, quindi rischio di allarmi ingiustificati
- Il test di recupero non valuta correttamente l'interferenza degli AbTg (BTA,RCP IV,C)
- Non esiste un valore soglia per l'interferenza degli AbTg
- Tg dosabile con metodo IMA è sospetta per persistenza di malattia
- La presenza di anticorpi eterofili può falsare i risultati della Tg
- Diffidare di una Tg indosabile ma non coerente con il quadro clinico della malattia
- Nei casi incerti è utile eseguire il dosaggio contemporaneo con metodi RIA e IMA
- Il test con rhTSH non elimina il problema dell'interferenza degli AbTg.

Conclusioni 2

Anticorpi anti Tireoglobulina

- Prevalenza nei DTT circa 20-25%
- Nessun significato prognostico favorevole o sfavorevole per la malattia
- La presenza di AbTg non modifica il profilo del rischio
- Persistono a lungo 3-5 anni e più anche in assenza di tessuto tiroideo normale o neoplastico dimostrabile
- Si riducono fino a scomparire in caso di guarigione
- Restano invariati, aumentano o compaiono ex novo in caso di recidiva
- Dosaggi seriati possono pertanto essere considerati un marker oncologico surrogato nei pazienti AbTg positivi e Tg negativi

Follow-up : cosa fare ?

Carcinoma Differenziato della Tiroide
Linee Guida SIE-AIMN-AIFM
per il trattamento ed il follow-up
2004

I pazienti con TgAb sierici devono essere seguiti con le metodiche di imaging e con l'esecuzione di STB

Follow-up : cosa fare ?

European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium
F.Pacini et Al. European Journal of Endocrinology 2006

Management of patients with positive AbTg

.. In patients with positive levels of AbTg, undetectable serum Tg levels cannot be interpreted as evidence of remission. These patients must be monitored with periodical ^{131} I diagnostic WBS and neck US.
Whenever there is a suspicion of distant disease, patients should also undergo imaging techniques such as CT, MRI, and FDG-PET.
The disappearance of AbTg during follow-up may in itself be considered as evidence of remission.

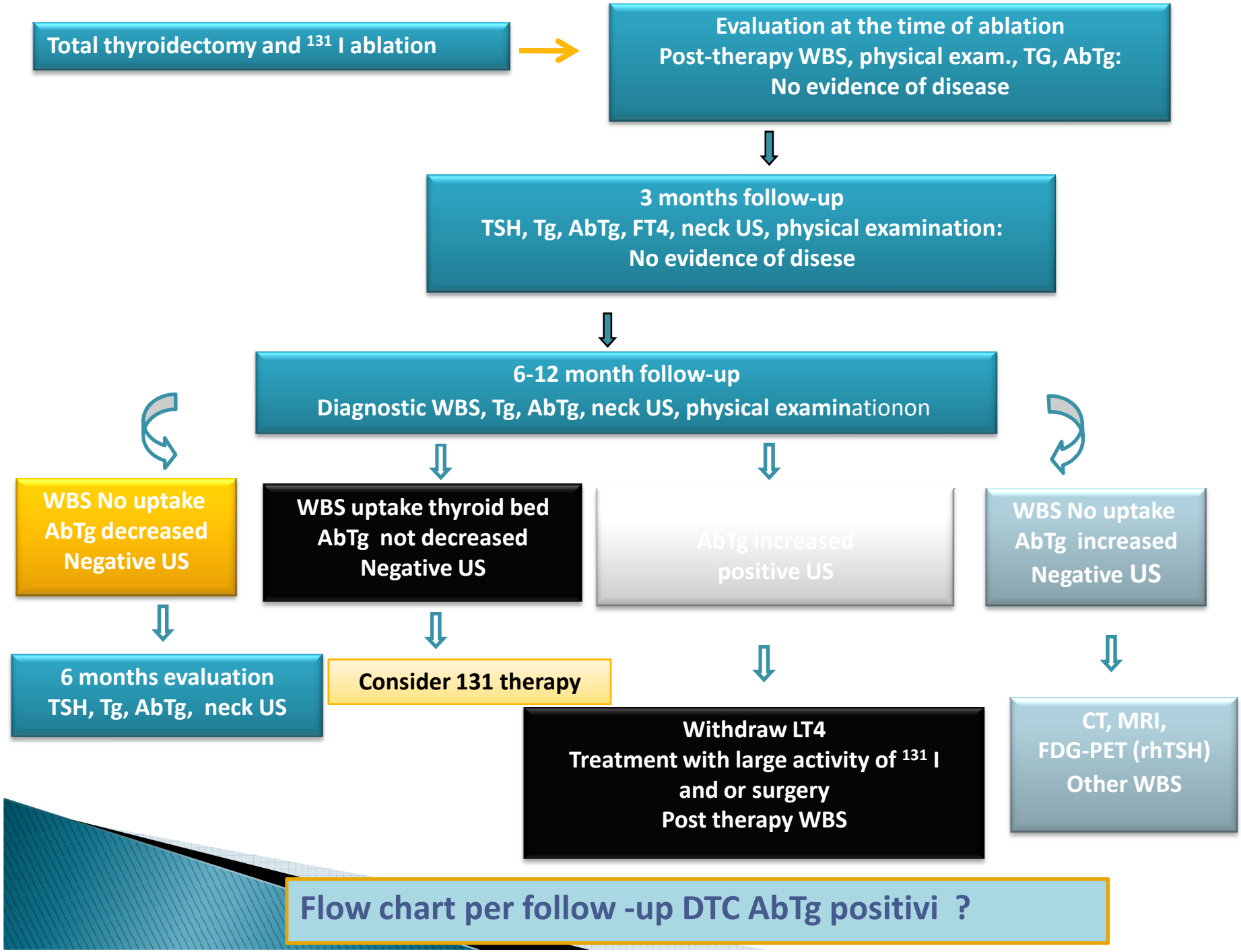
Follow-up : cosa fare ?

Guidelines for the management of thyroid cancer
Second edition 2007
British Thyroid Association, Royal College of Physicians

Ultrasonography may have a particular role when serum Tg measurements are unreliable because of the presence of assay interference.

… a single diagnostic WBS performed 6-8 months (but non sooner than 6 months) after ^{131}I ablation is generally indicated except in those with low-risk disease…(III,B)

… Patients with high-risk disease and with Tg antibodies interfering with serum Tg measurements may need additional radioiodine, ultrasound or other cross-sectional (eg CT or MRI) scans…



Flow chart per follow -up DTC AbTg positivi ?