



Bari,
7-10 novembre 2013

Follow-up del carcinoma tiroideo a rischio intermedio-alto Tg ultrasensibile o stimolo con rhTSH?

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Summary



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- Differentiated thyroid tumors follow-up (current guidelines)
- Recombinant human TSH (Thyrogen®)
- Ultra-sensitive thyroglobulin
- The next future



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Current guidelines



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Revised ATA guidelines 2009:

- No specific paragraphs regarding intermediate/high risk patients follow-up
- Recommended initial TSH suppression in all pts. to below 0.1 mU/l until Tg stimulation is performed (6-12 months later)



Current guidelines



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Criteria for absence or residual disease:

- **No clinical evidence of tumor**
- **No imaging evidence of tumor** (post-treatment WBS and neck US)
- **Undetectable Tg levels** during TSH suppression and stimulation, in the absence of Tg antibodies



What we know for sure



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The other two thirds will show undetectable or decreasing or stable Tg levels without any signs of residual disease



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Total thyroidectomy + ^{131}I

6 months: (LT4) TSH, Tg, TgAb

12 months: (LT4) **rhTSH-Tg** + US (if neg. TgAb)

Negative Tg, no other abnormalities

Low positive Tg : 1-5 ng/ml, no other abnormalities

Tg > 5 ng/ml, negative US

Substitutive LT4 dose
Yearly controls:
TSH, Tg, US

Repeat rhTSH-Tg
1-2 yrs later

Morphology (CT, PET/CT, etc.)
Eventually ^{131}I

Negative Tg

Stable/decreasing Tg:
no disease
Eventually repeat rhTSH-Tg
1-2 yrs later

**Increasing Tg:
presence of disease**

ETA 2006, modified



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rhTSH



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Rosario 2012:

Retrospective study:

318 intermediate/high-risk pts, negative for all parameters 8-12 months after ablation (including post-dose WBS, LT4-Tg <1 ng/ml, TgAb, neck US)

**WBS and stimulated Tg
(withdrawal or rhTSH)**



rhTSH



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<i>DxWBS</i>	<i>Tg measured after L-T4 withdrawal (number of patients)</i>			<i>Total</i>
	<i><1 ng/mL</i>	<i>1-10 ng/mL</i>	<i>>10 ng/mL</i>	
Negative	146	31	6	183
Uptake only in thyroid bed ^a	25	8	2	35
Ectopic uptake	0	0	0	0
Total	171	39	8	218

<i>DxWBS</i>	<i>Tg measured after rhTSH (number of patients)</i>			<i>Total</i>
	<i><1 ng/mL</i>	<i>1-5 ng/mL</i>	<i>>5 ng/mL</i>	
Negative	74	13	2	89
Uptake only in thyroid bed ^a	8	3	0	11
Ectopic uptake	0	0	0	0
Total	82	16	2	100



rhTSH



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Long term recurrence rate (24-96 months)

s-Tg <1 ng/ml 2% (5/253)

**NPV of sTg <1 ng/ml:
98%**

s-Tg >1 ng/ml

(3/7)



rhTSH



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	Patients	Persistent disease (%)	NPV of rhTSH1 US- and Tg- (%)	PPV of rhTSH1 US- and Tg+ (%)	Increased Tg at rhTSH2 (%)	Tg+ ↓ Tg- (%)
Castagna et al 2008	77 (67 Tg- 10 Tg+)	1/77 (1.3)	98.5	0	4/77 (5.2) (1 with disease)	4/10 (40)
Crocetti et al 2009	101 (89 Tg- 12 Tg+)	2/101 (2.0)	98.9	16.7	2/101 (2.0) (1 with disease)	6/12 (50)

Castagna et al, JCEM 2008
Crocetti et al, Thyroid 2009



rhTSH



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	rhTSH2 Tg-	rhTSH2 Tg+	Increased Tg	Confirmed residual disease
rhTSH	<p>NPV: 99% PPV: 0-16.7%: undetectable Tg at II rhTSH in 40-50% of Tg+</p>			

Castagna et al, JCEM 2008
Crocetti et al, Thyroid 2009



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Comparison of Seven Serum Thyroglobulin Assays in the Follow-Up of Papillary and Follicular Thyroid Cancer Patients

M. Schlumberger, A. Hitzel, M. E. Toubert, C. Corone, F. Troalen, M. H. Schlageter, F. Claustrat, S. Koscielny, D. Taieb, M. Toubeau, F. Bonichon, F. Borson-Chazot, L. Leenhardt, C. Schwartz, C. Dejax, I. Brenot-Rossi, M. Torlontano, F. Tenenbaum, S. Bardet, F. Bussière, J. J. Girard, O. Morel, O. Schneegans, J. L. Schlienger, A. Prost, D. So, F. Archambeaud, M. Ricard, and E. Benhamou

Tg1 (at 3 months):

Traditional assays (cut-off 0.9 g/ml):
sensitivity 19-40% (very low)

Ultra-sensitive assays (cut-off 0.2-0.3 ng/ml):
sensitivity 54-63%, specificity 89%



Long-Term Follow-Up of Patients with Papillary and Follicular Thyroid Cancer: A Prospective Study on 715 Patients

M. Brassard, I. Borget, A. Edet-Sanson, A.-L. Giraudet, O. Mundler, M. Toubeau, F. Bonichon, F. Borson-Chazot, L. Leenhardt, C. Schwartz, C. Deiax.



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84% of pts: Tg on Lt4 3 months after ablation (Tg1) < 0.27 pg/ml, with a NPV of 99%

Conclusions: Tg stimulation can be avoided in the great majority of patients



**Retrospective study: 1029 rhTSH tests in 849 TgAb-negative pts
rhTSH-Tg >2 ng/ml in only 2/655 tests with basal Tg <0.10 ng/ml: (NPV 99.7%)**

Conclusions: rhTSH test could be avoided if basal Tg <0.10 ng/ml

Similar results:

Smallridge et al 2007

Malandrino et al 2011

Chindris et al 2012

Trimboli et al 2013



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Pre-ablation Tg

Meta-analysis: 15 studies including 3947 pts.

Author, year (Ref.)	Country	Number of patients reported (included) ^a	Mean age (yr)	Timing of preablation Tg (d)	Outcome type ^b (A, B, C)	Follow-up (yr) (mean or range)	Tg cutoff (ng/ml)
Bernier, 2005 (6)	Germany	407	46.0	30	B	0.61	5.0
Familiar, 2009 (7)	Spain	63	41.0	NS	B, C	5.0	10.0
Giovanella, 2005 (8)	Switzerland	140	46.0	28	A, B, C	1.0	3.2
Heemstra, 2007 (9)	Netherlands	222	48.0	NS	C	8.3	27.5
Kim, 2005 (10)	South Korea	268	44.4	35	B, C	5.7	10.0
Lin, 2002 (11)	China	847 (654)	40.8	30	B, C	3.5–6.3	10.0
Oyen, 2000 (12)	Netherlands	206	45.0	28	C	2.7	6.6
Pelttari, 2010 (13)	Finland	495 (391)	40.6	28	B, C	10–24	10.0
Polachek, 2011 (14)	Israel	420	49.2	28	B, C	5.1	10.0
Ronga, 1999 (15)	Italy	334	41.6	40	C	4.0–16.0	11.1
Rosario, 2011 (16)	Brazil	237	43.0	90	A, B, C	0.7–1.0	10.0
Sawka, 2008 (17)	Canada	141	43.7	84	B	1.2–7.0	10.0
Tamila, 2011 (18)	Canada	193	45.5	63	B	1.0–1.5	10.0
Toubeau, 2004 (19)	France	212 (208)	47.0	28	B, C	1.0–12	30.0
Webb, 2011 (20)	United States	75 (63)	40.7	28	B, C	6.6	10.0

^a Included patients were those with sufficient data for meta-analysis. Total patients = 4260 (included 3947). NS, not stated.

^b A, Metastatic activity on posttreatment whole-body scan; B, surveillance stimulated Tg testing; C, recurrent structural disease.



Pre-ablation Tg

Study	TP	FN	FP	TN	TG	SN	SP	PPV	NPV	Sensitivity	Specificity
Bernier 2005	44	7	125	231	5.0	86.3	64.9	26.0	97.1	0.86	0.97
Familiar 2009	13	4	6	40	10.0	76.5	87.0	68.4	90.9	0.77	0.91
Giovanella 2005	6	1	9	124	3.2	85.7	93.2	40.0	99.2	0.86	0.99
Heemstra 2007	29	4	18	171	27.5	87.9	90.5	61.7	97.7	0.88	0.98
Kim 2005	48	18	16	186	10.0	72.7	92.1	75.0	91.2	0.73	0.92

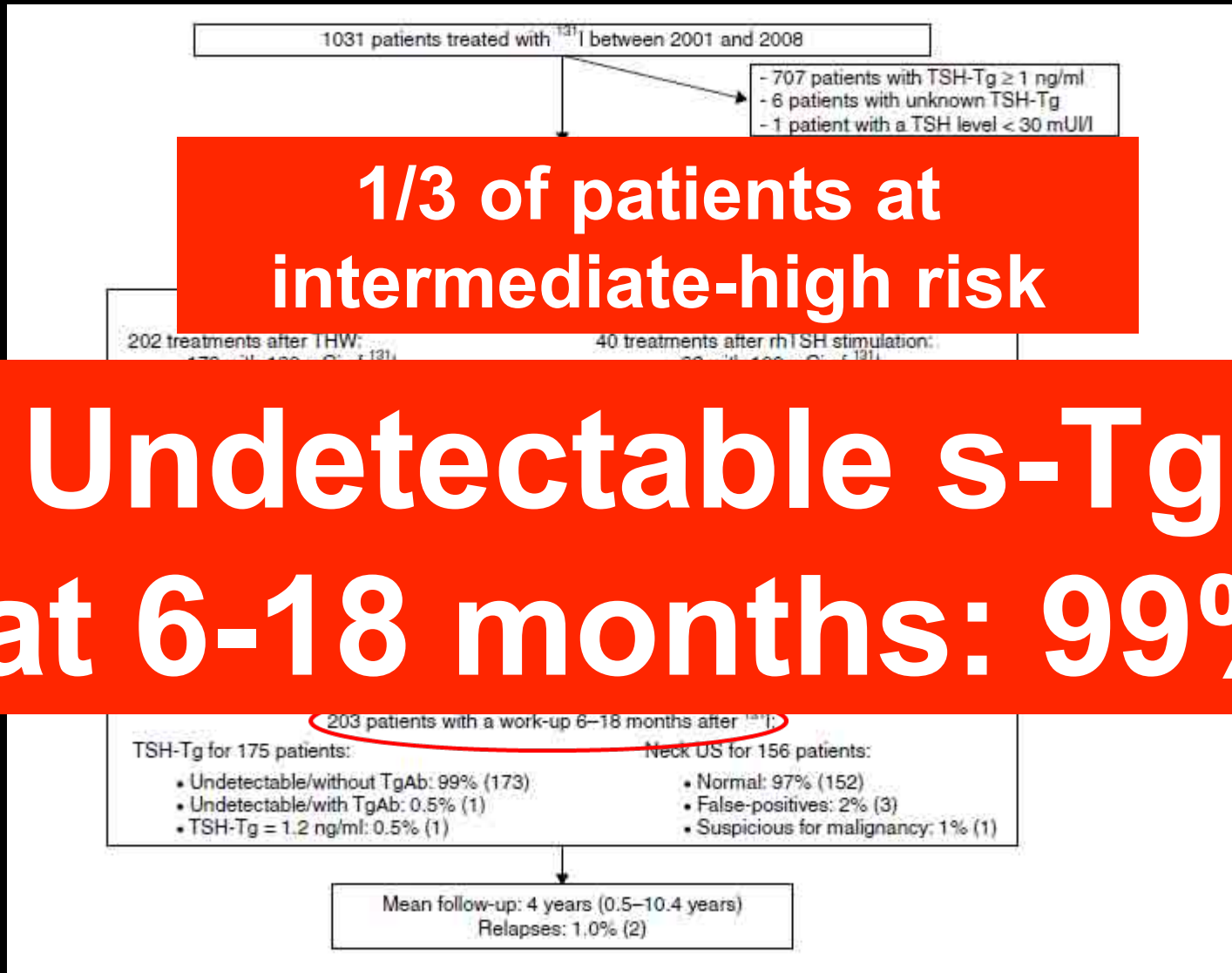
**Cut-off 10 ng/ml:
NPV 94%**

0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6 0.8 1

In most studies Tg cut-off 10 ng/ml



Pre-ablation Tg





Pre-ablation Tg



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**If s-Tg at ablation <1 ng/
ml and negative TgAb: Tg
stimulation 1 year later is
useless**



Tg doubling time



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THYROID
Volume 21, Number 7, 2011
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DOI: 10.1089/thy.2010.0355

THYROID CANCER AND NODULES

Prognostic Impact of Serum Thyroglobulin Doubling-Time Under Thyrotropin Suppression in Patients with Papillary Thyroid Carcinoma Who Underwent Total Thyroidectomy

Akira Miyauchi,¹ Takumi Kudo,² Akihiro Miya,¹ Kaoru Kobayashi,¹ Yasuhiro Ito,¹
Yuuki Takamura,¹ Takuya Higashiyama,¹ Mitsuhiro Fukushima,¹ Minoru Kihara,¹ Hiroyuki Inoue,¹
Chisato Tomoda,¹ Tomonori Yabuta,¹ and Hiroo Masuoka¹

426 DTC patients

**4 or more Tg determinations (1 at 1-3 months,
than twice or once a year) with TSH <0.1 mUI/L**

Median follow-up 87 months



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Tg doubling time

426 pts

Miyauchi et al, Thyroid 2011

201: undetect. Tg

**137: detect. Tg
≥4 measur.:
Tg DT**

88: detect. Tg but
<4 measur.

69 pts: Tg ↓

17 pts: <1 year

10-yrs Cause
Spec. Surv.:
50%

21 pts: 1-3 years

10-yrs Cause
Spec. Surv.:
95%

30 pts: >3 years

10-yrs Cause
Spec. Surv.:
100%



Tg doubling time



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Multivariate analysis

Tg DT only independent predictor of:

- Disease-specific mortality
- Loco-regional recurrence
- New distant metastases

**DT < 1 yr: 12% (17/137) of TG+ pts:
10 yr survival 50%**



Tg doubling time



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**102 Tg+ pts:
Tg DT<1 year predicts positive ¹⁸FDG-PET/
CT scan**

**Important:
¹⁸FDG-PET/CT scan accuracy
significantly improves also when basal
Tg >5.5 ng/ml**



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Total thyroidectomy + ¹³¹I



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Ablation-Tg ≤1ng/ml

Ablation-Tg >1 ng/ml

12 months:

T4-Tg ≤ 0.1 ng/ml

12 months:

T4-Tg > 0.1ng/ml

(LT4) rhTSH-Tg + US (if neg. TgAb)

Negative Tg, no abnormalities

Low positive Tg : 1-5 ng/ml, no other abnormalities

Tg > 5 ng/ml, negative US

Continue substitutive LT4 dose. Yearly controls: TSH, Tg, US

Repeat rhTSH-Tg 1-2 yrs later

Tg DT
PET/CT, ¹³¹I

Negative Tg

Stable/decreasing Tg:
no disease
Eventually repeat rhTSH-Tg 1-2 yrs later

Increasing Tg:
residual disease