VRAAG 2: RISICOSTRATIFICATIE

Study ID	Method	Patient characteristics	Prognostic factor(s)	Results primary outcome	Critical appraisal of study quality
Piccardo A 2010	• Retrospective cohort study • Funding/CoI: not reported • Setting: single university centre, Italy • Sample size: N=169 • Duration: inclusion 1/2001-6/2006, at least 2y follow-up	• Eligibility criteria: patients with DTC, $T_{1-2}N_{0-1}M_0$, absence of aggressive histological subtype (Hürthle cell, tall cell, columnar cell, insular), undetectable Tg-on (< 0.1 µg/l) 12 months after RAI, negative Tg-Ab; all patients underwent TT, RAI (2960-3700 MBq) 4-6 weeks after surgery and LT4 suppressive therapy • *A priori* patient characteristics: mean age 56y (17-81y), females 82%, papillary 92%	Tg-rhTSH 12 months post-RAI Tg was measured with immunometric assay: lower detection limit = 0.1 µg/l, functional sensitivity = 0.6 µg/l	Prognostic accuracy for disease-free status at 2y: (considering Tg-rhTSH ≤ 0.6 µg/l as negative test, and equivocal disease status as disease presence) • Se: 98% (157/161) • Sp: 100% (8/8) • PPV: 100% (157/157) • NPV: 67% (8/12)	Level of evidence: B • Consecutive patients • Blinding not reported, but unlikely • Definition of disease-free status: negative neck US and Tg-rhTSH ≤ 0.6 µg/l • Evidence of disease was verified by "extensive additional non-I131 imaging", if possible confirmed by cytology or histology ; unclear how disease-free status was verified • No multivariate analysis

Toubeau M 2004	• Retrospective cohort study
	• Funding/CoI: not reported
	• Setting: single university centre, France
	• Sample size: N=212
	• Duration: inclusion 1/1990-12/2000, median follow-up 5.1y (1-12y)
		• Eligibility criteria: patients with DTC, no initial distant metastases, proven absence of Tg-Ab; all patients underwent TT or NTT followed by RAI (3700 MBq) after a mean of 2.7 months; cervical LND in 56%; no uptake outside thyroid bed on post-RAI WBS
		• *A priori* patient characteristics: mean age 47y, females 72%, papillary 87%
			Tg-off 6-12 months post-RAI
			
			Tg was measured with IRMA assay: detection limit = 0.7 ng/ml, normal values 1.5-35 ng/ml; threshold = 10 ng/ml
				• Prognostic accuracy for progression-free status: (considering isolated elevated Tg as complete remission)
				  ○ Se: 92% (173/188)
				  ○ Sp: 75% (15/20)
				  ○ PPV: 97% (173/178)
				  ○ NPV: 50% (15/30)
				
				• Multivariate analysis: predictive factors 6-12 months post-RAI for disease progression:
				  ○ Tg > 10 ng/ml: OR 16.4 (95%CI 5.7-47.4)
				  ○ Node invasion: OR 2.7 (95%CI 1.0-7.2)
				
				• Progression-free survival: ≤ 10 ng/ml 97% vs. > 10 ng/ml 55%, p<0.0001
					Level of evidence: B
					
					• Consecutive patients
					• Blinding not reported, but unlikely
					• Definition of disease progression: first clinical reappearance of disease, after complete ablation of thyroid remnants (including all clinical events reported [nodal metastases, local relapses, and distant metastases] and confirmed by imaging modalities or surgery)
					• Exclusion of 4 patients with cervical node metastases after primary treatment
					• Cox proportional hazards model for multivariate analysis

Menendez Torre E 2004	• Cohort study • Funding/CoI: not reported • Setting: single centre, Spain • Sample size: N=194	• Eligibility criteria: patients with DTC treated with TT and remnant ablation with 100-150 mCi I131; no Tg-Ab or distant metastasis at diagnosis • *A priori* patient characteristics:	Tg-off (and WBS) 6-9 months post-RAI Tg was measured with IRMA assay: functional sensitivity =	Prognostic accuracy for disease-free status: • Se: 80% (131/163) • Sp: 94% (29/31) • PPV: 98% (131/133) • NPV: 48% (29/61)	Level of evidence: B • Consecutive patients • Blinding not reported, but unlikely • Definition of persistence or

Study ID	Method	Patient characteristics	Prognostic factor(s)	Results primary outcome	Critical appraisal of study quality
	• Duration: inclusion 1987-1998, mean follow-up 7.7y	mean age 43.7y, papillary 64%	0.5 ng/ml		recurrence: Tg-off > 2 ng/ml or positive uptake outside thyroid bed after I131-WBS or presence of disease demonstrated by other image methods • No multivariate analysis
Giovanella L 2009	• Prospective cohort study • Funding/CoI: not reported • Setting: 2 centres, Switzerland and Italy • Sample size: N=195 • Duration: period of enrollment not reported, mean follow-up 6.8y (4.7-8.9y)	• Eligibility criteria: patients with DTC, low risk according to ETA guidelines; exclusion if aggressive histotypes (i.e. papillary: tall-cell, columnar-cell, diffuse sclerosing; follicular: Hurtle-cell, widely invasive or poorly differentiated), maximum tumour diameter > 40 mm and/or lymph-node(s) involvement, distant metastases; all treated with TT and RAI (3700 MBq); no Tg-Ab or undetectable Tg before RAI • *A priori* patient characteristics: mean age 52y, females 76%, papillary 85%	Tg-on and neck US 6 months post-RAI Tg was measured with IRMA assay: functional sensitivity = 0.2 ng/ml Patients with detectable Tg-on and/or positive US underwent US-guided FNAC and/or other imaging procedures	Prognostic accuracy for disease-free status: • Se: 98% (185/188) • Sp: 57% (4/7) • PPV: 98% (185/188) • NPV: 57% (4/7)	Level of evidence: B • Unclear if consecutive series • Blinding not reported • Definition of “no evidence of disease”: no lesions were detected during follow-up or Tg spontaneously normalized without treatment • No multivariate analysis
Giovanella L 2006	• Cohort study • Funding/CoI: not reported • Setting: 2 centres, Switzerland and Italy • Sample size: N=117 • Duration: period of enrollment not reported, follow-up 22-69 months	• Eligibility criteria: patients with DTC, undergoing TT with neck LN central compartment dissection, RAI 4-6 weeks after surgery (3700 MBq); low risk based on histological confirmation of complete resection, absence of uptake outside thyroid bed on post-treatment WBS, undetectable Tg-on at 3 months • *A priori* patient characteristics: mean age 42y, females 61%, N1a 30%, N1b 8%	Tg-on, Tg-rhTSH and neck US at 1y post-RAI (range 9-14 months) Tg was measured with IRMA assay: functional sensitivity = 0.2 ng/ml, sensitivity = 0.04 ng/ml	Prognostic accuracy for disease-free status: • Tg-on: ○ Se: 97% (100/103) ○ Sp: 71% (10/14) ○ PPV: 96% (100/104) ○ NPV: 77% (10/13) • Neck US: ○ Se: 91% (94/103) ○ Sp: 77% (10/13) ○ PPV: 97% (94/97) ○ NPV: 53% (10/19) • Tg-on and neck US: ○ Se: 91% (94/103) ○ Sp: 93% (13/14) ○ PPV: 99% (94/95) ○ NPV: 59% (13/22) • Tg-rhTSH: ○ Se: 87% (90/103) ○ Sp: 86% (12/14) ○ PPV: 98% (90/92) ○ NPV: 48% (12/25) • Tg-rhTSH and neck US: ○ Se: 87% (90/103) ○ Sp: 100% (14/14)	Level of evidence: B • Unclear if consecutive series • Blinding not reported • No clear definition provided of “no evidence of disease” • No multivariate analysis

Study ID	Method	Patient characteristics	Prognostic factor(s)	Results primary outcome	Critical appraisal of study quality
				○ PPV: 100% (90/90) ○ NPV: 52% (14/27)	
Kim MH 2012	• Retrospective cohort study • Funding/CoI: none declared • Setting: single university centre, Korea • Sample size: N=359 • Duration: inclusion 1/2000-8/2006, median follow-up 66.3 months	• Eligibility criteria: patients with DTC who underwent TT and RAI (3700-5550 MBq), no distant metastasis at initial diagnosis • *A priori* patient characteristics: median age 46.6y, females 85%, papillary 50%; 226 patients with low risk according to ATA guidelines, only these are reported on	Tg-off at 6-12 months post-RAI Tg was measured with IRMA assay: cut-off = 2 ng/ml	Prognostic accuracy for disease-free status: • Se: 93% (196/210) • Sp: 88% (14/16) • PPV: 99% (196/198) • NPV: 50% (14/28)	Level of evidence: B • Unclear if consecutive series • Blinding not reported • Definition of persistent or recurrent disease: malignant results confirmed by cytology or pathology; and detectable stimulated Tg levels (≥2 ng/mL) with identifiable lesions found in imaging studies such as WBS, CT, or PET/CT scan • No multivariate analysis
Brassard M 2011	• Prospective cohort study • Funding/CoI: funding not reported, no CoI declared • Setting: multicentre (N=27), France • Sample size: N=715 • Duration: inclusion 6/2000-10/2003, median follow-up 6.2y	• Eligibility criteria: patients with DTC that underwent TT (with central neck dissection in 94%) and postoperative RAI (30-100 mCi); no uptake outside thyroid bed on post-treatment WBS • *A priori* patient characteristics: mean age 47y, females 77%, papillary 86%	Tg-stim (and WBS) at 9-12 months post-RAI Tg was measured with IRMA assay: functional sensitivity = 0.11 ng/ml; optimal cut-off 1.4 ng/ml Tg was stimulated through LT4-withdrawal or rhTSH	Prognostic accuracy for disease-free status: • Se: 90% (613/683) • Sp: 78% (25/32) • PPV: 99% (613/620) • NPV: 26% (25/95)	Level of evidence: B • Blinded evaluation of Tg results • Patients with positive Tg-Ab were excluded from analysis • Neck recurrence was confirmed by FNAB or surgical biopsy, I131-uptake or typical imaging features on WBS confirmed distant metastases • No multivariate analysis • Optimal cut-off for Tg-stim determined by ROC analysis
Castagna MG 2011	• Retrospective cohort study • Funding/CoI: grants from Ministero Italiano dell'Universita` e Ricerca; no CoI declared • Setting: single university centre, Italy • Sample size: N=512 • Duration: period of enrollment not reported, median follow-up 5.6y	• Eligibility criteria: patients with DTC treated with NTT (with LND of central neck compartment in 7.4% and lateral LND in 14.8%) and postoperative I131 (555-7400 MBq) • *A priori* patient characteristics: mean age 46.4y, females 73%, papillary 89%; M1 8.8%	Post-surgical risk assessment according to ATA and ETA guidelines vs. Delayed risk stratification with Tg-stim and neck US at 8-12 months post-RAI: - "clinical remission": undetectable basal and Tg-stim,	Risk stratification according to ATA: • Low risk: 47.6% (244/512) ○ Complete remission at 8-12 months: 87.2% ○ Complete remission at final follow-up: 90.8% • Intermediate/high risk: 52.4% (268/512) ○ Complete remission at 8-12 months: 52.2% ○ Complete remission at final follow-up: 60.8% • Prognostic accuracy for disease-free status: ○ Se: 58% ○ Sp: 82% ○ PPV: 91% ○ NPV: 39%	Level of evidence: B • Unclear if consecutive series • Blinding not reported • No multivariate analysis

Study ID	Method	Patient characteristics	Prognostic factor(s)	Results primary outcome	Critical appraisal of study quality
			negative Tg-Ab, and no evidence of disease (at clinical examination, neck US and diagnostic WBS when performed) - "persistent disease": any evidence of disease at clinical and neck US examination, imaging (chest X-ray, WBS, FDG-PET, CT, MRI and bone scan), and/or detectable basal or Tg-stim Tg was measured with chemiluminescent assay: functional sensitivity = 0.9 ng/ml	Risk stratification according to ETA: • Low risk: 45.1% (231/512) ○ Complete remission at 8-12 months: 87.8% ○ Complete remission at final follow-up: 91.4% • High risk: 54.9% (281/512) ○ Complete remission at 8-12 months: 53.3% ○ Complete remission at final follow-up: 61.6% • Prognostic accuracy for disease-free status: ○ Se: 55% ○ Sp: 84% ○ PPV: 91% ○ NPV: 38% Delayed risk stratification at 8-12 months: • Low risk: 68.9% (353/512) ○ Complete remission at final follow-up: 96.6%, p=0.005 compared with ATA and ETA • High risk: 31.1% (159/512) ○ Complete remission at final follow-up: 27.1% • Prognostic accuracy for disease-free status: ○ Se: 89% ○ Sp: 91% ○ PPV: 97% ○ NPV: 73%	

Abbreviations: xxx

References

Brassard M, Borget I, Edet-Sanson A, Giraudet AL, Mundler O, Toubeau M, et al. Long-term follow-up of patients with papillary and follicular thyroid cancer: a prospective study on 715 patients. J Clin Endocrinol Metab. 2011;96(5):1352-9.

Castagna MG, Maino F, Cipri C, Belardini V, Theodoropoulou A, Cevenini G, et al. Delayed risk stratification, to include the response to initial treatment (surgery and radioiodine ablation), has better outcome predictivity in differentiated thyroid cancer patients. Eur. J. Endocrinol. Suppl. 2011;165(3):441-6.

Giovanella L, Ceriani L, Ghelfo A, Keller F, Sacchi A, Maffioli M, et al. Thyroglobulin assay during thyroxine treatment in low-risk differentiated thyroid cancer management: Comparison with recombinant human thyrotropin-stimulated assay and imaging procedures. Clin. Chem. Lab. Med. 2006;44(5):648-52.

Giovanella L, Maffioli M, Ceriani L, De Palma D, Spriano G. Unstimulated high sensitive thyroglobulin measurement predicts outcome of differentiated thyroid carcinoma. Clinical Chemistry & Laboratory Medicine. 2009;47(8):1001-4.

Kim MH, Ko SH, Bae JS, Lim DJ, Baek KH, Lee JM, et al. Combination of initial stimulation thyroglobulins and staging system by revised ATA guidelines can elaborately discriminate prognosis of patients with differentiated thyroid carcinoma after high-dose remnant ablation. Clin. Nucl. Med. 2012.

Menendez Torre E, Lopez Carballo MT, Rodriguez Erdozain RM, Forga Llenas L, Goni Iriarte MJ, Barberia Layana JJ. Prognostic Value of Thyroglobulin Serum Levels and 131I Whole-Body Scan after Initial Treatment of Low-Risk Differentiated Thyroid Cancer. Thyroid. 2004;14(4):301-6.

Piccardo A, Arecco F, Morbelli S, Bianchi P, Barbera F, Finessi M, et al. Low thyroglobulin concentrations after thyroidectomy increase the prognostic value of undetectable thyroglobulin levels on levo-thyroxine suppressive treatment in low-risk differentiated thyroid cancer. J. Endocrinol. Invest. 2010;33(2):83-7.

Toubeau M, Touzery C, Arveux P, Chaplain G, Vaillant G, Berriolo A, et al. Predictive value for disease progression of serum thyroglobulin levels measured in the postoperative period and after (131)I ablation therapy in patients with differentiated thyroid cancer. J Nucl Med. 2004;45(6):988-94.