Clinical aspects of endogenous hypothyroidism and subclinical hyperthyroidism in patients with differentiated thyroid carcinoma

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02

Serum Thyroglobulin Concentrations Predict Disease-free remission and Death in Differentiated Thyroid Carcinoma

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Abstract

Objective: Most studies on the diagnostic value of serum thyroglobulin (Tg) concentrations in differentiated thyroid carcinoma (DTC) use fixed cut-off levels in heterogeneous groups of patients with respect to initial therapy and do not provide prognostic data. The objective was to investigate the prognostic values of serum Tg for disease-free remission and death, measured at fixed time points after initial therapy using receiver operator characteristic (ROC) curve analyses.
Design: Single-centre observational study with 366 consecutive patients with DTC, who had all been treated according to the same protocol for initial therapy and follow-up.
Methods: Tg concentrations were measured at five fixed time points after initial surgery. Tg cut-off values with highest accuracy were calculated with ROC analyses.
Results: During follow-up of 8.3±4.6 years, 84% of the patients were cured. Pre-ablative Tg levels were an independent prognostic indicator for cure (Tg cut off value 27.5 µg/L, positive predictive value 98%). Highest diagnostic accuracies of serum Tg for tumor presence were found during TSH stimulated Tg measurements, 6 months after initial therapy (Tg cut-off value 10 µg/L: sensitivity 100%, specificity 93%).
DTC related mortality was 14%. TSH stimulated Tg levels before ablation and 6 months after initial therapy were independent prognostic indicators for death.
Conclusion: Optimal institutional Tg cut-off levels for diagnosis and prognosis should be defined using ROC analyses for each condition and time-point. Tg measurements 6 months after initial therapy during TSH stimulation had an excellent diagnostic value. Tg levels are independent prognostic indicators for disease-free remission and death. Using this strategy, high-risk patient groups can be selected based on Tg levels, in addition to conventionally used prognostic indicators.

Introduction

Differentiated thyroid carcinoma (DTC) has an excellent prognosis with 10-year survival rates of 85-93 % (1). The purpose of follow-up protocols in DTC is the early detection of tumor recurrence or metastatic disease in order to optimize additional treatment. Most patients during follow up have been cured definitely, and consequently have a low pre-test probability for recurrent disease. Therefore, the sensitivity of the diagnostic test must be sufficient to detect the few patients with evident thyroid carcinoma, whereas specificity must also be high to avoid unnecessary treatments in patients without recurrent disease. In addition, the burden of diagnostic tests for the patient should be kept at a minimum.

Serum thyroglobulin (Tg) measurements are the cornerstone in the follow-up in DTC. Numerous studies have been performed on the diagnostic value of Tg measurements. We recently published a structured meta-analysis on the diagnostic value of Tg including 46 articles (2). The interpretation of many studies on Tg performed so far is difficult, because in most studies 1) heterogeneous patient groups with respect to initial therapy are included, 2) the time points of Tg measurements after diagnosis are not clearly indicated, and 3) fixed Tg cut-off levels are used, without receiver operator characteristic (ROC) curve analyses. The application of ROC data is essential, as a chosen cut-off level is a subjective choice based on the balance between a desired percentage of missed recurrences vs. unnecessary therapies. A recent European consensus paper recommended that there should be defined institutional Tg cut-off levels (3). Only a few studies have been published on the interpretation of Tg levels during follow up of DTC using ROC analyses. However, in those studies, heterogeneous patient groups were included and the time-points of Tg measurements were not clearly indicated (4-6). In addition, most studies provide data on the diagnostic value of Tg for tumor presence, but do not give data on the prognostic significance for disease-free remission or death. One large study (7) investigated the prognostic significance of 1-month post-surgical Tg levels and found a significant prognostic cut-off level of
10 μg/L. The few studies that were published on the prognostic significance of Tg measurements used fixed cut-off levels, contained selected subgroups of patients and included Tg measurements either at one time point or at undefined time points (8-12).

We therefore performed a study on the diagnostic and prognostic value of Tg in a homogeneous group of DTC patients with respect to initial therapy, using Tg measurements at 5 defined time-points after diagnosis, in combination with ROC analyses. In addition, we studied the diagnostic and prognostic value of Tg antibodies for tumor presence or death.

Patients and methods

Three-hundred-and-sixty-six consecutive patients were included in the study. These patients had received initial therapy for DTC between January 1986 and January 2000. All follow up data were collected until January 1, 2003. January 1986 was chosen as a starting date, because from that date forward, all relevant patient data were registered in a computerized database. Initial surgery and radioiodine ablation therapy were performed at the Leiden University Medical Centre or at one of the connected general hospitals. All hospitals are affiliated in the Regional Comprehensive Cancer Centre and use the same standardized protocol for the treatment and follow-up of DTC.

All patients were treated by near-total thyroidectomy, followed by routine radioiodine ablative therapy with 2800 MBq I-131.

Follow-up was performed according to a standard protocol. Serum Tg levels were measured at the following time-points: 1) after initial surgery during thyroxin withdrawal just before radioiodine ablation, 2) during T4 therapy, 3) 6 months after initial surgical therapy after T4 withdrawal ('off') and 4) annually during T4 therapy.

Although additional TSH stimulated Tg measurements were performed in selected subgroups of patients at other time points after initial therapy, we did not include those data as these tests were not uniformly done in all patients, and calculations of diagnostic values would have been biased. T4 therapy was aimed at suppressing TSH levels (below 0.1 mU/L). Six months after initial therapy a diagnostic 185 MBq I-131 scintigraphy was performed after T4 withdrawal.

Tumor presence during follow-up was defined as histologically or radiologically (X-ray, computed tomography (CT) scan, magnetic resonance imaging (MRI) scan, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) scan or I-131 scintigraphy) within a 1-year interval before or after the time of Tg measurements. Although we realize that Tg is considered the best parameter for tumor presence, Tg was not used as the 'gold standard' for tumor presence, as the diagnostic value of Tg was the subject of this study.

Disease-free remission was defined as the absence of thyroid carcinoma for a minimum of 3 years according to the above mentioned parameters.

The following data were registered: age at diagnosis, sex, date of diagnosis, histology, TNM stage, date of cure, date of recurrence, tumor localization, cause of death, Tg levels, TSH levels, Tg antibody levels and date of last follow up or death. TNM stage was registered according to the 5th edition of the *TNM Classification of Malignant Tumors* (13) because most patients were analysed before the latest edition of the TNM classification had been published. We used the following end-points of follow-up: date of death (82 patients), date of emigration (12 patients) and date of most recent contact (272 patients).

Causes of death were analysed in all 82 patients who had died during follow-up. Cause of death was investigated using medical records, death certificates, enquiries with physicians involved in the treatment of each patient, enquiries in other hospitals, enquiries of general practitioners and autopsy findings. Causes were divided into thyroid cancer related death and other causes. Analyses were performed in evaluable patients, defined as patients in whom all of four conditions were fulfilled: alive at time-point of Tg measurement, documented serum Tg measurements, documented serum Tg antibody measurements and documented gold standard parameters for the presence or absence of disease. If Tg antibodies were present, the Tg measurement at this time-point was excluded from the calculations because of possible interference with the Tg assay. The numbers of these patients are given in table 2.

Measurements of Tg and Tg-Ab

Until January 1997 serum Tg was measured using an immunoradiometric assay (IRMA), the Dynotest TG (Brahms Diagnostica GmbH, Germany) was used with a sensitivity of 0.03 μg/l. From January 1997, the Dynotest TG-s (Brahms Diagnostica GmbH) was used, with a sensitivity of 0.05 μg/l. Inter-assay variability was 0.3 μg/l. The comparability of the two methods is excellent: $R2=0.99$, slope 0.99, intercept 0.09 (14). Serum Tg-antibodies were also measured at these specific time points by the Ab-HTGK-3 IRMA (DiaSorin Biomedics, Italy).

Statistical analyses

Data are presented as mean ± SD. All statistical analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as number of patients (percentages), as mean ± Standard Deviation (SD) or as median (range). ROC analyses were used to find the cut-off value with highest accuracy. Prognostic indicators for recurrence or death were calculated using univariate- and multivariate Cox-regression analyses; indicators that were identified as significant for survival in univariate analysis were entered into a stepwise multivariate model. A p-value of < 0.05 was considered significant.

Table 2. Diagnostic Values of Serum Tg Measurements for Active Tumor Calculated with ROC Analysis. Patients with Tg antibodies were excluded.

	Evaluable patients (N)*	Patients with positive TgAb (N, % of evaluable patients)	Tumor Location	Patients with tumor (N, % of patients without Tg antibodies)	Tg Cut-Off (μg/L)	Sensitivity ±SE (%)	Specificity ±SE (%)	PPV (%)	NPV (%)
Pre-ablation	304	82 (27.0)	All	33 (15.1)	27.5	87.9 ± 5.7	90.3 ± 2.2	61.7	97.7
			Distant Metastases	21 (9.6)	27.5	85.7 ± 7.6	85.3 ± 2.5	38.3	98.2
Six months after initial therapy, suppressed TSH	287	79 (27.5)	All	37 (18.0)	2.5	89.2 ± 5.1	93.5 ± 2.0	75.0	97.5
			Distant Metastases	24 (11.7)	2.5	87.5 ± 6.8	87.3 ± 2.5	47.7	98.1
Six months after initial therapy, stimulated TSH	287	79 (27.5)	All	37 (18.0)	10.0	100.0 ± 0.0	93.1 ± 2.1	76.7	100.0
			Distant Metastases	24 (11.7)	10.0	100.0 ± 0.0	86.0 ± 2.8	48.8	100.0
Two years after initial therapy, suppressed TSH	244	32 (13.1)	All	43 (20.6)	2.0	85.0 ± 5.4	85.7 ± 2.7	60.6	95.7
			Distant Metastases	33 (15.8)	2.0	72.7 ± 7.8	88.6 ± 2.4	54.5	
Five years after initial therapy, suppressed TSH	182	23 (12.6)	All	35 (22.6)	2.5	82.9 ± 6.4	96.7 ± 1.6	87.9	95.1
			Distant Metastases	30 (19.4)	2.5	83.3 ± 6.8	93.6 ± 2.2	75.8	95.9

ROC=receiver operator characteristic, TgAb=thyroglobulin antibodies, PPV= positive predicted value, NVP = negative predicted value

* = Patients who were alive at the time-points of measurement and in whom Tg, TgAb and documentation of disease state according to the criteria for the 'gold standard' (see methods) could be evaluated.

Results

Characteristics of the patients are shown in Table 1. Mean age at time of surgery was 48 ± 18 years. Mean follow-up was 8.3 ± 4.6 years. Significant prognostic factors for cure and death are given in Table 4.

Table 1. Patient characteristics

Parameter	N	Cured Patients N (%)	Patients with Relapse after Cure (N, (%))	Thyroid Carcinoma Deaths (N (%))
Total	366	305 (84)	46 (13)	52 (14)
Gender (Male/ Female)	91/ 275	72 (80)/ 233 (85)	13 (14)/ 33 (13)	13 (14)/ 39 (14)
Stages				
T1	22	21 (96)	1 (5)	0 (0)
T2	188	176 (94)	17 (9)	10 (5)
T3	56	51 (91)	9 (16)	8 (14)
T4	96	53 (55) * #	17 (18)	32 (33) * #
T unknown	4	0 (0)	0 (0)	2 (50)
N1	107	76 (71) *	15 (14)	22 (21) *
M1	52	19 (36) * #	6 (11)	27 (54) * #
Histology				
Papillary	203	173 (86)	28 (14)	25 (12)
Follicular	72	58 (81) *	11 (15)	17 (24) *
Follicular variant papillary carcinoma	68	56 (82)	5 (7)	6 (9)
Hürthle Cell	23	18 (78)	2 (9)	4 (17)
Age (continuous)		* #		* #
< 55 yr	210	221 (95)	18 (8)	3 (1)
> 55 yr	156	84 (64)	28 (21)	49 (31)

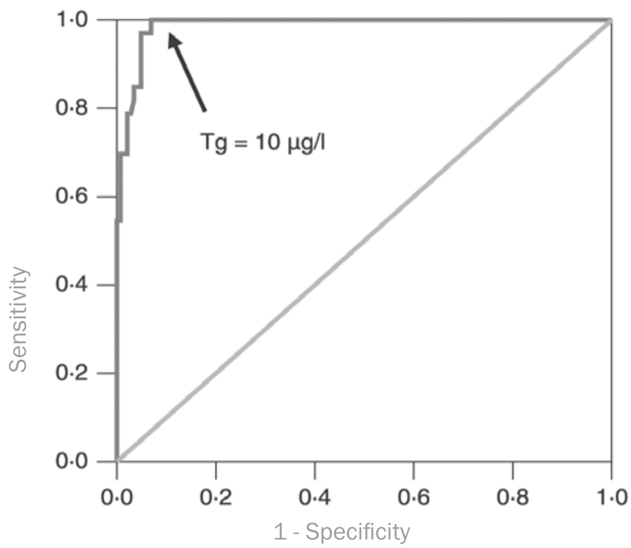
** Significant at univariate analysis, # Significant at multivariate analysis (see Table 4)*

Diagnostic value of Tg.

The diagnostic values of Tg measurements at the different time points are given in Tables 2. The diagnostic value of Tg before ablation therapy was reasonable in our analysis, with a sensitivity of 87.9% and a specificity of 90.3% at a cut-off value of 27.5 μg/L. When a cut-off level of 2 μg/L was used, sensitivity increased to 93.9%, whereas the specificity fell to 45% with a positive predictive value of only 23% instead of 62%, and with similar negative predictive value.

The highest diagnostic value of Tg was found during TSH stimulated Tg measurements 6 months after initial therapy (see Fig. 1). The Tg cut-off value with highest accuracy was 10.0 μg/L, with sensitivity and specificity of 100.0 and 93.1%, respectively. When the more commonly used cut-off value of 2 μg/L was used, the sensitivity remained similar, but the specificity fell to 82% with a positive predictive value of only 54%, instead of 77% (Fig. 1). We analysed the course of 9 patients with Tg values > 10 μg/L, 6 months after initial therapy during TSH stimulation: in three patients, tumors were detected 2-5 years after initial therapy. In four patients Tg became undetectable and they were considered cured. Two patients had persistent measurable Tg, but no tumor was detectable up to 15 years after initial therapy. Tg measurements on T4, 2 and 5 years after initial therapy had lower sensitivities, but comparable specificities and negative predictive values, albeit at lower Tg cut-off values.

Figure 1 Receiver Operator Curves six months after initial therapy, during TSH stimulation to obtain optimal cut-off levels of serum Tg measurements for the diagnosis of active tumor in patients with differentiated thyroid carcinoma.



Prognostic value of Tg

Disease-free remission. The prognostic value of Tg for disease-free remission is given in Tables 3 and 4. Tg before ablation had a high predictive value of 97.8% for disease-free remission at a cut-off value of 27.5 µg/L. Tg appeared to be an independent prognostic marker for disease-free remission (likelihood ratio for disease-free remission 43.2 for Tg < 27.5 µg/L, p<0.001), irrespective of TNM stages T4, M1 and age.

Table 3. Prognostic Value of Serum Tg Measurements for disease-free remission and thyroid carcinoma-related death. Patients with Tg antibodies were excluded.

	Outcome	Tg Cut-Off (µg/l)	Sensitivity ± SE (%)	Specificity ± SE (%)	PPV (%)	NPV (%)
Pre-ablation	Disease-free remission	27.5	84.4 ± 2.6	88.9 ± 5.6	97.8	49.1
	Death	21.5	66.7 ± 9.6	81.3 ± 2.8	30.2	95.3
Six months after initial therapy, suppressed TSH	Death	2.5	72.0 ± 9.0	85.7 ± 2.6	40.9	95.7
Six months after initial therapy, stimulated TSH	Death	10.0	85.0 ± 8.0	83.5 ± 2.9	39.5	97.8
Two years after initial therapy, suppressed TSH	Death	2.0	85.0 ± 8.0	85.7 ± 2.5	38.6	98.2
Five years after initial therapy, suppressed TSH	Death	2.0	82.4 ± 9.2	92.8 ± 2.2	58.3	97.7

PPV= positive predictive value, NVP = negative predictive value, ROC=Receiver Operator Characteristics Curve.

Table 4. Likelihood Ratios for Serum Tg values for Outcome (disease-free remission or thyroid carcinoma-related death) as calculated with Cox-survival Analysis. Patients with Tg antibodies were excluded. Tg Cut Off values are given in Table 3.

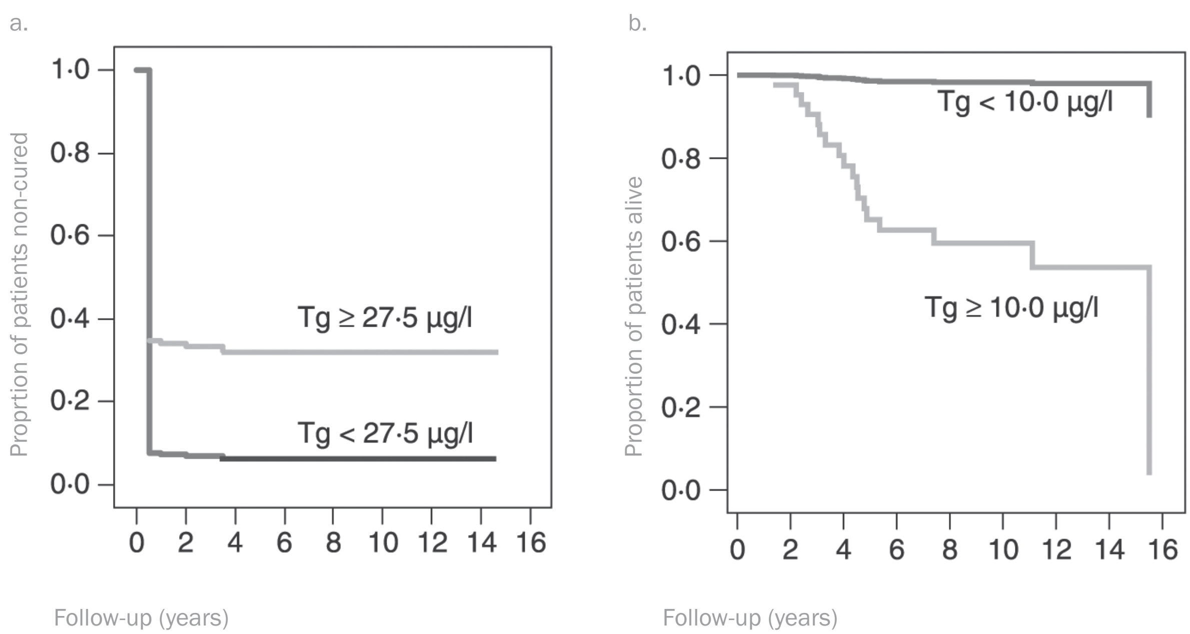
	Outcome	Univariate Analysis p	Likelihood Ratio (CI)	Multivariate Analysis p	Likelihood Ratio (CI)	Other Significant Parameters
Pre-ablation	Disease-free remission	<0.001	43.2 (15.0–124.3) #	<0.001	29.9(5.2–171.5) #	Age, M1, T4
	Death	<0.001	8.0 (3.4–18.7)*	Ns	--	Age, M1, T4
Six months after initial therapy, suppressed TSH	Death	<0.001	14.4 (5.7 – 36.7) *	ns.	--	Age, T4
Six months after initial therapy, stimulated TSH	Death	<0.001	31.2 (7.1–136.7) *	0.008	10.9 (1.9–63.5) *	Age, T4
Two years after initial therapy, suppressed TSH	Death	<0.001	30.9 (9.0–105.7) *	<0.001	12.9 (3.4–49.2) *	Age, M1
Five years after initial therapy, suppressed TSH	Death	<0.001	24.2 (5.0–116.2) *	0.001	29.1 (3.6–232.2) *	Age

CI=confidence interval. M1= metastases, T4=extra thyroidal extension

*# Likelihood Ratio for Tg value < Cut-Off, * Likelihood Ratio for Tg value > Cut-Off*

Thyroid-Specific Death. The prognostic values for Tg measurements for DTC-related death are given in Tables 3 and 4 and Fig. 2. The negative predictive value was high for all time-points of Tg measurements. Tg was an independent predictor for thyroid-related death during TSH stimulation, 6 months after initial therapy (hazard ratio 10.9 for Tg > 10.0 μg/L, p=0.008, Table 4, Fig. 2), 2 years after initial therapy (hazard ratio 12.9 for Tg > 2.0 μg/L, p<0.001) and 5 years after initial therapy (hazard ratio 29.1 for Tg > 2.0 μg/L, p=0.001).

Figure 2 Prognostic value of Tg measurements for Differentiated Thyroid Carcinoma a) Proportion of patients non-cured, Tg levels pre-ablation, four weeks after surgery; b) Survival according to TSH stimulated Tg, 6 months after initial therapy;



Tg antibodies. The percentage of patients with Tg antibodies decreases from 27 % immediately after initial surgery to 12 % 5 years after initial therapy (see Table 2). There were no significant differences in tumor presence between patients with and without Tg antibodies: 15 – 23% in patients without Tg antibodies and 16 – 33% in patients with Tg antibodies. The presence of Tg antibodies did not have a significant prognostic for disease-free remission or death.

Discussion

In the present study we investigated the diagnostic and prognostic value of serum Tg measurements for tumor presence, disease-free remission and death in the follow-up of DTC by ROC analysis in a homogeneous group of patients with respect to initial therapy. The study differed from earlier investigations with respect to the homogeneity of the patient group with respect to initial therapy, the fact that multiple Tg measurements were analysed at fixed time points during follow-up and the use of ROC.

We found an excellent diagnostic accuracy of serum Tg values during TSH stimulation 6 months after initial therapy (sensitivity 100%), with a higher Tg cut-off level (10.0 µg/L) than commonly reported (2;8;11;15;16). When we used the more commonly used cut-off value of 2 µg/L, the specificity and positive predictive value decreased considerably. We also found that Tg cut-off levels are dependent on the time-point of follow-up, which is an important finding, as in most papers on Tg, the time after diagnosis is not considered.

Tg levels are not only diagnostic indicators of tumor presence, but also predict disease-free remission or death. We found that serum Tg levels before radioiodine ablation are an independent predictor for disease-free remission, irrespective of the classical prognostic indicators. In our series a patient with Tg level pre-ablation of < 27.5 µg/L has an almost 98% chance of being cured irrespective of the prognostic indicators stage T4, follicular histology, metastases and higher age.

TSH-stimulated Tg measurements 6 months after initial therapy and at 2 and 5 years after initial therapy were independent predictors of thyroid carcinoma-related death. Negative predictive values for DTC-related death were high (95.3 – 98.2%) at all 5 time points of follow up, albeit with different Tg cut-off values.

In the discussion about the diagnostic value of Tg, specificity is a controversial issue. It has been argued that the specificity of Tg is, by definition, 100%. Although from a biological point of view it is undoubtedly correct that Tg is only synthesized by thyroid cells, in clinical practice the meaning of measurable Tg levels is not always clear, and even less so with the advent of high sensitive Tg assays. A less than 100% specificity of Tg for thyroid carcinoma can be explained by the limitations of current imaging techniques to detect thyroid carcinoma. In this respect, administering a high dose of radioiodine to patients with elevated Tg levels has been advocated, a policy that we agree with (17-20). However, we also observed that in only three of the nine patients with TSH-stimulated Tg levels > 10 µg/L without detectable tumor, did a tumor become apparent during follow up, which is in line with the observations of Baudin *et al*. (8). Therefore, in our opinion, a potential solution to circumvent the debate about specificity of Tg is to consider Tg a risk indicator. The independent prognostic value of serum Tg values for disease-free remission and death are arguments to include Tg in the conventional panel of risk factors. A potential consequence could be to administer higher dosages of radioiodine for ablation in patients with Tg levels above the above-mentioned thresholds. As such we do not advocate that patients with Tg levels below institutionally defined cut-off levels should not be followed up carefully, but we belief that the elimination of Tg should not be a treatment goal in itself.

Tg cut-off levels are influenced not only by clinical considerations, but also by analytical aspects. Analytical problems include the lack of universal standardisation of the Tg assays, (21), intra-assay variability, “Hook” effects and the presence of Tg auto-antibodies (22;23). Another important point, not addressed in this study, is the observation that Tg increases may be more informative than absolute Tg levels (8;24).

The percentage of patients with Tg antibodies (initially 27%) is in line with previous studies (23;25;26). The percentages of active tumor in patients with and without Tg antibodies were comparable, confirming the lack of diagnostic value of Tg antibodies.

Because our study involved a large cohort of patients studied before the introduction of rhTSH, we did not include rhTSH stimulated Tg measurements in our series. However, recent reports indicate that the diagnostic accuracy is comparable (2;3;15). It has been suggested that Tg cut-off levels for rhTSH should be lower than for thyroid hormone withdrawal (27). However, no systematic analyses have been published comparing optimal Tg cut-off levels for both strategies. Furthermore, in a large study, similar Tg cut-off values were used for rhTSH and T4 withdrawal (16).

Because our analysis is based on retrospective data, we believe that the prognostic Tg cut-off values as found in our study should be interpreted with some caution, and they should be confirmed in a prospective study. We maintain, however, that the main message is valid- that Tg cut-off levels should not be adopted from the literature, that Tg cut-off levels are dependent on the time-points, and that Tg has a prognostic value.

In conclusion, our studies illustrate the importance of the definition of institutional Tg cut-off levels. We analysed the diagnostic value of Tg at specific time-points and detected an excellent prognostic value 6 months after initial therapy during TSH stimulation. Our analyses allow the definition of groups of patients with an increased risk for residual disease or mortality, in addition to conventionally used prognostic indicators. Based on our analysis we recommend subjecting every patient, who has undergone thyroid surgery and thyroid remnant ablation, at least once to TSH-stimulated Tg measurements.

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References

1. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995. Cancer 1998; 83(12):2638-2648.
2. Eustatia-Rutten CF, Smit JW, Romijn JA et al. Diagnostic value of serum thyroglobulin measurements in the follow-up of differentiated thyroid carcinoma, a structured meta-analysis. Clin Endocrinol (Oxf) 2004; 61(1):61-74.
3. Schlumberger M, Pacini F, Wiersinga WM et al. Follow-up and management of differentiated thyroid carcinoma: a European perspective in clinical practice. Eur J Endocrinol 2004; 151(5):539-548.
4. Ronga G, Filesi M, Ventroni G, Vestri AR, Signore A. Value of the first serum thyroglobulin level after total thyroidectomy for the diagnosis of metastases from differentiated thyroid carcinoma. Eur J Nucl Med 1999; 26(11):1448-1452.
5. Hannequin P, Liehn JC, Delisle MJ, Deltour G, Valeyre J. ROC analysis in radioimmunoassay: an application to the interpretation of thyroglobulin measurement in the follow-up of thyroid carcinoma. Eur J Nucl Med 1987; 13(4):203-206.
6. Giovanella L, Ceriani L, Garancini S. High-sensitive 2nd generation thyroglobulin immunoradiometric assay. Clinical application in differentiated thyroid cancer management. Q J Nucl Med 2002; 46(4):319-322.
7. Lin JD, Huang MJ, Hsu BR et al. Significance of postoperative serum thyroglobulin levels in patients with papillary and follicular thyroid carcinomas. J Surg Oncol 2002; 80(1):45-51.
8. Baudin E, Do CC, Cailleux AF, Leboulleux S, Travagli JP, Schlumberger M. Positive predictive value of serum thyroglobulin levels, measured during the first year of follow-up after thyroid hormone withdrawal, in thyroid cancer patients. J Clin Endocrinol Metab 2003; 88(3):1107-1111.
9. Cailleux AF, Baudin E, Travagli JP, Ricard M, Schlumberger M. Is diagnostic iodine-131 scanning useful after total thyroid ablation for differentiated thyroid cancer? J Clin Endocrinol Metab 2000; 85(1):175-178.
10. Kim TY, Kim WB, Kim ES et al. Serum thyroglobulin levels at the time of 131I remnant ablation just after thyroidectomy are useful for early prediction of clinical recurrence in low-risk patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 2005; 90(3):1440-1445.
11. Kloos RT, Mazzaferri EL. A single recombinant human thyrotropin-stimulated serum thyroglobulin measurement predicts differentiated thyroid carcinoma metastases three to five years later. J Clin Endocrinol Metab 2005; 90(9):5047-5057.
12. Menendez TE, Lopez Carballo MT, Rodriguez Erdozain RM, Forga LL, 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):301-306.
13. Wittekind C, Wagner G. TNM Classification of malignant tumors. 5 ed. Springer Berlin, 1997.
14. Morgenthaler NG, Froehlich J, Rendl J et al. Technical evaluation of a new immunoradiometric and a new immunoluminometric assay for thyroglobulin. Clin Chem 2002; 48(7):1077-1083.
15. Mazzaferri EL, Robbins RJ, Spencer CA et al. A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab 2003 Apr ;88 (4):1433 -41 88(4):1433-1441.
16. Pacini F, Molinaro E, Lippi F et al. Prediction of disease status by recombinant human TSH-stimulated serum Tg in the postsurgical follow-up of differentiated thyroid carcinoma. J Clin Endocrinol Metab 2001; 86(12):5686-5690.
17. de KB, Koppeschaar HP, Zelissen PM et al. Efficacy of high therapeutic doses of iodine-131 in patients with differentiated thyroid cancer and detectable serum thyroglobulin. Eur J Nucl Med 2001; 28(2):198-202.
18. Koh JM, Kim ES, Ryu JS, Hong SJ, Kim WB, Shong YK. Effects of therapeutic doses of 131I in thyroid papillary carcinoma patients with elevated thyroglobulin level and negative 131I whole-body scan: comparative study. Clin Endocrinol (Oxf) 2003; 58(4):421-427.
19. Pacini F, Agate L, Elisei R et al. Outcome of differentiated thyroid cancer with detectable serum Tg and negative diagnostic (131)I whole body scan: comparison of patients treated with high (131)I activities versus untreated patients. J Clin Endocrinol Metab 2001; 86(9):4092-4097.
20. Van Tol KM, Jager PL, de Vries EG et al. Outcome in patients with differentiated thyroid cancer with

negative diagnostic whole-body scanning and detectable stimulated thyroglobulin. Eur J Endocrinol 2003; 148(6):589-596.
21. Spencer CA, Takeuchi M, Kazarosyan M. Current status and performance goals for serum thyroglobulin assays. Clin Chem 1996; 42(1):164-173.
22. Ligabue A, Poggioli MC, Zacchini A. Interference of specific autoantibodies in the assessment of serum thyroglobulin. J Nucl Biol Med 1993; 37(4):273-279.
23. Spencer CA, Takeuchi M, Kazarosyan M et al. Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin measurement, and prognostic significance in patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 1998; 83(4):1121-1127.
24. Schaap J, Eustatia-Rutten CF, Stokkel M et al. Does radioiodine therapy have disadvantageous effects in non-iodine accumulating differentiated thyroid carcinoma? Clin Endocrinol (Oxf) 2002; 57(1):117-124.
25. Ericsson UB, Christensen SB, Thorell JI. A high prevalence of thyroglobulin autoantibodies in adults with and without thyroid disease as measured with a sensitive solid-phase immunosorbent radioassay. Clin Immunol Immunopathol 1985; 37(2):154-162.
26. Akamizu T, Inoue D, Kosugi S, Kohn LD, Mori T. Further studies of amino acids (268-304) in thyrotropin (TSH)--lutropin/chorionic gonadotropin (LH/CG) receptor chimeras: cysteine-301 is important in TSH binding and receptor tertiary structure. Thyroid 1994; 4(1):43-48.
27. Baloch Z, Carayon P, Conte-Devolx B et al. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid 2003; 13(1):3-126.