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Long-term predictive value of highly sensitive thyroglobulin measurement

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Abstract

Objective: To examine the predictive value of unremarkable nonstimulated highly sensitive thyroglobulin (hsTg) measurement with regard to the results of stimulated thyroglobulin (Tg) measurement, diagnostic whole-body scintigraphy, recurrence and differentiated thyroid cancer (DTC)-related death.

Design, Patients and Measurements: We retrospectively analysed the data of all 461 (410 without anti-Tg-antibodies [TgAbs], 51 with) DTC patients who were referred to our department for treatment and follow-up care of differentiated thyroid cancer from 2004 onwards, and in whom at least one posttreatment Tg value was measured in our hospital at least 3 months after I-131 ablation.

Results: In the group of TgAb-negative patients, 2.0% of patients with an unstimulated Tg < 0.1 ng/ml showed a stimulated Tg ≥ 1.0 ng/ml, whereas this happened in 77.6% with an unstimulated Tg ≥ 0.1 but <1.0 ng/ml. An unstimulated hsTg ≥ 0.1 ng/ml had a sensitivity specificity positive and negative predictive value of 90.0%, 94.1%, 77.6% and 97.6%, respectively, for a stimulated Tg ≥ 1.0 ng/ml. In TgAb-positive patients, this was 75%, 97%, 75% and 97%, respectively. An unstimulated Tg ≥ 0.1 ng/ml did not significantly discriminate with regard to the risk of DTC-related death ($p = .06$), but ≥1.0 ng/ml did ($p = .012$), as did a stimulated Tg ≥ 1.0 ng/ml ($p = .029$). Excluding patients with distant metastases at diagnosis nullifies this significance.

Conclusion: Except for patients with distant metastases, both TgAb negative and TgAb positive patients with an undetectable nonstimulated hsTg measurement have a very good prognosis. The high net present value of unstimulated hsTg testing means that further diagnostic procedures can be omitted in such patients.

KEYWORDS

assay, autoantibodies, patient care, prognosis, thyroglobulin, thyroid cancer, thyroid gland

1 | INTRODUCTION

In more recent years, highly sensitive thyroglobulin (hsTg) measurement has found entry into clinical practice in the follow-up of differentiated thyroid carcinoma (DTC), potentially obviating the need for stimulated thyroglobulin (Tg) measurement. hsTg in an international expert consensus was defined as any Tg measurement method, which under unstimulated conditions using a method-specific cutoff (usually 0.1 ng/ml) is able to predict a stimulated Tg < 1.0 ng/ml with sufficient sensitivity and specificity for clinical use.[1]

Unremarkable stimulated Tg levels, often combined with other follow-up procedures such as neck ultrasound and/or diagnostic I-131 whole body scintigraphy, are a good predictor of excellent prognosis.[2] This prognostic value has been validated in numerous long-term observational cohort studies, usually of a retrospective nature.[3–7] For hsTg, such long-term outcome studies are not yet available.

Our hospital belonged to the early adopters of hsTg measurement, using hsTg for the regular follow-up of DTC from 2004 onwards. As a considerable follow-up time is now potentially available in our patient collective, the primary aim of the present study is to examine the predictive value for long-term patient-relevant outcome measures of unremarkable nonstimulated hsTg measurement. A secondary aim is the further validation of the predictive value of basal, unstimulated hsTg for the results of consecutive stimulated Tg measurement.

2 | PATIENTS AND METHODS

2.1 | Patients

We retrospectively collected and analysed the data of all 461 DTC patients who were referred to our department for treatment and follow-up care of differentiated thyroid cancer from 2004 onwards, and in whom at least one posttreatment Tg value was measured in our hospital at least 3 months after I-131 ablation. The items gathered included data on initial pathology, surgical and radioiodine therapy as well as follow-up investigations including sonography, I-131 diagnostic whole-body scintigraphy and laboratory measurements including hsTg measurements. Included patients' characteristics are given in Table 1.

TABLE 1 Patient characteristics

Variable	Category	Value
No. of patients		461
Sex	*Male*	120 (26%)
	Female	341 (74%)
Age		53 (9–92)
Histology	*Papillary*	374 (81%)
	Follicular	83 (18%)
	Both	4 (1%)
T-stage	*Tx*	18 (4%)
	T1a	81 (18%)
	T1b	113 (25%)
	T2	81 (18%)
	T3	157 (34%)
	T4a	8 (2%)
	T4b	2 (0%)
N-stage	*Nx*	177 (38%)
	N0	135 (29%)
	N1	149 (32%)
M-stage	*M0*	442 (96%)
	M1	19 (4%)
Initial I-131 therapy activity (MBq)		3700 (909–11,700)

Note: Values are given as the number of patients or as median (minimum–maximum).

2.2 | Treatment

As a tertiary referral center for radioiodine therapy, patients are referred to us when radioiodine therapy is needed; therefore, our collective did not contain patients with isolated microcarcinoma (≤10 mm) without unfavourable histological characteristics or metastases. All 461 patients underwent a total thyroidectomy followed by at least one course of radioiodine (I-131) therapy. Patients in principle were prescribed a standard fixed activity of 3700 MBq. Young patients with a low tumour stage (≤pT2N0M0) were occasionally prescribed a lower fixed activity of 2000 MBq I-131 at the discretion of the attending physician. Patients with the advanced disease received higher initial therapy activities ranging, depending on the precise extent of the disease, between approximately 5550 and 11,100 MBq I-131. Paediatric patients received bodyweight a body weight-adjusted activity of 50 MBq/kg body weight. Details on the initial I-131 activity are given in Table 1.

As a rule, at least three months after the initial radioiodine therapy we performed a diagnostic I-131 whole-body scintigraphy (dxWBS) with 370 Mbq I-131 and laboratory measurements including thyroid-stimulating hormone (TSH)-stimulated hsTg measurement. Depending on the time period, patients were either stimulated by means of levothyroxine withdrawal for 4 weeks before I-131 administration or by injection of recombinant human TSH (rhTSH). In case of an inconspicuous result of this procedure, patients were followed by means of unstimulated Tg measurement and ultrasound of the neck in half-yearly intervals for 5 years after diagnosis, after which follow-up was performed in yearly intervals. In case of a pathological stimulated follow-up or recurrent disease occurring in the course of follow-up, patients were treated further as appropriate

and as decided on a case-by-case basis employing treatment modalities including surgery, I-131 therapy, radiation therapy, or tyrosine kinase inhibitor therapy.

2.3 | Laboratory measurements

For TSH, FT3, FT4, hsTg and anti-Tg antibody (TgAb) measurement, we used an immunometric assay on the fully automated Roche Elecsys system, which for Tg measurement had a reported lower detection limit of 0.1 ng/ml (2004–2012) and 0.04 ng/ml from 2013 onwards.

In the present study, we only considered Tg values obtained at least 3 months after I-131 therapy to allow for sufficient time for the working of I-131 to unfold.

2.4 | Pathological analysis and staging

Surgical specimens were analysed and classified as PTC or FTC applying the World Health Organization classification valid at the time of diagnosis. For the present study, we employed the histological diagnosis and tumour, node, metastasis staging as stated in the original pathology report, with the exception of M-stage; here, M0 was assumed if staging including posttherapy I-131 scanning after initial I-131 therapy did not reveal any distant metastases. A patient was regarded as having distant metastases either in case of histological verification or in case of highly plausible nonhistological evidence, such as a positive posttherapy I-131 whole-body scan, computed tomography scan or magnetic resonance imaging, was present or uncovered during the initial treatment.

2.5 | Definitions

For the categorization of dxWBS results, the report as written at the time of the procedure was used. A dxWBS was considered positive if foci suspicious for lymph node or distant metastasis were reported. The remaining thyroid remnant foci were not considered pathological.

For the present study, complete remission (CR) was defined as a negative neck ultrasound combined with a TSH-stimulated Tg < 0.1 ng/ml; based on recent results by Giovanella et al.[8] this criterium can also validly be employed in patients positive for the presence of TgAb.

Recurrence was defined as any of the following events occurring during follow-up after:

- cytologic/histologic evidence of disease;
- reoccurrence of detectable Tg levels during thyroid hormone replacement and/or after endogenous or exogenous TSH stimulation; and
- new foci of pathologic uptake on an I-131 dxWBS.

A patient was considered to have died of DTC if this was stated in his file as the main or contributing cause of death.

2.6 | Analysis

We compared the results of unstimulated hsTg measurements with:

- results of TSH-stimulated hsTg measurement;
- results of TSH-stimulated diagnostic I-131 dxWBS;
- recurrences during follow-up; and
- DTC-related death during follow-up.

Statistical analyses were performed using SPSS version 23 (IBM Corp.). $p < .05$ were considered statistically significant. The normality of the distribution of variables was tested using the Kolmogorov–Smirnov test. Survival times were analysed using the Kaplan–Meier method; differences between survival curves were assessed using log-rank tests. Values for the diagnostic performance of the unstimulated Tg test including the 95% confidence interval were calculated using the online calculator from MedCalc (www.medcalc.org/calc/diagnostic_test.php; last Accessed February 18, 2020).

3 | RESULTS

3.1 | Antibody status

In 51/461 patients a positive TgAb test was found. These patients will be analysed separately from TgAb-negative patients.

3.2 | Patients without TgAb

3.2.1 | Results of initial follow-up

In 269/410 (65.6%) patients, a nonstimulated Tg measured in our laboratory at least 3 months after initial radioiodine therapy was available in addition to a stimulated Tg value. In 305 patients, a diagnostic I-131 whole-body scintigraphy as well as an unstimulated Tg value was available. A total of 357 patients returned to our center for TSH-stimulated follow-up (levothyroxine withdrawal, $n = 142$; rhTSH, $n = 215$). An overview of key data with regard to diagnostic performance is given in Table 2 and will be discussed in more detail hereafter.

Patients with unstimulated follow-up Tg available: Diagnostic performance with regard to stimulated TgA: total of 58/269 unstimulated postablation Tg values were ≥0.1 ng/ml. Of these, 29 were ≥1.0 ng/ml. Of the 58 patients with an unstimulated Tg ≥ 0.1 ng/ml, 45 (77.6%) showed a stimulated Tg ≥ 1.0 ng/ml. Furthermore, in 5/269 (2.0%) cases with an available unstimulated Tg, a patient with an unstimulated Tg < 0.1 ng/ml showed a stimulated Tg ≥ 1.0 ng/ml.

TABLE 2 Overview of the predictive performance of basal, unstimulated hsTg measurement with regard to results of TSH-stimulated hsTg measurement and the results of I-131 diagnostic whole-body scintigraphy in patients negative or positive for the presence of antithyroglobulin autoantibodies

TgAb negative patients				TgAb negative patients			
	Stimulated hsTg ≥ 1.0	***Stimulated hsTg < 1.0***			***dxWBS positive***	***dxWBS negative***	
Basal hsTg ≥ 0.1	45	13	PPV 77.6%	*Basal hsTg ≥ 0.1*	13	44	PPV 22.8%
Basal hsTg < 0.1	5	203	NPV 97.6%	*Basal hsTg < 0.1*	9	239	NPV 95.8%
	Sensitivity 90.0%	Specificity 94.1%	Accuracy 93.3%		Sensitivity 59.1%	Specificity 82.2%	Accuracy 80.3%
TgAb positive patients				**TgAb positive patients**			
	Stimulated hsTg ≥ 1.0	*Stimulated hsTg < 1.0*			*dxWBS positive*	*dxWBS negative*	
Basal hsTg ≥ 0.1	3	1	PPV 75%	*Basal hsTg ≥ 0.1*	1	3	PPV 25%
Basal hsTg < 0.1	1	31	NPV 97%	*Basal hsTg < 0.1*	2	30	NPV 94%
	Sensitivity 75%	Specificity 97%	Accuracy 94%		Sensitivity 33%	Specificity 91%	Accuracy 86%

Note: Data are given as a number of patients or percentages.

Abbreviations: dxWBS, I-131 diagnostic whole-body scintigraphy; hsTg, highly sensitive thyroglobulin measurement; NPV, negative predictive values; PPV, positive predictive value; TgAb, antithyroglobulin autoantibodies.

Thus, an unstimulated hsTg test using 0.1 ng/ml as the threshold for positivity has a sensitivity of 90.0 (95% confidence interval: 78.2%–96.7%), a specificity of 94.1% (90.1%–96.8%), a positive predictive value of 77.6% (67.0%–85.5%), a negative predictive value of 97.6% (94.7%–99.0%) and an accuracy of 93.3% (89.6%–96.0%) for a TSH-stimulated Tg ≥ 1.0 ng/ml.

Patients with unstimulated follow-up Tg available: *Diagnostic performance with regard to dxWBS*: Out of 305 patients with an available unstimulated Tg who also received a dxWBS, 22 (7.2%) had a positive dxWBS. In 13 cases, this concerned lymph node metastases, in 9 cases distant metastases were encountered. In 9/305 (3.0%), a patient with an unstimulated Tg < 0.1 ng/ml showed a positive I-131 dxWBS. Thus, an unstimulated hsTg test using 0.1 ng/ml as the threshold for positivity has a sensitivity of 59.1% (95% confidence interval: 36.4%–79.3%), a specificity of 82.2% (76.8%–86.8%), a positive predictive value of 22.8% (16.0%–31.4%), a negative predictive value of 95.8% (93.2%–97.4%) and an accuracy of 80.3% (75.0%–84.9%) for predicting a positive dxWBS.

Follow-up: The median available follow-up duration was 3.7 (0.4–14.0) years.

During follow-up, 2/410 (0.5%) patients developed a recurrence. Neither of these patients died at the end of the follow-up. The cases of recurrent disease were diagnosed 6 and 60 months after diagnosis, respectively. A total of 32 patients (7.8%) showed progressive disease, 2 (0.5% of the study group) of whom died of DTC. The patients who died, succumbed to their disease 17 and 55 months after diagnosis, respectively. Both these patients already suffered from distant metastases at the time of DTC diagnosis.

Once CR, as defined, is reached, the Kaplan–Meier adjuster risk of recurrence at 1, 5 and 10 years was 0.5 ± 0.5%, 0.5 ± 0.5% and 2.0 ± 1.6%. As all patients with the recurrent disease by definition had an undetectable Tg level after I-131 ablation under both unstimulated and TSH-stimulated conditions, a comparative Kaplan–Meier analysis is not possible.

Total DTC-related, Kaplan–Meier adjusted mortality was 1.1 ± 0.8% at both 5 and 10 years, respectively. Kaplan–Meier analysis further revealed that an unstimulated Tg threshold of 0.1 ng/ml was not able to significantly discriminate with regard to the risk of DTC-related death ($p = .06$), but a threshold of 1 ng/ml was ($p = .012$; Figure 1A). Similarly, a stimulated Tg with a threshold of 0.1 was unable to discriminate significantly with regard to the risk of DTC-related death ($p = .15$). In contrast, a stimulated Tg with a threshold of 1 ng/ml was able to significantly distinguish between those at lower and higher risk of death ($p = .029$) (see also Figure 1B). However, this effect is nullified if patients with distant metastases at diagnosis are excluded, as no patients without distant metastases at diagnosis have died in the course of follow-up.

3.3 | Patients positive for TgAb

3.3.1 | Results of initial follow-up

In 36/51 (71%) TgAb positive patients, a nonstimulated Tg measured in our laboratory at least 3 months after ablation was available in addition to a stimulated Tg. In each of these patients, a dxWBS was

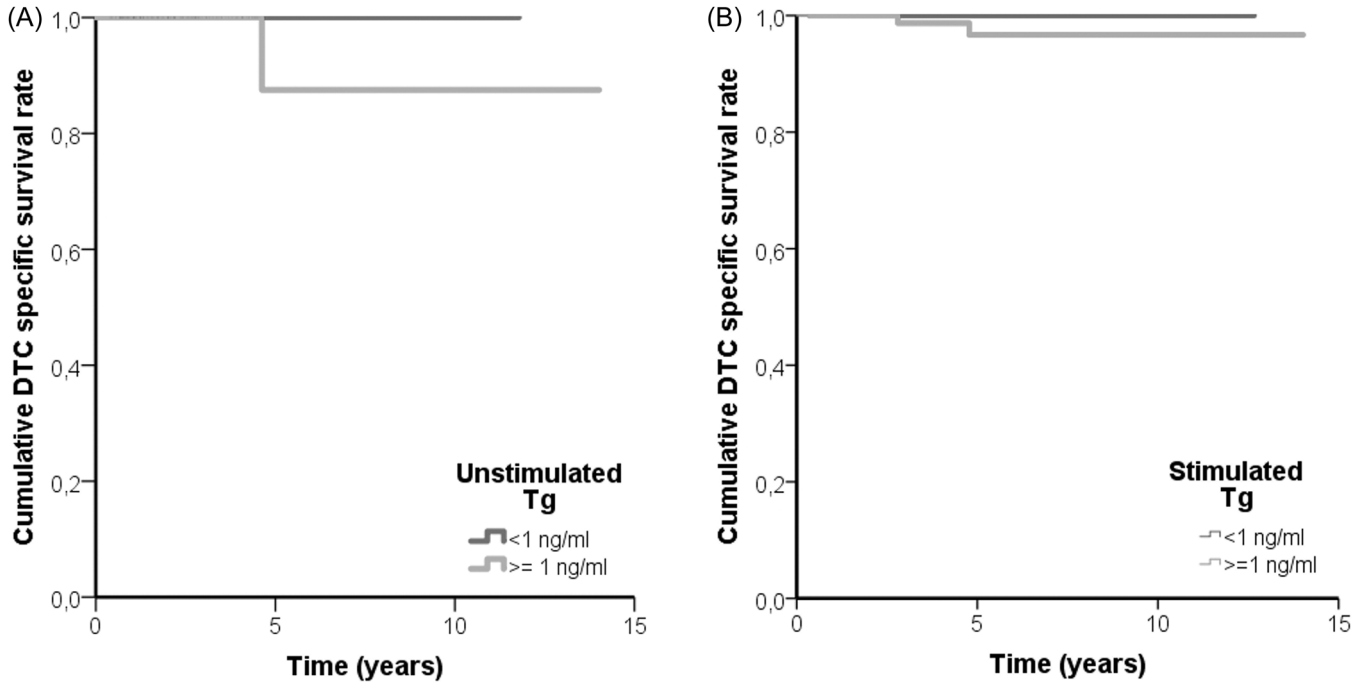

FIGURE 1 Kaplan–Meier survival curve of patients with (A) an unstimulated high-sensitive thyroglobulin (Tg) level below or ≥1 ng/ml, including patients with distant metastases at diagnosis. (B) A stimulated high-sensitive Tg level below or ≥1 ng/ml, including patients with distant metastases at diagnosis. DTC, differentiated thyroid cancer.

also performed. A total of 44/51 patients returned to our center for TSH-stimulated follow-up (levothyroxine withdrawal, $n = 12$; rhTSH, $n = 32$).

Patients with unstimulated follow-up Tg available: *Diagnostic performance with regard to stimulated Tg*: A total of 4/36 unstimulated postablation Tg values were ≥0.1 ng/ml. Of these, two were ≥1.0 ng/ml. In one case, a patient with an available unstimulated Tg (3%) <0.1 ng/ml showed a stimulated Tg ≥ 1.0 ng/ml. Of the four patients with an unstimulated Tg ≥ 0.1 ng/ml, three showed a stimulated Tg ≥ 1.0 ng/ml. Thus, an unstimulated hsTg test using 0.1 ng/ml as the threshold for positivity in patients with TgAb has a sensitivity of 75% (95% confidence interval: 19%–99%), a specificity of 97% (84%–100%), a positive predictive value of 75% (29%–96%), a negative predictive value of 97% (85%–99%) and an accuracy of 94% (81%–99%) for a TSH-stimulated Tg ≥ 1.0 ng/ml in patients with positive TgAb.

Patients with unstimulated follow-up Tg available: Diagnostic performance with regard to dxWBS:Out of the 36 patients with an available unstimulated Tg, 3 (8%) had a positive dxWBS. In one case, this concerned lymph node metastases, in two cases distant metastases were encountered. In 2/36 cases (6%), a patient with an unstimulated Tg < 0.1 ng/ml showed a positive I-131 dxWBS. Of the four patients with a stimulated Tg ≥ 0.1 ng/ml, one showed a positive dxWBS. Thus, an unstimulated hsTg test using 0.1 ng/ml as the threshold for positivity has a sensitivity of 33% (95% confidence interval: 1%–91%), a specificity of 91% (76%–98%), a positive predictive value of 25% (5%–70%), a negative predictive value of 94% (87%–97%) and an accuracy of 86% (71%–95%) for predicting a positive dxWBS in patients with positive TgAb.

Follow-up: The median available follow-up duration was 2.8 (0.6–12.1) years.

During follow-up, 2/51 (4%) patients developed a recurrence. The cases of recurrent disease were diagnosed 20 and 85 months after diagnosis, respectively. A total of two patients (4%) showed progressive disease, none of whom died of DTC. Once CR, as defined, is reached, the Kaplan–Meier adjusted risk of recurrence at 1, 5 and 10 years was 0%, 4.5 ± 4.4%, 0.5 ± 0.5% and 23.4 ± 17.4%. As all patients with the recurrent disease by definition had an undetectable Tg level after I-131 ablation under both unstimulated and TSH-stimulated conditions, a comparative Kaplan–Meier analysis is not possible.

As no patients in the patient group with TgAb died of DTC, further Kaplan–Meier survival analysis was not possible.

4 | DISCUSSION

To the best of our knowledge, the present study is the largest to report on the relationship between hsTg measurement and long-term prognosis. The present report clearly shows that prognosis generally speaking is excellent, with a very low mortality rate even in patients with distant metastases and nearly nonexistent in patients without distant metastases at diagnosis; mortality rates reported here are on the low end of the spectrum reported in the literature and on par

with rates reported in other more recent studies such as, for example, by Hulse et al.,[9] Verburg et al.[4] and Thies et al.[5]

The recurrence and mortality rates presented here in patients with a negative stimulated hsTg are low as well. However, when compared with other works such as by Thies et al.,[5] where the authors employed a non-hsTg assay with a functional sensitivity of 0.4 ng/ml as calibrated against the reference standard CRM 457, no significant further improvement is offered.

Giovanella et al.[8] in a slightly smaller patient series already reported, that assay-specific cutoffs for hsTg assays are able to predict long-term prognosis in terms of structural recurrence. To the best of our knowledge, however, the present study is the first one to report on the predictive ability of hsTg assays in terms of DTC-related mortality. Even though the threshold of 0.1 ng/ml just missed statistical significance, it is, in view of the very small number of DTC-related death cases which limit the statistical power of the present analysis, likely still a very good indicator of excellent prognosis, considering that no patient below this threshold, either with or without evidence of TgAb, died of DTC.

Several studies have already reported the excellent negative predictive value of a negative unstimulated hsTg for the presence of stimulated Tg of 1 ng/ml or higher. The present study confirms this excellent net present value (NPV) in the general DTC population. Our results, therefore, support the expert recommendation given in a 2014 expert consensus,[1] that in DTC patients with an undetectable unstimulated Tg, a TSH stimulated test can be omitted.

An indication for TSH-stimulated Tg measurement is also supported by the present results. As Giovanella et al.[1] recommended, a nonstimulated Tg between the assay functional sensitivity and 1 ng/ml is considered to be a 'grey zone'. In the present results, 23% of our patients with a nonstimulated Tg in this range did not show an increase to 1 ng/ml or more, thus obviating the need for considering additional I-131 therapy courses, as is usually recommended by guidelines at such levels.[2,10]

Another contentious issue to which the present results contribute is the matter of I-131 dxWBS after I-131 therapy. Whereas in general the need for this imaging procedure is contested, with a number of guidelines, such as, for example, the American Thyroid Association 2016[2] no longer indicating a need for it except in selected cases, whereas others, such as, for example, Verburg et al.[10] still propose a comparatively wide indication. Regardless of how one may stand on this issue, the present results offer additional evidence for the selection of patients in whom dxWBS can and perhaps even should be omitted. When applying the criterion stated by Giovanella et al.[1] of an NPV of at least 95% to obviate the need for a follow-up test, unstimulated hsTg levels can also be used to select patients for dxWBS.

This study, like any retrospective study, is of course hampered by weaknesses inherent to this particular type of study. First, our present population suffers from a referral bias, so only patients with a need for I-131 therapy are referred to us. This precludes us from evaluating the use of hsTg measurement in patients who do not have an indication for I-131 therapy, particularly isolated, nonmetastasized papillary microcarcinomas without unfavourable histological features.

Furthermore, the power of the present study suffers from the very good prognosis of DTC patients in our hands. Although highly desirable for our population, the very low number of recurrences and DTC-related deaths precludes us from performing a powerful statistical analysis and will undoubtedly leave a more subtle effect covered. Conversely, however, any effect which already shows statistical significance in spite of this very low number of events is likely not just statistically significant, but also clinically relevant.

Also, our treatment protocol can be considered a more aggressive one compared with what some internationally accepted guidelines prescribe. Therefore, the members of our population of low to intermediate-risk patient population all receive I-131 therapy, precluding us from assessing the value of unstimulated hsTg measurements in such patients without I-131 therapy. Our results, therefore, are only valid for patients who have received I-131 therapy, and cannot be extrapolated to other patients without further study.

Lastly, and perhaps most importantly, the present study is hampered in its predictive power by the comparably short available median follow-up. As most patients with an uncomplicated, low-risk course of disease receive long-term outpatient follow-up in peripheral practices rather than in our tertiary hospital, we have a comparably short available median follow-up. However, considering that the usual practice in our area of adherence is that patients in case of a sign of recurrence would be referred back to us for surgery and/or I-131 therapy, it is likely that few if any cases of recurrence and/or DTC-related death were missed.

Nonetheless, certainly in light of the last discussed weakness, the present results require further, preferably prospective, confirmation. However, the long follow-up interval, we now have thanks to the early adoption of hsTg assays nonetheless allows a first estimate of the value of this technique for long-term prognostication for use in patient consultations. The present results show that in patients without distant metastases at diagnosis, an undetectable hsTg signals an extremely good long-term prognosis with a very low risk of recurrence. As this risk of recurrence is unfortunately not non-existent, it remains advisable nonetheless to perform regular follow-ups at half-yearly to yearly intervals based on unstimulated Tg measurements—whether ultrasound, as a screening method is still needed in this setting, is, however, currently subject of debate in literature.[11,12]

5 | CONCLUSION

Except for patients with distant metastases, both TgAb negative and TgAb positive patients with an undetectable nonstimulated hsTg measurement have a very good prognosis with a very low risk of recurrence and negligible risk of differentiated thyroid cancer-related death. The high NPV of unstimulated hsTg testing means that further diagnostic procedures can be omitted in such patients.

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CONFLICT OF INTEREST

Larissa R. Bögershausen has participated in the speaker programme and acted as an advisor for Roche Diagnostics and Sanofi Genzyme, and has received speaker honoraria from IBSA SA, Roche Diagnostics, Sanofi and BRAHMS GmbH. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available upon request from the authors.

ETHICS STATEMENT

The need for complete ethical approval was waived by the medical ethical commission of the University of Marburg as the present study exclusively concerns anonymized, retrospective data analysis.

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