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Original Scientific Paper

DIAGNOSTIC VALUE OF STIMULATED SERUM THYROGLOBULIN IN THE FOLLOW-UP OF PATIENTS WITH DIFFERENTIATED THYROID CANCER

Vlado Wagenhofer[1,2], Ivan Mihaljević[1,2,3], Tatjana Kralj[1,2], Dubravka Vrdoljak[1] and Tomislav Kizivat[1,2]

[1]Clinical Institute of Nuclear Medicine and Radiation Protection, University Hospital Osijek, Osijek, Croatia;
[2]Faculty of Medicine Osijek, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia
[3] Academy of Medical Sciences of Croatia, Croatia

SUMMARY – The aim was to determine the diagnostic value of stimulated serum thyroglobulin (sTg) for the follow-up of patients with differentiated thyroid cancer (DTC) and to evaluate whether repeated sTg measurement provides additional clinical benefit in detecting persistent or recurrent structural disease if the initial sTg was negative. The retrospective study included 388 consecutive patients with DTC treated and followed-up between 2004 and 2018 at the Clinical Institute of Nuclear Medicine and Radiation Protection, Osijek University Hospital. The negative predictive value (NPV) of the first sTg measured 12 months after the initial treatment was compared with NPV of sTg measured annually during 3 consecutive years of follow-up. The first sTg NPV was 99.5% in the group of low-risk patients and 96.1% in the group of intermediate-risk patients. In both low- and intermediate-risk groups, there were no differences between the first sTg NPV and NPV of sTg measured annually during 3 years of follow-up period. Repeated measurement of the sTg after initially negative result had a limited clinical value for detecting persistent or recurrent structural disease and cannot be recommended in routine follow-up of low- and intermediate-risk patients with DTC.

Keywords: *Thyroid cancer; Risk assessment; Thyroglobulin*

Introduction

The incidence of differentiated thyroid cancer (DTC) has significantly increased in the last several decades (1). One of the reasons for such a trend is the improvement of diagnostic tools, especially ultrasound (2). The main clinical consequence of a widespread use of neck ultrasound with fine-needle aspiration biopsy of small nodules is a growing number of patients with the disease diagnosed at the early stages (small localised cancers), i.e. low-risk patients (3). The latest trends in the follow-up and long-term surveillance of DTC patients are focused on adjusting the intensity and type of diagnostic tests during follow-up to the

Corespondence to: *Vlado Wagenhofer*, Clinical Institute of Nuclear Medicine and Radiation Protection, University Hospital Osijek, Croatia, Phone: + 385 99 2533 813
E-mail address: vladowagenhofer@yahoo.com

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assessed risk of disease recurrence. This implies more frequent and more aggressive follow-up of DTC patients with high risk of disease recurrence and mortality and less frequent and less intensive follow-up of patients with low risk of disease recurrence. European and international guidelines increasingly recommend reducing the frequency or omitting certain diagnostic tests during follow-up, given the growing proportion of low-risk DTC patients (4-10). However, such recommendations are still burdened by controversies regarding the most efficient diagnostic tool for the follow-up of DTC patients (11,12).

The aim of this study was to evaluate the diagnostic value of the initial stimulated serum thyroglobulin (sTg) measured 12 months after the surgical treatment and radioiodine ablation therapy in the assessment of complete disease remission in DTC patients and to compare the negative predictive value (NPV) of the initially measured sTg and NPV of repeated sTg measured over a minimum of 3 years of follow-up period (including 3 consecutive sTg tests under TSH stimulation).

In addition, NPV of sTg was analyzed for each risk group of DTC patients. The main purpose of this study was to determine if the repeated measurements of sTg improve the efficiency of detection of recurrent or persistent structural disease in the follow-up of DTC patients.

Patients and methods

This was a retrospective study that included 388 patients with well-differentiated thyroid cancer who were treated and followed-up at the Clinical Institute of Nuclear Medicine and Radiation Protection, Osijek University Hospital from 2004 to 2018 with a median follow-up of 9 years (interquartile range: 6-12 years). All DTC patients underwent an initial treatment that included at least total thyroidectomy (with or without neck dissection) followed by radioiodine I-131 ablation therapy. Low-risk patients mostly received a dose of 50 mCi I-131, whereas intermediate- and high-risk patients mostly received a dose of 100 mCi I-131. The standard procedure for all DTC patients consisted of at least 3 periodically performed TSH-stimulation tests. This procedure included measurement of sTg, diagnostic whole-body scan, and neck ultrasound (with fine-needle aspiration biopsy of a suspicious nodule). TSH stimulation for sTg measurement was achieved by withdrawing thyroxine therapy for 4-5 weeks to reach the target value of TSH >30 mU/L (13,14).

To be included in the study, patients had to have a well-differentiated thyroid carcinoma (papillary, follicular or Hürthle cell carcinoma), undergo at least total thyroidectomy, complete I-131 radioiodine ablation therapy, and have at least 3 years of regular follow-up, including at least 3 consecutive examinations and TSH-stimulation tests (sTg, diagnostic whole-body scan, and neck ultrasound). Patients with poorly-differentiated thyroid cancers and other subcategories of thyroid cancer that do not represent a well-differentiated thyroid cancer (medullary thyroid cancer, anaplastic thyroid cancer, metastasis of some other primary tumours, etc.), those whose surgical treatment that did not include at least total thyroidectomy, patients who did not undergo I-131 radioiodine ablation therapy, patients who were not regularly followed-up, and patients who underwent less than 3 consecutive examinations and TSH-stimulation tests were excluded from the study.

Patients were categorized in risk groups according to the 2015 American Thyroid Association (ATA) classification criteria (10). Based on the data on their clinical outcomes, all DTC patients were classified into the following categories: patients with recurrent or persistent structural disease, patients with biochemical disease, patients with no evidence of disease (NED), and patients with indeterminate response to the initial therapy. Patients with biochemical disease were defined as having either thyroglobulinemia (sTg >2 ng/mL) or subsequent increase in thyroglobulin antibody levels with no evidence of recurrent or persistent structural disease.

Measurement of serum thyroglobulin

In the study period, different immunometric assays were used for thyroglobulin measurement. All the assays had high sensitivity (minimum functional sensitivity <0.9 ng/mL) and lower limit of detection of at least 0.2 ng/mL. In addition, thyroglobulin assays were standardized against the certified reference material for human Tg (CRM 457) (15). The result of

stimulated Tg test was negative if Tg <1 ng/mL (undetectable or very low Tg) and positive if Tg ≥2 ng/mL. A stimulated Tg value between 1 and 2 ng/mL was considered a limit value indicating a non-specific test result. Patients with initially high levels of thyroglobulin antibodies (TgAb), the presence of which interferes with thyroglobulin measurements, were excluded from the study.

Statistical analysis

The validity of sTg as a diagnostic test was assessed by determining its sensitivity, specificity, positive predictive value, and negative predictive value. Nominal indicators were presented as frequency distribution for each group and ratio. To determine proportion differences between two independent causes or between three or more independent causes, χ^2-test was used. The values of $p<0.05$ were considered statistically significant. Statistical analysis was performed with statistical software MedCalc ver. 18.11.3 (MedCalc Software, Ostend, Belgium).

Results

Low-risk DTC patients accounted for 68.8% (n=267) of all DTC patients. In the group of low-risk patients, the risk of recurrent or persistent structural disease after the initial treatment was 3% (8/267). In patients with no evidence of disease during 12 months after the initial treatment (including the first TSH-stimulation tests – sTg, diagnostic whole-body scan, and neck ultrasound), the risk of recurrent or persistent structural disease was only 0.6% (1/177) in the group of low-risk patients. In the group of intermediate-risk DTC patients, who accounted for 24% (n=93) of all DTC patients, the risk of recurrent or persistent structural disease after the initial treatment was 14% (13/93). In patients with no evidence of disease during 12 months after the initial treatment (including the first TSH stimulation tests – sTg, diagnostic whole-body scan, and neck ultrasound), the risk of recurrent or persistent structural disease was 2.1% (1/48) in the group of intermediate-risk patients. In the group of high-risk DTC patients, who accounted for 7.2% (n=28) of all DTC patients, the risk of recurrent or persistent structural disease after the initial treatment was 78.6% (22/28). In patients with no evidence of disease during 12 months after the initial treatment (including the first TSH-stimulation tests – sTg, diagnostic whole-body scan, and neck ultrasound), the risk of recurrent or persistent structural disease amounted to 33.3% (1/3) in the group of high-risk patients.

With respect to clinical outcomes, there was a statistically significant difference in the distribution of structural recurrences between the ATA risk groups ($p<0.001$) (Table 1).

The proportion of recurrent or persistent structural disease was the highest in the group of high-risk patients (78.6%), followed by the group of intermediate-risk patients (14%) and low-risk patients (3%). The analysis of paired patient groups (ATA risk groups) showed a statistically significant difference in the distribution of structural recurrences between high-risk and intermediate-risk patients, high-risk and low-risk patients, and intermediate-risk and low-risk patients ($p<0.001$ for all).

There was no statistically significant difference in the distribution of biochemical disease between different risk groups ($p=0.226$). The highest proportion of biochemical disease was 17.2% (n=16), found in the

Table 1. Distribution of recurrent or persistent structural disease according to American Thyroid Association (ATA) risk groups of patients with differentiated thyroid cancer

Structural recurrent/persistent disease	**No. of patients**				
	low-risk	**intermediate-risk**	**high-risk**	**total**	**P***
Yes	8	13	22	43	**<0.0001**
No	259	80	6	345	
Total	267	93	28	**388**	

***X^2 test**

Table 2. Distribution of biochemical disease according to American Thyroid Association (ATA) risk groups of patients with differentiated thyroid cancer

Biochemical disease	No. of patients				
	low-risk	intermediate-risk	high-risk	total	P*
Yes	28	16	3	47	**0.226**
No	239	77	25	341	
Total	267	93	28	**388**	

***X^2 test**

intermediate-risk group, followed by 10.7% (n=3) in the high-risk group and 10.5% (n=28) in the low-risk group (Table 2).

Stimulated serum thyroglobulin

The diagnostic value of sTg for detecting recurrent or persistent structural disease was assessed in 339 patients (Table 3), after excluding 49 patients (30 with positive TgAb measured 12 months after the initial treatment and 19 with sTg value between 1 and 2 ng/mL, i.e. with indeterminate response to the initial treatment).

Table 3. Recurrent or persistent structural disease in 339 patients with differentiated thyroid cancer and the first stimulated serum thyroglobulin (sTg) measured 12 months after the initial treatment

Recurrent/persistent structural disease	sTg (+)*	sTg (-)†
Yes	39	4
No	44	252

* (+) positive test result: sTg ≥2 ng/mL
† (-) negative test result: sTg <1 ng/mL

In DTC patients, the sensitivity and specificity of sTg measured 12 months after initial treatment were 90.7% and 85.1%, respectively. Negative predictive value (NPV) of sTg was 98.4%, i.e. only 4 of 256 patients with a negative result of the first sTg test developed a clear recurrent structural disease during the follow-up period. Positive predictive value (PPV) of sTg measured 12 months after initial treatment was 47%. NPV of the first TSH-stimulated Tg in DTC patients and repeated TSH-stimulated Tg measurements over a minimum of 3-year follow-up period (including 3 consecutive sTg tests) was 98.4%. There were only two patients with subsequent positive thyroglobulin antibody test result (recurrent biochemical disease). In the group of low-risk patients, NPV of the first TSH-stimulated Tg measured 12 months after the initial treatment was 99.5%. In this group of patients, the sensitivity and specificity of sTg measured 12 months after the initial treatment were 87.5% and 88.5%, respectively, and PPV was 21.2%. In the group of intermediate-risk patients, NPV of the first TSH-stimulated Tg measured 12 months after the initial treatment was 96.1%. In this group of patients, the sensitivity and specificity of sTg measured 12 months after the initial treatment were 84.6% and 76.6%, respectively, and PPV was 42.3%. In the group of high-risk patients, NPV of the first TSH-stimulated Tg measured 12 months after the initial treatment was 66.7%. In this group of patients, the sensitivity and specificity of sTg measured 12 months after the initial treatment were 95.5% and 40%, respectively, and PPV was 87.5%.

Discussion

Our study results confirmed the high sensitivity of the first TSH-stimulated Tg measured 12 months after the initial treatment for detecting recurrent or persistent structural disease during the follow-up of patients with differentiated thyroid cancer (16-23). In addition, the first TSH-stimulated Tg measured 12 months after

the initial treatment had a very high NPV for detecting structural recurrent or persistent disease.

The first measurement of stimulated Tg yielded false negative test results in four patients. In two of these four patients, recurrent structural disease was detected on neck ultrasound with fine-needle aspiration. NPV of TSH-stimulated Tg in combination with neck ultrasound with fine-needle aspiration was as high as 99.3%. The other two patients with recurrent structural disease, which had not been detected by TSH-stimulated Tg (false negative sTg), exhibited clear signs of dedifferentiation of thyroid cancer with a particularly aggressive clinical course. The research found that PPV of the first TSH-stimulated Tg is relatively low. The main reason for this is the high ratio (12.1%) of patients with thyroglobulinemia (sTg >2 ng/mL) without clear morphological signs of recurrent structural disease during further follow-up period (biochemical disease). Furthermore, our results showed that, in the group of low- and intermediate-risk patients, there was no difference between the number of detected structural recurrences based on the first sTg measurement and successive multiple sTg measurements. This means that repeated measurement of stimulated Tg was not diagnostically useful when the first sTg was negative. This study confirmed that negative findings of all diagnostic tests at the first postoperative examination (12 months after the initial treatment) were highly predictive of positive outcomes, with low risk of structural recurrence in the group of low- and intermediate-risk DTC patients (24-26). In the group of low- and intermediate-risk patients with excellent response to the initial treatment, there were only two patients with biochemically recurrent disease, i.e. subsequent increase in the thyroglobulin antibody levels. The very high NPV value of the first TSH-stimulated Tg (99.5% in the group of low-risk and 96.1% in the group of intermediate-risk patients) implies a high degree of reliability when deciding either to use it less frequently or to omit it completely during the follow-up of patients with negative sTg. Also, all patients with positive sTg and high-risk patients should be additionally monitored and subject to a procedure for detecting possible structural signs of the recurrent or persistent disease.

In conclusion, our study showed that repeated measurement of TSH-stimulated Tg after the initially negative result had a limited clinical value for detecting recurrent or persistent structural disease. Therefore, repeated TSH-stimulated Tg measurement cannot be recommended for routine follow-up in the group of low- and intermediate-risk DTC patients.

References

1. Hall SF, Walker H, Siemens R, Schneeberg A. Increasing detection and increasing incidence in thyroid cancer. World J Surg. 2009;33(12):2567-71. doi: 10.1007/s00268-009-0226-9
2. Grodski S, Brown T, Sidhu S, Gill A, Robinson B, Learoyd D, et al. Increasing incidence of thyroid cancer is due to increased pathologic detection. Surgery. 2008;144(6):1038-43; discussion 43. doi: 10.1016/j.surg.2008.08.023
3. Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988-2005. Cancer. 2009;115(16):3801-7. doi: 10.1002/cncr.24416
4. Cooper DS, Doherty GM, Haugen BR, Hauger BR, Kloos RT, Lee SL, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-214. doi: 10.1089/thy.2009.0110
5. Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, et al. Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxf). 2014;81 Suppl 1:1-122. doi: 10.1111/cen.12515
6. Milas Z, Shin J, Milas M. New guidelines for the management of thyroid nodules and differentiated thyroid cancer. Minerva Endocrinol. 2011;36(1):53-70.
7. Pacini F, Castagna MG, Brilli L, Pentheroudakis G, Group EGW. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23 Suppl 7:vii110-9. doi: 10.1093/annonc/mds230
8. Pitoia F, Ward L, Wohllk N, Friguglietti C, Tomimori E, Gauna A, et al. Recommendations of the Latin American Thyroid Society on diagnosis and management of differentiated thyroid cancer. Arq Bras Endocrinol Metabol. 2009;53(7):884-7
9. Kusić Z, Jukić T, Dabelić N, Franceschi M. Croatian Thyroid Society guidelines for the management of patients with differentiated thyroid cancer. Lijec Vjesn. 2008;130(9-10):213-27.
10. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid

Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1-133.

11. Ahmadieh H, Azar ST. Controversies in the management and follow-up of differentiated thyroid cancer: beyond the guidelines. J Thyroid Res. 2012;2012:512401. Epub 2012/12/30. doi: 10.1155/2012/512401
12. Rondeau G, Tuttle RM. Similarities and differences in follicular cell-derived thyroid cancer management guidelines used in Europe and the United States. Semin Nucl Med. 2011;41(2):89-95. doi: 10.1053/j.semnuclmed.2010.10.001
13. Schlumberger M, Charbord P, Fragu P, Lumbroso J, Parmentier C, Tubiana M. Circulating thyroglobulin and thyroid hormones in patients with metastases of differentiated thyroid carcinoma: relationship to serum thyrotropin levels. J Clin Endocrinol Metab. 1980;51(3):513-9. doi: 10.1210/jcem-51-3-513
14. Edmonds CJ, Hayes S, Kermode JC, Thompson BD. Measurement of serum TSH and thyroid hormones in the management of treatment of thyroid carcinoma with radioiodine. Br J Radiol. 1977;50(599):799-807. doi: 10.1259/0007-1285-50-599-799
15. Feldt-Rasmussen U, Profilis C, Colinet E, Black E, Bornet H, Bourdoux P, et al. Human thyroglobulin reference material (CRM 457). 2nd Part: Physicochemical characterization and certification. Ann Biol Clin (Paris). 1996;54(10-11):343-8.
16. 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. Epub 2009/07/28. doi: 10.1007/BF03346558.
17. Castagna MG, Brilli L, Pilli T, Montanaro A, Cipri C, Fioravanti C, et al. Limited value of repeat recombinant human thyrotropin (rhTSH)-stimulated thyroglobulin testing in differentiated thyroid carcinoma patients with previous negative rhTSH-stimulated thyroglobulin and undetectable basal serum thyroglobulin levels. J Clin Endocrinol Metab. 2008;93(1):76-81. Epub 2007/10/30. doi: 10.1210/jc.2007-1404
18. 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):5047-57. Epub 2005/06/21. doi: 10.1210/jc.2005-0492
19. Kloos RT. Thyroid cancer recurrence in patients clinically free of disease with undetectable or very low serum thyroglobulin values. J Clin Endocrinol Metab. 2010;95(12):5241-8. Epub 2010/09/15. doi: 10.1210/jc.2010-1500
20. Han JM, Kim WB, Yim JH, Kim WG, Kim TY, Ryu JS, et al. Long-term clinical outcome of differentiated thyroid cancer patients with undetectable stimulated thyroglobulin level one year after initial treatment. Thyroid. 2012;22(8):784-90. Epub 2012/07/10. doi: 10.1089/thy.2011.0322
21. Rosario PW, Furtado MS, Mineiro Filho AF, Lacerda RX, Calsolari MR. Value of repeat stimulated thyroglobulin testing in patients with differentiated thyroid carcinoma considered to be free of disease in the first year after ablation. Thyroid. 2012;22(5):482-6. Epub 2011/12/16. doi: 10.1089/thy.2011.0214
22. 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. Epub 2011/03/09. doi: 10.1210/jc.2010-2708
23. Prpić M, Franceschi M, Romić M, Jukić T, Kusić Z. Thyroglobulin as a tumor marker in differentiated thyroid cancer – clinical considerations. Acta Clin Croat. 2018;57(3):518-27. doi: 10.20471/acc.2018.57.03.16
24. Pacini F, Molinaro E, Castagna MG, Agate L, Elisei R, Ceccarelli C, et al. Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2003;88(8):3668-73. doi: 10.1210/jc.2002-021925
25. Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M, et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. Thyroid. 2010;20(12):1341-9. Epub 2010/10/29. doi: 10.1089/thy.2010.0178
26. Kowalska A, Walczyk A, Pałyga I, Gąsior-Perczak D, Gadawska-Juszczyk K, Szymonek M, et al. The Delayed risk stratification system in the risk of differentiated thyroid cancer recurrence. PloS One. 2016;11(4):e0153242. doi: 10.1371/journal.pone.0153242

Sažetak

DIJAGNOSTIČKA VRIJEDNOST STIMULIRAJUĆEG SERUMSKOG TIREOGLOBULINA U PRAĆENJU BOLESNIKA S DIFERENCIRANIM KARCINOMOM ŠTITNJAČE

V. Wagenhofer, I. Mihaljević, T. Kralj, D. Vrdoljak i *T. Kizivat*

Cilj ovoga istraživanja bio je ocijeniti dijagnostičku vrijednost stimulirajućega serumskog tireoglobulina (sTg) tijekom praćenja bolesnika s diferenciranim karcinomom štitnjače (DTC) i utvrditi hoće li ponovno mjerenje sTg-a nakon urednoga prvog nalaza pokazati kliničku korist u otkrivanju strukturnih recidiva bolesti tijekom praćenja bolesnika s DTC-om. Uspoređena je negativna prediktivna vrijednost (NPV) prvoga sTg-a izmjerenoga godinu dana nakon inicijalnog liječenja te nakon minimalno tri godine ponavljanja tog dijagnostičkog testa. Ispitivanje je obuhvatilo 388 bolesnika s DTC-om liječenih i kontroliranih u Kliničkom zavodu za nuklearnu medicinu Kliničkog bolničkog centra Osijek od 2004. do 2018. godine. NPV prvog izmjerenog sTg-a (godinu dana nakon inicijalnog liječenja) u otkrivanju strukturnog recidiva bolesti u skupini niskorizičnih bolesnika iznosila je 99,5 %, a u skupini srednjerizičnih bolesnika 96,1 %. U te dvije skupine bolesnika s DTC-om nije utvrđena razlika u vrijednosti NPV-a prvoga sTg-a i NPV-a sTg-a nakon višegodišnjega testiranja u uvjetima TSH stimulacije tijekom minimalno 3 godine praćenja oboljelih. Ponavljanje mjerenja sTg-a nakon urednog prvog nalaza izmjerenog godinu dana nakon kirurškog liječenja i radiojodne ablacijske terapije ima ograničenu kliničku korist u otkrivanju strukturnih recidiva bolesti i ne preporučuje se za rutinsko izvođenje tijekom praćenja niskorizičnih i srednjerizičnih bolesnika s DTC-om.

Ključne riječi: *Karcinomi štitnjače; Procjena rizika; Tireoglobulin*