

CLINICAL STUDY

Recombinant human thyrotropin in follow-up of patients with differentiated thyroid cancer

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Abstract: *Background:* Despite very good prognosis patients with previously treated well-differentiated thyroid cancer (DTC) require lifelong monitoring for recurrent disease. Apart from neck ultrasonography (USG) two diagnostic tests play a central role in follow-up of these patients: radioiodine whole body scanning and serum thyroglobulin (Tg) measurement. The diagnostic value of both tests is most accurate during thyroid stimulating hormone (TSH) stimulation. Temporary discontinuation of thyroid hormone therapy was previously the sole effective approach for TSH-stimulated testing. However, hormone withdrawal was associated with the morbidity of severe hypothyroidism. The introduction of recombinant human TSH (rhTSH)-stimulated testing offers an alternative way. Recent clinical trials have shown that measurement of the rhTSH-stimulated serum Tg concentration (rhTSH-Tg) alone is the most sensitive way to detect residual or recurrent thyroid cancer.

Objectives: The aim of the study was to investigate rhTSH-Tg in patients considered to be cured with already finished radioiodine treatment 1–3 years ago (routine follow-up) and in patients more years after radioiodine therapy with a new indefinite (mild) suspicion for DTC recurrence and to report the first experience with this diagnostic procedure in Slovakia.

Patients and methods: RhTSH-Tg was examined in 84 patients (72 women and 12 men) clinically free of disease, 1–3 years after finishing radioiodine therapy. Second group consisted of 4 patients (2 women and 2 men) 5, 9, 12 and 38 years after ¹³¹I treatment with a mild suspicion of DTC recurrence.

Results: RhTSH testing was well tolerated. No adverse events were detected. In the first group clinically free of disease undetectable rhTSH-Tg (<0.2 ng/ml) was found in 77 patients (91.7 %), Tg above diagnostic cutoff (>2 ng/ml) in 4 patients (4.8 %) and Tg in the range 0.6–2 ng/ml in 3 cases (3.6 %). In all patients of second group previous indefinite suspicion of DTC recurrence was confirmed by the rhTSH-Tg rise (2.9–7.3 ng/ml).

Conclusion: In accordance with the literature rhTSH-Tg concentration in combination with neck USG has the highest sensitivity and negative predictive value in detecting residual or recurrent DTC (Tab. 1, Fig. 1, Ref. 14). Full Text (Free, PDF) www.bmj.sk.

Key words: differentiated thyroid cancer, residual and recurrent, neck ultrasonography, recombinant human thyrotropin.

Primary treatment of well-differentiated thyroid cancer (papillary and follicular carcinoma) is effective. Patients undergo total thyroidectomy followed by ¹³¹I remnant ablation and long-term suppressive thyroid hormone therapy (TSH suppression) (1, 2, 3, 4). The main rationale for this practice is based on the following assumptions. 1) ¹³¹I treatment of small (microscopic) residual postoperative tumor foci may decrease the DTC recurrence and, possibly, mortality rates. 2) ¹³¹I ablation of residual normal thyroid tissue facilitates the early detection of recurrence based on serum Tg measurement and eventually on ¹³¹I-whole body scan (¹³¹I-WBS). 3) Large activity of ¹³¹I allows a highly sensitive post-therapy WBS that may reveal previously undetected tumor foci outside the thyroid bed or distant metastases (5, 6).

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Despite the efficacy of these treatments and despite very good prognosis, patients with previously treated DTC face lifelong risk of recurrent disease, which can cause significant late morbidity and mortality.

The early discovery of persistent or recurrent disease is of paramount importance for cure and survival rates. In the lifelong monitoring of the patients neck USG, ¹³¹I-WBS (diagnostic or posttherapeutic) and serum Tg measurement play central role. There is growing recognition of the value of serum Tg as a part of routine surveillance. An undetectable serum Tg measured during thyroid hormone suppressive therapy (THST) is often misleading, it does not rule out the cancer recurrence. The diagnostic value of serum Tg concentration and ¹³¹I-WBS is most accurate during TSH stimulation. Serum TSH should be above an empirically determined level >30 mIU/l (3, 4, 5, 6, 7, 8).

Periodic withdrawal of thyroid hormone therapy has been the traditional approach to enhance TSH secretion and to stimulate endogenously potential residual or recurrent tumor foci. Although effective for testing and subsequent ¹³¹I therapy this procedure has several drawbacks: 1) it is associated with the pre-

Tab. 1. Characteristics of serum TSH (mIU/l) values on the day 3 (TSH 1) and day 5 (TSH 2) after administration of rhTSH (0.9 mg i.m. on the day 1 and day 2).

	Patients n=88		Men n=14		Women n=74	
	TSH1	TSH2	TSH1	TSH2	TSH1	TSH2
median	100.0	13.9	80.5	11.1	100.6	14.3
min	32.2	3.2	41.5	3.2	32.2	4.8
Q1	82.1	10.4	71.7	7.6	87.7	10.8
Q3	134.2	21.3	88.81	6.3	139.8	22.4
max	306.00	49.70	135.60	28.80	306.00	49.70

dictable and almost universal morbidity of transient severe hypothyroidism with its attendant decrease in quality of life and diminished productivity, 2) the prolonged stimulation of any residual cancer can occasionally induce tumor progression (with clinical consequences in several special localisations of metastases), 3) some patients cannot surmount a sufficient endogenous TSH rise (9). The introduction of rhTSH into routine clinical practice during last decade offers a new alternative. Recent clinical trials have shown that the sensitivity of combined rhTSH stimulated radioiodine scanning and serum Tg measurement has equivalent sensitivity to testing after thyroid hormone withdrawal (10). Furthermore, measurement of the rhTSH-Tg concentration was found to have the highest sensitivity and is sufficient by itself (without WBS) in monitoring DTC (11), especially in low-risk patients (12). The cutoff value for rhTSH-Tg concentration >2 ng/ml is generally considered to be diagnostic for persistent or recurrent disease. RhTSH-Tg concentration in the range 0.6–2 ng/ml requires periodic annual examination (3, 4, 7, 9). This diagnostic method is very simple, providing sensitive Tg measurements while avoiding the effects of hypothyroidism and disruption of patient's physical and mental functioning. RhTSH administration substantially promotes compliance with DTC monitoring (13, 14).

In view of this recent knowledge, we introduced rhTSH testing into routine follow-up of patients with previously treated DTC considered to be cured and into diagnostic algorithm of suspicion of disease recurrence.

Patients and methods

In the period from July 2007 till June 2008 we examined rhTSH-Tg in 2 groups of patients. Group 1 consisted of 84 consecutive patients (72 women, age range 28–80 years, and 12 men, age range 30–64 years) previously treated for DTC, clinically free of disease. They underwent total thyroidectomy, ^{131}I -emnant ablation followed by further radioiodine therapy. The ^{131}I treatment was finished when endogenously stimulated serum Tg concentration was undetectable (<0.2 ng/ml) and post-therapeutic WBS was negative. Using TNM scoring system in the initial phase of treatment 5 patients belonged to T4 stage, 3 patients to T3 and 76 remaining to T1–2 stage. 1 patient had distant lung metastases. It was not possible to assess exactly the percentage of N0 and N1 stage, because many patients underwent only total thyroidectomy without central lymph node dis-

section when not enlarged. All patients had suppressed serum TSH level (<0.1 mIU/l) and a undetectable basal serum Tg concentration (<0.2 ng/ml) under THST. Investigation of rhTSH-Tg was performed 1–3 years after finishing ^{131}I treatment. Group 2 consisted of 4 patients 5, 9, 12 and 38 years after ^{131}I treatment with a new mild (indefinite) suspicion for DTC recurrence based either on neck USG (small lymph nodes $<5 \times 5 \times 10$ mm with abnormal echostructure) or on low but measurable serum Tg concentration (<1.0 ng/ml) during THST. RhTSH was administered as a 0,9 mg i.m. injection (Thyrogen, Genzyme) on two consecutive days (monday and tuesday) approximately 24 hours apart. On wednesday (day 3) TSH was determined and on friday (day 5) serum TSH and Tg concentrations were analysed. Serum Tg was measured with an automated immunofluorescent assay (B.R.A.H.M.S. hTg KRYPTOR), TSH with chemiluminiscent immunoassay (ARCHITECT TSH, Abbott).

Results

Sufficient TSH rise was achieved after rhTSH administration (Fig. 1). Surprisingly the TSH value characteristics were statistically significantly lower in men compared to women ($p < 0.0003$) (Tab. 1). Thyrogen was well tolerated, no adverse events were recorded.

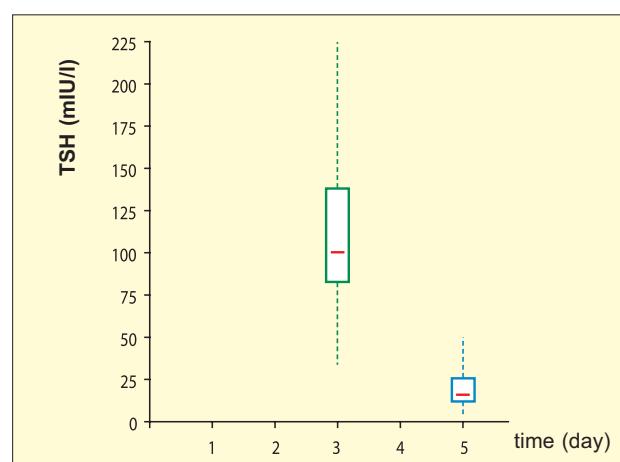


Fig. 1. TSH dynamics after rhTSH administration (Box & Whisker plot – minimum, 1st quartile, median, 3rd quartile, maximum* – maximal value 306.0 is not shown on the graph).

In group 1 (84 clinically disease free patients on routine follow-up) rhTSH-Tg increase above the cutoff value >2 ng/ml was recorded in 4 patients (4.8 %). No one belonged to T3 or T4 stage before. These patients were sent for additional 131I treatment and diagnostics. In 3 patients (3.6 %) rhTSH-Tg rose to the range 0.6–2.0 ng/ml. In this group rhTSH-Tg will be examined repeatedly annually. 77 patients (91.7 %), including five T4 stage cases, had undetectable Tg concentration (<0.2 ng/ml) after rhTSH stimulation indicating remission of the disease.

In group 2 rhTSH-Tg increase above the cutoff value (Tg 2.9–7.3 ng/ml) was recorded in all 4 patients (100 %) confirming the previous suspicion for DTC recurrence years after initial complex treatment.

Discussion

Discovered at an early stage, most thyroid carcinomas are curable with modern therapy. Despite good prognosis, patients with previously treated DTC face lifelong risk of recurrent disease. Much has been done in recent years to improve follow-up paradigms, which now rely heavily upon TSH stimulated Tg measurements made with rhTSH or after thyroid hormone withdrawal, neck USG, diagnostic and/or posttreatment 131I-WBS and in selected cases 18 fluorodeoxyglucose (18FDG) positron emission tomography (PET). It is important that tests for thyroid cancer have a high negative predictive value. Subsequent studies have consistently shown that USG and rhTSH-Tg together have the highest sensitivity for detecting residual tumor in low-risk patients affirming that the diagnostic WBS has little place in their follow-up management, and that an undetectable TG during THST is unreliable.

Many patients appear cured by initial complex therapy. Recurrence of the disease can reach 10 % after 10 years. In the Department of clinical endocrinology St. Elizabeth Cancer Institute we introduced rhTSH-Tg to the routine follow-up of patients after finishing 131I treatment. We detected persistent disease in 4.8 % of patients considered to be cured. In patients with mild (indefinite) suspicion of DTC recurrence (e.g. small lymph nodes, low detectable Tg during THST) rhTSH-Tg was useful to confirm recurrent disease many years after initial treatment.

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