

Recombinant human TSH in radioiodine treatment of differentiated thyroid cancer

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Abstract

BACKGROUND: Recombinant human TSH (rhTSH) has been developed to facilitate the follow-up for persistent or recurrent differentiated thyroid cancer (DTC), avoiding the hypothyroid symptoms after the withdrawal of Levothyroxine (L-T₄) suppressive therapy.

MATERIAL AND METHODS: To analyse the effect of rhTSH in providing stimulation of radioiodine uptake (RAIU) for the ablation of thyroid remnant and/or malignant thyroid tissue in patients with metastatic DTC. Ten subjects (4 women, 6 men), mean age 53 years, with DTC (7 papillary, 2 follicular and 1 Hürthle-cell), requiring radioiodine therapy (RIT) were studied. Nine of them had a positive diagnostic whole body scan (dWBS) or CT for thyroid remnant, lymph nodes and/or distant metastases. One patient with an invasive tall cell PTC had an increased serum Tg and a negative dWBS. Serum TSH was measured before and two days after the rhTSH injection. Thyroglobulin measurements were performed before the rhTSH administration, 3 and 6 months after RIT. There were no serious side effects of the rhTSH application.

RESULTS: Serum TSH after the rhTSH injection rose to 156.5 ± 60.9 mIU/L and induced RAIU in 8 out of 10 patients. Basal serum Tg was increased in 6 patients and decreased three

months later in 2 of them. The post-therapy WBS (pthWBS) showed: 1) additional metastatic lesions in 3 patients with positive dWBS, 2) lung nodular metastases in 1 patient with negative dWBS, 3) similar image as the dWBS in 4 patients, 4) negative image in 1 patient with positive dWBS.

CONCLUSION: RhTSH is a safe and promising method for the stimulation of RAIU in patients with thyroid remnant and/or persistent or recurrent DTC, avoiding L-T₄ withdrawal.

Key words: differentiated thyroid cancer, radioiodine therapy, recombinant human TSH

Introduction

The standard protocol of treatment and follow-up of patients with advanced differentiated thyroid cancer includes radioiodine ablation of the thyroid remnant after a total or near-total thyroidectomy and subsequent suppression of endogenous TSH with thyroid hormones [1, 2]. However, 5–20% of patients will have local or regional recurrence, and 10–15% will develop distant metastases that may require further radioiodine treatment in a hypothyroid condition [3]. Serum TSH should be 30 mIU/L or more for an optimal RAIU [4, 5].

The rise in endogenous TSH is usually achieved by 4–6 weeks of thyroxine withdrawal, accompanied by more or less severe symptoms of hypothyroidism. Some patients experience paralyzing fatigue, concentration difficulties, severe depression, hallucinations and other symptoms such as constipation, cold intolerance, weight gain, paraesthesias, transient deafness [6, 7]. Sometimes, the result is poor compliance, especially in young patients. In the elderly and/or in patients in poor physical condition [8, 9], hypothyroidism increases the risk of severe cardiac, cerebrovascular and neurological complications, which may even be fatal. In addition, some patients may be unable to generate endogenous TSH levels sufficient for stimulating radioiodine RAIU because of hypothalamic-pituitary disease (secondary hypothyroidism due to pituitary adenoma or brain metastases) or medications that suppress TSH [10–13].

The administration of recombinant human TSH as an alternative to L-T₄ withdrawal has proven to be effective in the diagnostic follow-up of patients with DTC [14, 15]. Large clinical trials [9, 16,

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17] have demonstrated that rhTSH successfully stimulates thyroglobulin (Tg) release from thyroid tissue and induces RAIU for a whole body scan (WBS) [18–20]. No related serious adverse events have been reported to date. Most recent results show a high concordance of WBS performed after rhTSH with scans obtained after L-T₄ withdrawal in detecting recurrent or residual disease [21, 22]. In addition, the use of rhTSH is associated with a higher quality of life compared with L-T₄ discontinuation.

There is an increased attention to the use of rhTSH before ablative RIT in patients with a thyroid remnant and/or recurrent DTC. Studies to date have included a limited number of patients with advanced DTC. We describe the first 10 patients with DTC, referred to our centre, who received rhTSH under euthyroid conditions before radioablative therapy, as a part of the manufacturer's "Compassionate Use Program".

Material and methods

Patients

From January to June 2000, 10 patients (4 women and 6 men) with advanced recurrent and/or residual DTC were treated with ¹³¹I after stimulation with rhTSH (thyrotropin alpha, Thyrogen, Genzyme Corporation, Nycomed) at the Medical University of Sofia (Sofia, Bulgaria) with a follow-up period of 18 months. The mean age of the whole group was 53 years (range: 22–74 yrs), men — 49 years (range: 22–67 yrs) and women — 59 years (range: 42–74 yrs). The primary diagnosis was established between 1975 and 2000. Seven patients had papillary cancer, two of them — tall cell variant; two patients — follicular cancer and one — Hürthle cell cancer. At the time of referral, 7 of 10 patients were in stage IV (TNM, 1998), 2 — in stage II, 1 — in stage I (Table 1). In 4 patients the disease was limited to neck lymph nodes, 5 patients presented lung, bone and soft tissue metastases and one patient with follicular cancer had only a thyroid remnant.

Nine of the patients had undergone a total or near-total thyroidectomy and one patient — a subtotal thyroidectomy. Most patients (8 of 10) had also received previous RIT(s) (median number of treatments — 2; range, 1–6) after L-T₄ withdrawal, with cumulative activity

ranging from 3.1 to 27.4 GBq (mean 9.6 ± 9.4 GBq). The time since the last RIT varied from 4 to 61 months. Six patients had also been treated by external beam therapy (EBT) of the thyroid bed, neck lymph nodes or distant metastasis (bone, soft tissue) with a mean dose of 59.7 ± 5.6 Gy, 4 to 309 months before referral.

The indications for using rhTSH and avoiding hypothyroidism were life-threatening conditions due to cardiovascular diseases, symptoms of myxoedema psychosis and an inability to generate sufficient endogenous TSH (Tab. 1).

All patients were given rhTSH under the manufacturer's "Compassionate Use Program". They signed written informed consent after the approval of compassionate use by the local ethics committee.

Treatment protocol

Patients remained on L-T₄ suppressive therapy (150–200 µg/daily, mean 160 ± 16 µg/d). Each patient was given one intramuscular injection of 0.9 mg rhTSH in two consecutive days before RIT. On the third day they received RIT with ¹³¹I activities ranging from 3.3 to 4.4 GBq (mean activity 3.9 ± 0.3 GBq) (Fig. 1). According to Bulgarian Radiation Basic Safety Standards patients were hospitalised in an active unit of our radiotherapy clinic, during the treatment period and experienced medical personnel were monitoring them for adverse events. Baseline serum TSH was obtained before rhTSH application, in the 24th hour after each rhTSH administration, as well as after 3 months (under L-T₄ suppression) and 6 months (after 4 weeks L-T₄ withdrawal). Serum Tg was measured at the baseline, 3 and 6 months after RIT. Post-therapy WBS (pWBS) was performed 4 days after RIT, including spot images of the cervical region and other sites of pathological RAIU. A follow-up dWBS was carried out 6 and 18 months after RIT (Fig. 1).

Thyrogen had not been registered in our country, so all patients further had to discontinue L-T₄ therapy and to face all the problems related to their hypothyroid condition or inability to generate sufficient TSH levels.

Serum TSH and Tg were measured using commercially available kits (Delfia, with reference interval 0.3–4.0 mIU/L for TSH and 2–35 ng/ml for Tg). When anti-Tg antibodies were present, the

Table 1. Clinical characteristics of patients

Patients	Sex	Age [years]	Tumor histology	Tumor stage at the moment of RIT	Prior RIT [GBq]	Prior TGT [Gy]	Target of rhTSH RIT	Reason for compassionate use of rhTSH
1	F	74	PTC (G2)	T ₂ N _{1b} M ₀	10.7	64	Bilateral neck and mediastinal lymph nodes metastases	Heart failure
2	F	52	PTC	T ₄ N _{1b} M _{1r}	27.4	56	Lung metastases	Insufficient endogenous TSH stimulation
3	F	42	FTC	T ₂ N ₀ M ₁	3.7	50	Remnant, bone metastases	Insufficient endogenous TSH stimulation
4	F	68	FTC	T ₄ N ₀ M ₀	0	0	Remnant	Endogenous depression
5	M	60	PTC	T ₄ N _{1b} M ₁	3.4	62	Lung metastases	Insufficient endogenous TSH stimulation
6	M	38	PTC (tall cell)	T ₂ N _{1b} M ₁	3.7	0	Neck lymph nodes and lung metastases	Myxoedema psychosis
7	M	67	Hürthle cell	T ₄ N _{1b} M ₁	20.4	64	Lung and soft tissue metastases	Heart failure
8	M	54	PTC	T ₄ N _{1a} M ₀	0	0	Remnant, lymph nodes	Malignant hypertension
9	M	53	PTC (tall cell)	T ₄ N ₀ M ₀	4.0	62	Remnant, lymph nodes	Malignant hypertension
10	M	22	PTC	T ₂ N _{1a} M ₀	3.1	0	Neck lymph nodes	Myxoedema psychosis

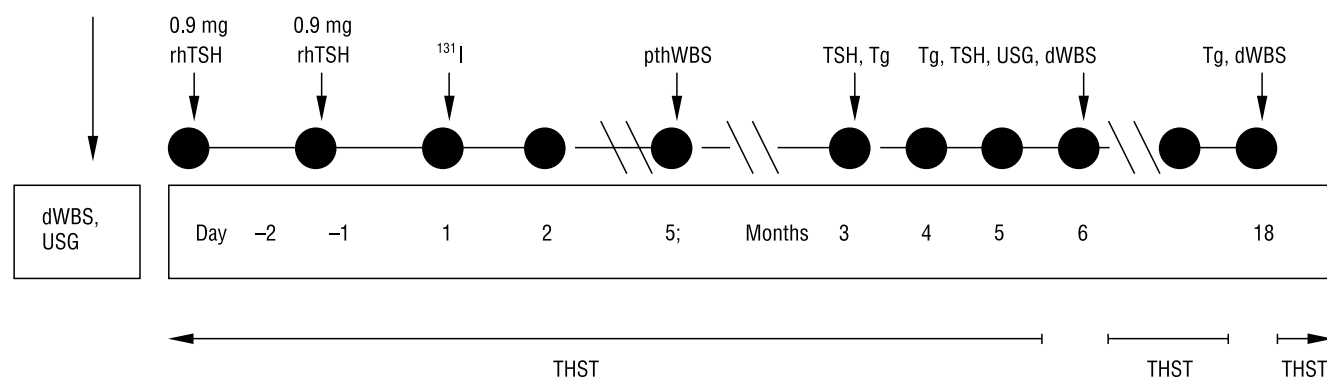


Figure 1. Protocol for treatment and follow-up.

results of Tg were falsely low. Therefore, a recovery test was made for each sample and a recovery rate of 80% was considered a normal value.

A diagnostic WBS was performed after 4 weeks of L-T₄ withdrawal with 5 mCi ¹³¹I, using a SPECT gamma camera (DIACAM, Siemens). Ultrasonography (USG) of the neck was performed before RIT and 6 months after with an Ultramark 9, ATL, 5–10 MHz transducer.

A computed tomography scan and/or magnetic resonance imaging were conducted in selected cases. During the follow-up period, the patients were in permanent contact with their physician. For statistic analysis a Student t-test was used (standard package Statistica, 1995).

Two patients received following RIT after L-T₄ withdrawal 8–10 months later. Because of their progressive disease, they died 12–18 months after the administration of rhTSH.

Results

Serum TSH after rhTSH administration

The mean value of TSH under L-T₄ suppression was 0.8 ± 0.68 mIU/L (0.28–2.10 mIU/L). In 3 patients TSH suppression was not effective, but they remained on 150 µg L-T₄ because of palpitations or symptoms of ischemic heart disease. After 2 days of application of rhTSH serum TSH rose significantly to 156.5 ± 60.9 mIU/L (range 89.3–260 mIU/L) (Fig. 2). There was a significant difference ($p < 0.001$) between the endogenous TSH after L-T₄ withdrawal 6 months later and the serum TSH after the application of rhTSH (Fig. 3). Four patients (No. 2, 3, 5, 7) could not generate sufficient endogenous TSH after 4 weeks L-T₄ withdrawal at the 6th month.

The serum Tg before rhTSH stimulated RIT and 3 months later remained below 1.0 ng/ml in 3 patients with thyroid remnant, decreased in 2 patients, increased in 1 patient and did not change in 1 patient (Table 2). Patient No. 7 with serum Tg below 1.0 ng/ml was with high titer of anti-Tg antibodies (1718 E/ml) and a recovery test of 2%.

Post-therapy WBS

The pthWBS after rhTSH stimulated RIT, visualized local or metastatic sites in 8 of 10 studied patients (Table 2). A comparison to previous dWBS or pthWBS showed additional sites of RAIU in 4 patients: 3 with positive dWBS (No. 2, 3, 6) (Fig. 4), 1 with

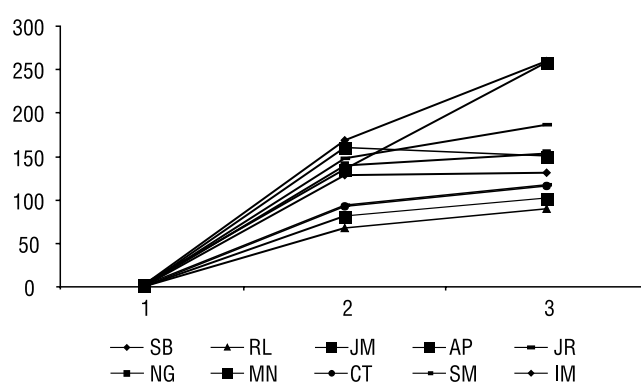


Figure 2. TSH values before and after 2 days rhTSH application.

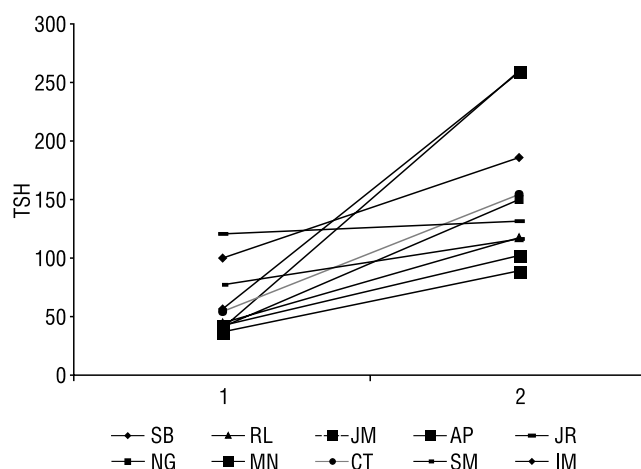


Figure 3. Comparison of serum TSH after 4 weeks of L-T₄ withdrawal and after two injections of 0.9 mg Thyrogen.

negative dWBS and lung nodular metastasis on pthWBS (No. 5) who was complaining of haemoptoe. All cases with additional lesions after rhTSH stimulated RIT had elevated Tg under L-T₄ suppression (Table 2, Column 3). Three patients had comparable dWBS and pthWBS with low Tg. They all had only thyroid remnants. In two patients pthWBS were negative, irrespective of the

Table 2. WBS and Tg before and after rhTSH stimulated RIT

Patients	Before rhTSH stimulated RIT		Post-therapy WBS	3 months after RIT	6 months after RIT	18 months after RIT
	Previous WBS	Tg under L-T ₄ [ng/ml]		Tg under L-T ₄ [ng/ml]	Diagnostic WBS	Diagnostic WBS
1. SB	Positive	7.6	Negative	17.1	Negative	ND
2. NG	Positive	10.8	Positive ⁺⁺	NA	Negative	Negative
3. RL	Positive	409.0	Positive ⁺⁺	NA	Positive	Negative
4. MN	Positive ^r	< 1.0	Positive ^r	< 1.0	Positive ^r	Positive ^r
5. JM	Negative	9.6	Positive ⁺⁺	9.0	Negative	Negative
6. CT	Positive	42.3	Positive ⁺⁺	29.0	Positive	Negative
7. AP	Positive	—	Positive	—	Positive	ND
8. SM	Positive ^r	< 1.0	Positive ^r	< 1.0	Negative	Negative
9. JR	Negative	2.6	Negative	2.7	Negative	Negative
10. IM	Positive ^r	< 1.0	Positive ^r	< 1.0	Positive ^r	Negative

^rthyroid remnant; ⁺⁺ additional sites of RAIU; — positive anti-Tg antibodies; NA — not available; ND — not done

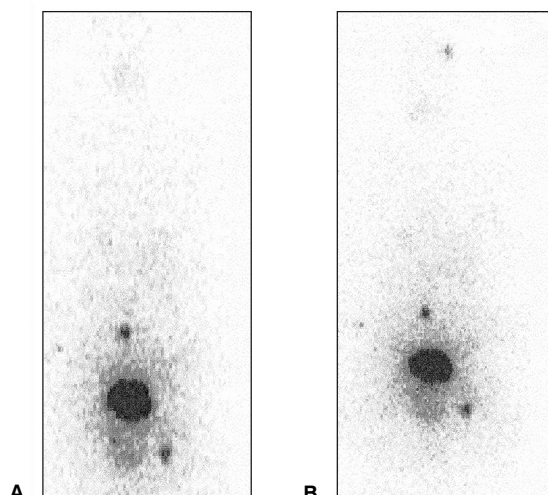


Figure 4. Additional metastatic lesion in the skull on pthWBS of patient No. 3 after rhTSH stimulated RIT. **A.** dWBS (PA view) — metastases in the sacrum and right femur; **B.** rhTSH stimulated RAIU (pthWBS, PA view) — additional metastasis in the right part of the skull.

elevated Tg (No. 1, 9). In case 7, both dWBS and pthWBS were positive with low Tg, due to high titer of anti-Tg antibodies.

Neck ultrasonography

The ultrasonography of the neck before RIT revealed suspicious lymph nodes (concerning size, form, echostructure and localization) in 7 patients and thyroid tissue in 2 patients (Tab. 3). There was a coincidence of USG with pthWBS in 5 patients (4 positive/positive and 1 negative/negative): 2 patients with remnants, 2 patients with lymph nodes > 10 mm and 1 patient with lung metastases. In 5 patients there was no coincidence between USG and pthWBS (positive/negative). Two of them had experienced previous EBT of the neck region (62–64 Gy) and 3 patients had small size (< 10 mm) neck lymph nodes together with distant metastases.

At the 6th month after RIT, the USG revealed lymph node metastases in the neck in 2 patients (No. 1, 9) with increased Tg

and negative dWBS, without other data of distant metastases (Tab. 3).

RhTSH side effects

Our patients tolerated generally well the rhTSH stimulated RIT. In all patients, no adverse events, including no signs of hypothyroidism, were seen. Only one of them felt some dizziness after the first injection of rhTSH. The death of patients No. 7 and 1 (18 months later) was not connected with the application of rhTSH.

Discussion

Comparing the serum TSH after rhTSH injections and after L-T₄ withdrawal it is obvious that the stimulation with rhTSH is stronger than the endogenous hypothyroidism. The effectiveness of this short but powerful stimulus regarding the pthWBS is very promising, especially for patients with insufficient endogenous TSH stimulation. The low TSH values on endogenous stimulation are probably related to previous RIT and concomitant medications taken for other diseases.

This study confirms the ability of rhTSH to induce RAIU in normal thyroid remnants, lymph nodes and distant metastases of DTC in euthyroid patients, on L-T₄ suppressive therapy. RhTSH promoted RAIU in 8 out of 10 patients. In 3 of them, additional metastatic lesions were seen. In 1 patient, the pthWBS visualized a small lung deposit that was not detected on the dWBS.

Data from Mazzaferri and Kloos [14] clearly show that thyroid remnant ablation significantly lowers both recurrence and death rates over a follow-up period of 40 years. In our study group there were three patients (No. 4, 8 and 10), addressed for rhTSH stimulated remnant ablation and one had a thyroid remnant together with bone metastases (No. 3). In 3 of them (No. 3, 8, 10) the rhTSH-stimulated ablation was successful. Our results support Robbins et al. [23] conclusion that rhTSH is as effective for remnant ablation as L-T₄ withdrawal, but further randomized controlled trials are needed.

Six of our ten patients, referred for rhTSH-stimulated RIT had advanced metastatic disease and is not surprising that the baseline and post-therapy Tg levels varied substantially, preventing further statistical analysis. We considered rhTSH-stimulated RIT

Table 3. Parallels of data from serum Tg, neck USG and neck scintigraphy

Patients	Before rhTSH stimulated RIT		Post-therapy WBS (neck)	Comments	6 months after RIT		
	Tg under L-T ₄ [ng/ml]	Neck USG			Tg off L-T ₄ [ng/ml]	Neck USG	Diagnostic WBS (neck)
1	7.6	Positive (lymph nodes)	Negative	Recurrence of primary tumor	52.0	Positive (lymph nodes, ↑ in size)	Negative
2	10.8	Negative	Negative	Lung metastases	67.4	Negative	Negative
3	409.0	Positive (1 lymph node)	Negative	Bone metastases	> 1000	Positive (lymph node, ↓ in size)	Negative
4	< 1.0	Positive (remnant)	Positive (remnant)	No metastases	< 1.0	Positive (remnant, ↓ in size)	Positive (remnant)
5	9.6	Positive (1 lymph node)	Negative	Lung metastases	29.0	Positive (lymph node, ↓ in size)	Negative
6	42.3	Positive (1 lymph node)	Positive (1 lymph node)	Lung metastases	334.0	Positive (2 lymph nodes, one ↓ in size)	Positive (1 lymph node)
7	–	Positive (1 lymph node)	Negative	Lung and soft tissue metastases	–	Positive (lymph node, ↓ in size)	Negative
8	< 1.0	Positive (remnant)	Positive (remnant)	No other metastases	< 1.0	Positive (remnant, ↓ in size)	Negative
9	2.6	Positive (1 lymph node)	Negative	No other metastases	23.5	Positive (lymph node)	Negative
10	< 1.0	Positive (1 lymph node)	Positive (1 lymph node)	No other metastases	< 1.0	Positive (lymph node)	Positive (lymph node)

– positive anti-Tg antibodies

as being helpful for four of them — No. 2, 3, 5, 6. In No. 5 and 6 the follow-up of 18 months showed tumor control and in No. 2 and 3 the disease was stabilized with no RAIU on the dWBS but with elevated Tg (Tab. 2). The treatment was without effect in two patients (No. 1 and 7) with advanced progressive disease. Case 1 was a 75 year old woman (Tab. 1) with recurrent G2 papillary cancer with extrathyroid tumor and mediastinal lymphnode metastases (pT4pN1bMo). She underwent EBT and two RIT. We expected a better response to rhTSH stimulated RIT, but no RAIU were registered, either on pthWBS, or at 6th month dWBS. The serum Tg increased at the 6th month. We suspected tumor cell dedifferentiation related to the RAIU. Later the patient developed bone metastases and died 18 months after rhTSH.

Case 7 (Tab. 1) had a ten year long disease history of advanced Hürthle cell cancer with mediastinal, lung and soft tissue metastases. He was submitted to EBT of the neck and mediastinal region and 5 previous courses of RIT. The Tg have been always elevated, but later high titer of anti-Tg antibodies was detected. DWBS at the 6th month did not show any tumor reduction. The patient died 6 months later.

We additionally analyzed the usefulness of neck USG in the follow-up of DTC. Patient No. 9 had elevated serum Tg, but the WBS remained negative even after rhTSH-stimulated RIT. The USG of the neck showed new lymph node metastasis. In our opinion, these are the cases one should perform neck USG which is more sensitive for neck lymph node metastases than dWBS and palpation [24, 25]. Lymph nodes size < 10 mm and previous EBT of the neck region seemed to be limitations for RAIU. Even the high TSH value (186.0 UI /ml) did not stimulate RAIU. Surgery is the treatment of choice in such cases.

One of the most important advantages of rhTSH is the possibility to induce RAIU in patients with negative dWBS or in additional sites of pathology, not seen on the dWBS. Similar results have been reported by Lippi et al. and others [28–31]. RhTSH is very important for patients that were not able to generate sufficient endogenous TSH. We have shown this effect in 3 of our 4 patients with additional sites of rhTSH stimulated RAIU (No. 2, 3, 5) (Fig. 2).

The major benefit from rhTSH application was to escape the inconvenience of several weeks of hypothyroidism. Moreover, hypothyroidism is frequently leading to refrain from work, as well as its known physiological sequelae. Our study was performed according to the “Compassionate Use Program” protocol, selecting patients with advanced age, progressive metastatic disease and high-risk prognosis. Despite all these conditions, rhTSH was generally well tolerated, without serious side effects [26, 29, 32]. We have not observed swelling of the lesions or local pain in patients with bone metastases as it was stated in other papers [26, 29, 33–35]. The death of two patients during the 18 months follow-up was related to their progressive disease.

Although this study is small in patient numbers, with selected, late-stage population and relatively short follow-up period, it confirms that rhTSH stimulated RIT is a safe and promising method, avoiding hypothyroidism and patient discomfort. It enables us to offer high dose RIT in the DTC patients, considered in the past too ill to discontinue TSHT in order to be treated. The preservation of euthyroid state and quality of life is especially important for severely ill patients as those with advanced brain, lung, bone and spinalcord metastases [27, 36]. Stimulation of tumor growth is less plausible than after L-T₄ withdrawal. The administration of rhTSH gives also the unique chance for patients with insufficient

generation of endogenous TSH after L-T₄ withdrawal.

The dedifferentiation of DTC during the course of the disease is a well-recognized phenomenon. RhTSH can not induce RAIU in dedifferentiated cancer cells if they do not present TSH receptors [37]. In our study there was one similar case (No. 1). A combination of retinoid acid and rhTSH appears promising.

Further clinical and dosimetric studies and long follow-up are needed to better assess the rhTSH stimulated therapeutic effect of radioiodine.

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