Recombinant Thyroid-Stimulating Hormone in Differentiated Thyroid Cancer

Yodphat Krausz MD[1], Beatrice Uziely MD[2], Rafael Nesher PhD[3], Roland Chisin MD[1] and Benjamin Glaser MD[3]

Departments of [1]Medical Biophysics and Nuclear Medicine, [2]Oncology, and [3]Endocrinology and Metabolism, Hadassah University Hospital, Jerusalem, Israel

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Differentiated thyroid carcinoma accounts for 80–90% of 28,000 new thyroid cancer cases diagnosed each year in Europe and in the USA [1]. Of the 376,000 DTC patients in these regions, approximately 2,300 will die of their disease each year. The incidence of malignant thyroid tumors is in the range of 2.7 per year per 100,000 inhabitants in Germany [2]. The incidence is 4/100,000 in women and 1.5/100,000 in men [3]. In Israel, the corresponding rates are 10.5 and 3.3, respectively, per year (Israel cancer registry).

The majority of patients with DTC have an excellent prognosis. Thirty percent of patients, however, develop recurrent disease over three decades, and 15% die of their recurrence [4]. Thus, there is a need for optimal long-term surveillance and therapy, applied particularly to patients with poor prognostic factors at presentation [5].

Management of patients with DTC

The recommended initial treatment of patients with DTC is total or near-total thyroidectomy. Following surgery, a whole-body iodine scan is performed to identify the extent of thyroid remnant and to detect residual tumor. Thereafter, radioiodine is administered for ablation and treatment. Both the radioiodine scan and the radioiodine ablation or treatment are performed under hypothyroid conditions (TSH $\geqslant$ 30 mU/L) to allow for uptake of the tracer into the thyroid remnant or into the tumor. Suppressive therapy with thyroid hormone is then initiated in order to prevent symptomatic hypothyroidism and to diminish the risk of recurrent disease. Subsequently, patients are monitored for local recurrence and distant metastases by two methods: a) radioiodine WBS after withdrawal of THST, and b) serum thyroglobulin determination, with or without THST withdrawal [4]. These tests, when used together, are superior to either alone, and can detect the recurrent disease at a stage when it is not visible by computed tomography or by ultrasound.

Serum thyroglobulin, produced only by thyroid follicular cells, serves as a sensitive tumor marker and a prognostic indicator [1,6]. This marker occasionally signals the presence of metastatic disease even prior to WBS [7] or when the I-131 scan is negative [8,9]. Following thyroidectomy and radioiodine ablation, endogenous thyroglobulin levels should not be measurable [1], although up to 3 months may elapse before thyroglobulin concentration decreases below detectable levels [10]. A low serum thyroglobulin by the second postoperative year signifies a low 5 year recurrence risk, whereas elevated levels provide evidence for recurrent tumor [6]. At the Institut Goustave Roussy, 99% of patients with undetectable thyroglobulin after withdrawal of THST during the initial follow-up have remained disease-free for up to 20 years. Twenty percent of patients with low but detectable levels (< 10 ng/ml) develop recurrence, whereas 60–80% of those with levels > 40 ng/ml eventually have recurrent disease [1].

The sensitivity of thyroglobulin for detecting recurrent disease is reduced if measured while the patient is on THST, and is enhanced by elevated TSH after withdrawal of THST. However, treatment withdrawal is frequently associated with multiple, occasionally severe, hypothyroid symptoms. Studies are currently in progress to determine if an exogenous source of TSH can provide sufficient TSH stimulation to increase the sensitivity of thyroglobulin testing while the patient remains on THST (see below). Thyroglobulin testing is also limited by the presence of anti-thyroglobulin autoantibodies, which interfere with the thyroglobulin assay sensitivity [9]. Elevated anti-thyroglobulin antibody levels, however, often decrease with

DTC = differentiated thyroid cancer
TSH = thyroid-stimulating hormone
WBS = whole-body scan
THST = thyroid hormone

time after total thyroidectomy [11], and persistence of this antibody suggests the presence of metastatic cancer [1,12].

Radioiodine scan is based on selective iodine uptake by thyroid follicular cells. This uptake is mediated by the sodium iodine symporter and is stimulated by high serum TSH concentration. A diagnostic WBS is usually performed annually during the first few years after initial surgery, and every 2 to 3 years thereafter. Focal uptake of radioiodine on the scan indicates the extent and site of the tumor. If surgery is indicated, the tumor can be precisely localized using gamma camera-mounted X-ray tomography [13]. Alternatively, when surgery is not possible such as when multiple foci or diffuse metastatic disease are present, radioiodine therapy may be administered. When metastases are detected on WBS prior to visualization by conventional techniques such as CT, they may be more likely to respond to high doses of radioiodine therapy.

Following radioiodine ablation or treatment, a post-treatment scan is performed for confirmation of the uptake of I-131 and for identification of additional occult I-131-avid sites of disease. This scan may show new areas of tracer uptake not seen on the diagnostic scan in 10% [14] and in 15% of cases [15].

At the time of radioiodine WBS, ablation or treatment, high TSH level is required for the stimulation of iodine uptake in tumor cells. The current method used to increase the endogenous TSH levels is to withdraw THST for 4–6 weeks before the scan [16]. This withdrawal, however, produces 2–4 weeks of severe hypothyroidism that may result in substantial discomfort and morbidity, including mental and physical slowing, cold intolerance, weight gain and irritability [17]. These symptoms may persist for an additional 3–4 weeks after the scan, before adequate thyroid hormone levels can be attained [18]. These extended periods of elevated TSH level may also be associated with increased growth of metastatic thyroid tissue. Finally, on occasion, patients fail to elicit sufficient endogenous TSH rise needed for adequate uptake at the site of tumor. Thus, the administration of exogenous TSH has been suggested.

In the 1950s–1970s, bovine TSH was found effective in stimulating radioiodine uptake for WBS, but led to adverse hypersensitivity reactions and to the development of neutralizing antibodies that limited its repeated use. Consequently, the product was removed from the market. As an alternative, recombinant human TSH was recently developed [19–21].

Recombinant human TSH

Recombinant human TSH is secreted by a Chinese hamster ovary cell line transfected with the DNA sequence of human chorionic gonadotropin alpha and human TSH beta minigenes. The product glycoprotein, in a highly purified form, was introduced into clinical practice by Genzyme Corporation (Cambridge, MA, USA), and has been approved by the Food and Drug Administration for use in the USA and by the Ministry of Health for use in Israel. The preparation is supplied for intramuscular administration. After a single 0.9 mg i.m. dose, a peak serum TSH concentration of 116 $\pm$ 38 mU/L is reached within 3–24 hours (median 10 hours), with mean time to maximum concentration of 12.9 hours, mean half-life elimination of 22.3 hours and mean clearance rate of 36.3 ml/min [22].

Recombinant TSH has the properties and actions of native TSH. It binds to TSH receptors and stimulates cyclic AMP production in cultured rat thyroid cancer cells [20], promotes epithelial cell growth and thyroglobulin production in primary human fetal thyrocytes [21], and stimulates radioiodine uptake and thyroid hormone production in primate thyroid glands [23]. rTSH[1] effectively stimulates the uptake of radioiodine by residual and cancerous thyroid tissue after initial surgery for thyroid cancer [22], and increases the sensitivity of serum thyroglobulin as a tumor marker in patients maintained on THST [24]. Furthermore, it eliminates the debilitating effects of a prolonged hypothyroid state induced by thyroxine withdrawal. The risk of stimulating metastatic cell growth is probably also decreased, since the duration of exposure to elevated TSH levels is significantly reduced.

Clinical trials using rTSH

Three multicenter clinical studies compared rTSH-stimulated testing to conventional withdrawal of THST in patients with DTC [22,25,26]. A non-randomized, two-phase protocol was used. WBS was preformed first after rTSH, and then after THST withdrawal. The scans were reviewed by one or three specialists, and were rated for stage of cancer and for number and distribution of lesions. The results were compared, with each patient serving as his own control.

Phase I/II safety and dose-ranging study

The preliminary phase I/II trial reported the safety, dose ranging, pharmacokinetics, and the efficacy of rTSH for stimulating radioiodine uptake in 19 patients with DTC [22]. To ensure the availability of sufficient thyroid tissue for rTSH stimulation, patients in this study were enrolled after surgery, without having had radioiodine ablation. Seven different dosing regimens were examined for future use: 0.9 mg (10 U/day for 1, 2, or 3 days), 1.8 mg (20 U/day for 1 or 2 days), 2.7 mg (30 U/day for 1 day), or 3.6 mg (40 U/day for 1 day). Blood samples were drawn for pharmacokinetic studies at various time points after administration of rTSH and showed persistent elevation of TSH levels for at least 48 hours after the final dose. Twenty-four hours after the last dose of rTSH, 1–2 mCi of I-131 was given and WBS was performed 48 hours following tracer administration. Subsequently, thyroid hormone treatment was withdrawn and WBS performed when TSH exceeded 25 mU/L. After rTSH, all 19 patients had evidence of radioiodine uptake, as observed on WBS and quantified by uptake measurements. The percent uptake in the thyroid bed was higher in 13 patients (72%) after thyroxine withdrawal. However, equivalent uptake was observed

rTSH = recombinant TSH

after the 10 U/day rTSH one and two day regimen and the 20 U/day one day regimens. Comparison of WBS after rTSH and THST withdrawal showed that the quality of I-131 scans and the number of abnormal foci were similar in 12 patients (63%), with more defined areas of uptake in 4 patients (21%) only after rTSH, and in 3 patients (16%) only after thyroxine withdrawal. Thus, recombinant TSH produced WBS images equivalent or superior to the withdrawal method in 16 of 19 patients scanned following recent thyroidectomy and prior to ablation.

The kinetics of thyroglobulin response to endogenous TSH has been studied previously. Following thyroxine withdrawal, serum endogenous TSH and thyroglobulin levels generally rise in parallel, the elevation of TSH levels occurring first, followed in approximately 2–4 days by an elevation in serum thyroglobulin levels [27]. The thyroglobulin response to rTSH was studied in this phase I/II trial. In the first six patients, serum thyroglobulin was determined 24 hours after rTSH, but this time point was found to be sub-optimal. In the subsequent 13 patients, thyroglobulin was determined at 24, 48 and 72 hours after rTSH administration and a delayed increase was observed, with a maximum response observed after 72 hours. A twofold increase in thyroglobulin was observed in 11 of the 19 patients (58%) after rTSH, and in 15 (79%) after THST withdrawal.

In this preliminary study, the quality of life of each patient was measured by two psychometric scales at three points during the study: before rTSH, after rTSH administration, and during thyroid hormone withdrawal. A physician-rated scale, the Billewicz Scale, was used to document the presence or absence of hypothyroid symptoms [28], and the patient-scored Profile of Mood States comparison scale was used to assess the psychological impact of these treatments [29]. In this study, 3 and 15 patients experienced some symptoms of hypothyroidism after rTSH and after THST withdrawal, respectively, with overt hypothyroidism in none and in four patients, respectively. In the POMS comparison, 94% of the patients felt increased fatigue, and 89% experienced decreased vigor and activity after THST withdrawal, compared to 0% and 5% after rTSH administration, respectively. Adverse effects were not observed in patients receiving 10 U rTSH for one or more consecutive days, but three patients receiving the higher doses (30 or 40 U) complained of nausea.

Based on pharmacokinetics, imaging and side effects, it was suggested that the optimal dose regimen of rTSH should be 10–20 U given daily for one or more days prior to radioiodine administration. The 10 U dose was used in the subsequent phase III trials.

Initial phase III trial

The first phase III trial [25] was aimed at assessing the efficacy and safety of rTSH administration for detection of thyroid remnant or cancer by I-131. In this study, 152 patients were given 0.9 mg (10 U) intramuscularly daily for 2 days. On the third day, 2–4 mCi of I-131 were administered and 48 hours later a WBS was obtained. The patients were then withdrawn from THST until serum TSH $\geqslant$ 25 mU/L was achieved, 48 hours after which a further I-131 WBS was obtained. Scans were classified as concordant or discordant based on the number and location of foci of radioiodine activity. Among the 127 patients who completed the study, serum TSH rose from a mean baseline of 0.2 $\pm$ 0.3 mU/L to 101 $\pm$ 60 mU/L 24 hours after the first dose, and to 132 $\pm$ 89 mU/L after the second dose. After THST withdrawal, mean serum TSH was 101 $\pm$ 77 mU/L on the day of radioiodine administration. The rTSH scan was rated equivalent to the withdrawal scan in 106 patients (84%), superior in 3 (2%), and inferior in 18 (14%). Sixty-two of the 127 patients had positive scans by one or both techniques. Of the positive scans, 45 patients had uptake limited to the thyroid bed, indicative of thyroid remnant tissue or thyroid cancer, and 17 patients had evidence of metastatic disease outside the thyroid bed. The rTSH and withdrawal scans were concordant in 41 of these patients (66%), superior after rTSH in 3 patients (5%), and superior after withdrawal in 18 patients (29%) ($P = 0.001$). Of the 18 patients with superior withdrawal scan, 10 were subsequently treated with I-131: 5 for ablation of thyroid remnant, 3 for treatment of cervical activity outside the thyroid bed, and 2 with uptake in the thyroid bed including an additional focus after withdrawal. Of the eight patients with withdrawal-superior scan who were not treated with I-131, only thyroid-bed activity was seen in five patients, and a single focus was seen outside the thyroid bed in three patients. However, no I-131 was given because of low serum thyroglobulin (one patient) and suspicion of artifact (two patients). In this study, the superior sensitivity of the withdrawal scan may have been due to different kinetics of I-131, with marked reduction of iodine clearance and increased bioavailability of I-131 in hypothyroid patients, as compared to euthyroid patients receiving rTSH. In fact, the first phase I/II trial documented that the whole-body retention of I-131 was twofold higher after THST withdrawal than after rTSH [22]. Alternatively, the degree and duration of stimulation by TSH may have been non-optimal, with maintenance of serum concentration TSH greater than 20 mU/L for only 4.5 days in comparison with the prolonged period of TSH stimulation occurring after hormone withdrawal.

In this study, serum thyroglobulin was measured before and at various time intervals after rTSH in 33 patients, and was determined to be highest at 72 hours or 96 hours after the first injection of rTSH. Thyroglobulin levels increased to $\geqslant$ 5 ng/ml in 13 patients after rTSH and in 14 patients after withdrawal, with a higher increase in the latter group.

Signs and symptoms of hypothyroidism, as measured by the Billewicz Scale, were markedly more evident after THST withdrawal than after rTSH ($P < 0.001$). Similarly, significant differences were observed for all six mood states of the POMS ($P < 0.001$). The only adverse effect associated with rTSH was nausea, observed in 25 patients (16%), but this was mild and short-lived. No patients had detectable serum anti-TSH antibodies after rTSH.

POMS = Profile of Mood States

Confirmatory phase III trial

The second phase III trial of 229 patients [26] was designed to study the effect of more prolonged rTSH stimulation on WBS and the contribution of rTSH-stimulated thyroglobulin determination. Two different dosing regimens of rTSH were compared with THST withdrawal: two 0.9 mg (10 U) i.m. injections of rTSH given 24 hours apart (arm I), or one dose every 72 hours for three doses (arm II). The latter dosing regimen was selected because it potentially extends the period of TSH stimulation safely and was more suitable to the logistic time constraints. Based on dose-regimen modeling of pharmacokinetic data, the 3x72 hour regimen, as compared to the 2x24 hour regimen, extended the period of maximal TSH stimulation approximately twofold, to 9 days and 4 days respectively. In this clinical trial, an improved imaging technique and a standardized dose of radioiodine were used, with I-131 (4 $\pm$ 0.4 mCi) given at 24 hours after the last dose of rTSH, and serum thyroglobulin concentration was determined in a central laboratory. The scan classification criteria were rationalized to identify only clinically important scan findings, with discordance considered only when a patient was classified differently with each technique, rather than comparing the number and distribution of lesions, as was done in the first phase III trial. The results are summarized in Table 1. Among the 220 patients with evaluable scans, 195 (89%) had concordant scans, 8 (4%) had superior rTSH scans, and 17 (8%) had superior withdrawal scans. Although the difference between the two scans was not significant ($P = 0.108$), the trend still favored thyroid hormone withdrawal. There was no significant difference within either study arm separately (two-dose arm, $P = 0.146$; three-dose arm, $P = 0.581$), or between the arms ($P = 0.76$). Among 108 patients with at least one positive scan, 83 (77%) had concordant scans, 8 (7%) had superior rTSH scans, and 17 (16%) had superior withdrawal scans ($P = 0.108$), with no difference within either study arm (arm I, $P = 0.146$; arm II, $P = 0.581$), or between arms ($P = 0.78$). Among 49 patients with metastatic disease, 39 patients (80%) had concordant scans, 2 (4%) had superior rTSH scans, and 8 (16%) had superior withdrawal scans, with no significant difference ($P = 0.109$). No significance was observed within either study arm (arm I, $P = 0.375$; arm II, $P = 0.375$), or between arms ($P = 0.85$).

The non-significant difference between the rTSH and the withdrawal scans in the second phase III trial is in contrast with the first phase III trial, where the withdrawal scan was superior to the rTSH scan. This may be related to the slower scanning speed and standardized radioiodine dose in the second clinical trial, with compensation for the reduced radioiodine clearance during THST withdrawal compared to the euthyroid rTSH phase. Thus, a diagnostic activity of $\geqslant$ 4 mCi (148 mBq) has been suggested to compensate for the faster radioiodine clearance in euthyroid state on rTSH [30]. In this second clinical trial, there was no significant difference between the two dosing regimens of rTSH; and the two-dose regimen, given 24 hours apart, was recommended for further use due to convenience of administration [26].

In this study, serum thyroglobulin was measured on the final day of the rTSH administration in each arm, and at 24 hours, 48 hours, 72 hours and 7 days after the final dose, and its contribution for disease detection was assessed when determined alone and in combination with WBS. Peak serum thyroglobulin levels were observed 72 hours after the final rTSH injection in the two-dose regimen, and 24–72 hours after the final rTSH injection in the three-dose regimen. These studies also showed that rTSH-stimulated thyroglobulin determination is more sensitive for the detection of residual thyroid tissue or cancer than thyroglobulin assay on continued thyroid hormone therapy, 74% versus 43% respectively [24]. The following data show the high sensitivity of rTSH-stimulated thyroglobulin for detecting persistent or recurrent disease [Table 2]. Using an arbitrary thyroglobulin cutoff level of 2 ng/ml, the addition of rTSH to THST improved the thyroid cancer/tissue detection rate from 22% (10 of 46) to 52% (24 of 46) in patients with radioiodine uptake limited to the thyroid bed on a diagnostic or post-therapeutic scan. Furthermore, it improved the detection rate from 80% (24 of 30) to 100% (30 of 30) in patients with metastatic disease according to a diagnostic or post-therapeutic scan. After THSH withdrawal, elevated thyroglobulin was detected in 56% and 100% of patients with uptake in the thyroid bed and cancer outside the thyroid bed, respectively [26]. Furthermore, the combination of thyroglobulin measurement (cutoff value of 2 ng/ml)

Table 1. Post-rTSH I-131 whole-body scan compared to scan after THST withdrawal: confirmatory phase III trial [ref 24]

	Arm 1	Arm 2	Total
Treatment regimen			
rTSH dose:	10 U	10 U	
No. of doses	2	3	
No. of subjects	113	107	220
Scan findings (all subjects)			
Concordant	101 (89%)	94 (88%)	195 (89%)
Superior rTSH	3 (3%)	5 (5%)	8 (4%)
Superior withdrawal	9 (8%)	8 (7%)	17 (8%)
Positive scans only			108 (49%)
Concordant			83 (77%)
Superior rTSH			8 (7%)
Superior withdrawal			17 (16%)
Scans demonstrating metastatic disease		49 (22%)	
Concordant			39 (80%)
Superior rTSH			2 (4%)
Superior withdrawal			8 (16%)

Table 2. Efficacy of serum thyroglobulin for identification of patients with residual or recurrent DTC: confirmatory phase III trial

	THST	THST+rTSH	THST withdrawal
	No. of patients positive* with each regimen (%)		
Site of disease, as defined by I-131 scan			
Thyroid bed only (n=46)	10 (22%)	24 (52%)	26 (56%)
Metastatic disease (n=30)	24 (80%)	30 (100%)	30 (100%)

*Thyroglobulin ⩾ 2 ng/ml

with WBS after rTSH greatly improved the detection of remnant tissue or cancer, with identification of 93% of patients (43 of 46) with uptake limited to the thyroid bed, and 100% of patients (30 of 30) with metastatic disease [24]. Thus, despite the more favorable withdrawal scan, the combined use of thyroglobulin-stimulated rTSH with WBS improves the detection of residual thyroid tissue or cancer.

In the second phase III clinical trial, symptoms and signs of hypothyroidism were also based on the Billewicz Scale, but the POMS comparison scale was replaced by the SF-36 QOL questionnaire, a patient self-administered scale that measures eight health concepts, including physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health [31]. Again, patient morbidity and discomfort were lower and QOL higher after rTSH (P = 0.05) in both Billewicz and SF ratings. There were no significant differences in the rate of adverse events after rTSH administration between the two study arms (P = 0.08). Transient headache and nausea were the most common events: 9.2% and 6.1% respectively. None of the patients developed antibodies to rTSH, suggesting that rTSH can be used in multiple administrations [26].

Additional studies were performed for the evaluation of the diagnostic accuracy of the rTSH scan. Reiners et al. [30] found that 92% of their 26 patients were correctly categorized after rTSH WBS, 100% after withdrawal, and 100% after combination of rTSH WBS with serum thyroglobulin testing. Robbins et al. [32] also found the withdrawal scan to be more sensitive than the rTSH scan, 80% versus 69% respectively. However, the predictive values of these tests, used for clinical decision-making, were not different between the groups. Furthermore, the combination of the diagnostic WBS and serum thyroglobulin had similar positive and negative predictive value, whether performed after rTSH or after thyroxine withdrawal [32].

Recombinant TSH for I-131 therapy

Since April 1995, recombinant TSH has been introduced for remnant ablation or treatment of advanced and/or recurrent DTC, and was found to be safe and efficacious in 12 patients [33]. Patients were given rTSH prior to therapy when the hypothyroid state was contraindicated due to risk of exacerbation of ischemic heart disease, or when intolerable, such as with metastases to the central nervous system causing excruciating pain and neurological symptoms, pulmonary metastases associated with severe hypoxia, or progression of disease during prior thyroxine withdrawal. Patients were also given rTSH prior to therapy when an adequate level of TSH could not be elicited after thyroxine withdrawal [34], such as in secondary hypothyroidism [35], or with overproduction of thyroid hormone by thyroid remnant or metastases [36]. In addition, rTSH has been suggested for patients who have had an adequate surgery but are poor candidates for completion of thyroidectomy [37]. When administered before therapy, rTSH was well tolerated and was efficacious in stimulating radioiodine uptake, as demonstrated by a post-therapy scan and by a decrease in serum thyroglobulin and/or clinical improvement [33]. It may preserve the quality of life and prevent the severe hypothyroid complications, and probably the progression of disease. Furthermore, the rapid clearance of radioiodine in euthyroidism reduces the I-131 retention and the resulting radiation exposure of healthy tissue.

Summary

Recombinant TSH is effective in providing exogenous TSH stimulation for patients with differentiated thyroid cancer on thyroid hormone-suppressive therapy. It allows for detection of thyroid remnant and metastases by radioiodine scan and by serum thyroglobulin determination. The sensitivity and image quality of the WBS are similar after rTSH and after THSH withdrawal in the majority of patients. The equivalent 100% sensitivity of rTSH- and withdrawal-stimulated serum thyroglobulin measurement alone in identifying patients with radioiodine uptake outside the thyroid bed [38] may eventually lead to more extensive use of serum thyroglobulin testing after rTSH, with more selective application of radioiodine WBS [39]. Currently, a phase IV trial is in progress to evaluate the efficacy of rTSH-stimulated thyroglobulin levels as the primary modality for long-term follow-up of low risk thyroid cancer patients. The use of rTSH prevents the morbidity, metabolic impairment and the risk of tumor progression associated with THST withdrawal, because of shorter exposure time to elevated TSH [38]. Furthermore, it decreases the radiation exposure of healthy tissues due to faster iodine clearance in euthyroidism. rTSH is well tolerated, with transient nausea in 10.5% and headache in 7.3% of patients. No antibodies specific to rTSH were documented, even after multiple courses of the drug.

Currently, rTSH is suggested for patients who do not respond to hormone withdrawal or cannot tolerate hypothyroidism. For patients with low risk of tumor recurrence, rTSH-stimulated testing may be used at 6–12 months after postoperative I-131 ablation and with a repeat cycle of rTSH one year later, followed by testing every 3–5 years. In high risk patients, one set of negative I-131 scan and thyroglobulin test results after hormone withdrawal are recommended before using rTSH testing, because of a greater sensitivity of the withdrawal scan and because rTSH is not currently approved for subsequent I-131

therapy often indicated in these patients [24]. Subsequently, two cycles of rTSH testing are recommended at 6–12 month intervals, followed by testing every 1–3 years for at least the first decade after initial diagnosis.

The cost of this commercially available form of rTSH has been considered a major impediment to its common use; however, this should be weighed against the loss of productivity of working hours related to withdrawal [40]. In the therapeutic setting, rTSH is the only acceptable option in a subgroup of patients with hypopituitarism, ischemic heart disease, a history of "myxedema madness," debilitation due to advanced disease, or inability to elicit TSH elevation due to continued production of thyroxine by thyroid remnant or metastatic tumor [33,38].

In conclusion, recombinant TSH facilitates the management of patients with differentiated thyroid carcinoma. It increases the sensitivity of thyroglobulin testing during thyroid hormone suppression therapy and enables radioiodine uptake for whole-body scan and occasionally for radioiodine therapy, without the need for prolonged THST withdrawal and its associated hypothyroidism, reduced quality of life and risk of tumor progression.

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Correspondence: Dr. Y. Krausz, Dept. of Nuclear Medicine, Hadassah University Hospital, P.O. Box 12000, Jerusalem 91120, Israel. Phone: (972-2) 677-7860, Fax: (972-2) 643-7940, email: yodphat@hadassah.org.il