# Recombinant Human Thyroid-Stimulating Hormone in Radioiodine Thyroid Remnant Ablation

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**ABSTRACT:** **Background:** To prevent the unwarranted effects of post-thyroidectomy hypothyroidism prior to radiodine (RAI) ablation, patients with well-differentiated thyroid cancer can currently undergo this treatment while in a euthyroid state. This is achieved with the use of recombinant human thyroid-stimulating hormone (rhTSH) injections prior to the ablation.

**Objectives:** To demonstrate the efficacy of rhTSH in radioiodine thyroid ablation in patients with differentiated thyroid cancer.

**Methods:** We conducted a retrospective study of patients who underwent total thyroidectomy for well-differentiated thyroid cancer with different levels of risk, treated with rhTSH prior to remnant ablation with radioiodine.

**Results:** Seventeen patients with thyroid cancer were studied and followed for a median of 25 months (range 8–49 months). Ablation (defined as stimulated thyroglobulin < 1 mg/ml and negative neck ultrasonography) was successful in 15 patients (88.2%). One of the patients was lost to follow-up.

**Conclusions:** The use of rhTSH with postoperative radioiodine ablation may be an efficient tool for sufficient thyroid remnant ablation, avoiding hypothyroidal state in the management of thyroid cancer patients.

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**KEY WORDS:** thyroid cancer, recombinant human thyroid-stimulating hormone (rhTSH), thyroid remnant ablation

Thyroid cancer is the most frequently occurring endocrine cancer, with more than 2100 new cases each year in the United Kingdom and more than 48,000 in the United States [1,2]. In Israel more than 400 new cases are diagnosed every year. Most cases are differentiated papillary thyroid cancer, which has a high 10 year survival rate (90%–95%) [3]. Furthermore, the yearly incidence has increased, which has doubled the prevalence of thyroid cancer in Israel in the last decade [4] and has led to greater numbers of people who will undergo surgery and receive post-surgical care including radioiodine ablation.

The role of radioiodine administration after total thyroidectomy is three-pronged: a) to eradicate normal-thyroid remnants (ablation) in order to achieve an undetectable serum thyroglobulin level, b) to irradiate any possible neoplastic focus and thus decrease the risk of recurrence, and c) to enable detection of persistent cancer by follow-up radioiodine scintigraphy [5-7].

The benefit of $^{131}$I ablation in low risk patients is questionable [6,8,9], since the consequences of iatrogenic hypothyroidism [10] and the adverse effects of radioiodine [11-15] may supersede the eventual gains [8,9,12]. Ways of decreasing patients' exposure to hypothyroidism and high doses of radioiodine are desired. Ablation with 1.1 GBq $^{131}$I using recombinant human thyroid-stimulating hormone prevents hypothyroidism, reduces radio toxicity, and avoids potential hospitalization costs, thus mitigating the negative aspects of this procedure [16-18].

The aim of the present study was to evaluate the efficacy of rhTSH in thyroid remnant ablation using $^{131}$I in patients with low risk for disease relapse. The patients in this study were the first in Israel to receive rhTSH as an adjunct to radioiodine.

## PATIENTS AND METHODS

We assessed the files of all patients who received $^{131}$I radioiodine therapy with rhTSH during the period 2005 through 2011. Missing data on patients' current clinical state were retrieved either from electronic health records or by re-evaluation, i.e., measurement of serum thyroglobulin and neck ultrasound. Table 1 presents the patients' characteristics.

By the time of ablation all patients were being treated with thyroid hormone-suppressive therapy and there were no specific diet recommendations at ablation. Recombinant human thyrotropin (Thyrogen®, Genzyme, USA) [19] was administered at a dose of 0.9 mg intramuscularly on 2 consecutive days, and radioiodine was administered on the day after the second injection. The radioactive iodine ablative dose administered was based on individual criteria according to the staging of the disease (about 40% of the patients received more

rhTSH = recombinant human thyroid-stimulating hormone

**Table 1.** Patients characteristics and results

| | |
|---|---|
| Patients | n=17 |
| Female | 13 (76.4%) |
| Male | 4 (23.5%) |
| Age (yr) | 50 ± 23 |
| **Tumor characteristics** | |
| **Histological type** | |
| Papillary | 14 (82.3%) |
| Mixed papillary/follicular | 1 (5.88%) |
| Hurthle cell | 1 (5.88%) |
| Less differentiated | 1 (5.88%) |
| | 8 (47.0%) |
| **Staging** | |
| $T_1N_0M_0$ | 1 (5.88%) |
| $T_1N_1M_0$ | 1 (5.88%) |
| $T_2N_0M_0$ | 4 (23.5%) |
| $T_3N_0M_0$ | 1 (5.88%) |
| $T_3N_1M_0$ | 1 (5.88%) |
| $TxN_1M_x$ | 1 (5.88%) |
| $T_xN_xM_x$ (missing data) | |
| **Suppressed Tg prior to ablation** | |
| ‹ 1 ng/ml | 7 (41.1%) |
| 1 ng/ml | 3 (17.6%) |
| Test not performed/missing data | 7 (41.1%) |
| Tg antibodies positive prior to ablation | 4 (23.5%) |
| Stimulated Tg at ablation › 1 ng/ml | 5 (29.4%) |
| Suppressed Tg at follow up › 1 ng/ml | 1 (5.88%) |
| Stimulated Tg at follow up › 1 ng/ ml | 1 (5.88%) |
| Median time from ablation to final follow-up | 25 months |
| Negative neck ultrasound (6–12 mo after ablation) | 16 (94.1%) |

Tg = thyroglobulin

than 100 mCi) [Figure 1]. Serum thyrotropin, thyroglobulin and antithyroglobulin antibody levels were measured before radioiodine administration. An $^{131}I$ total-body scan was performed 7 to 10 days after radioiodine administration. Thyroidal remnants as well as other iodophyllic ectopic neck or other body regions findings were assessed on the scan.

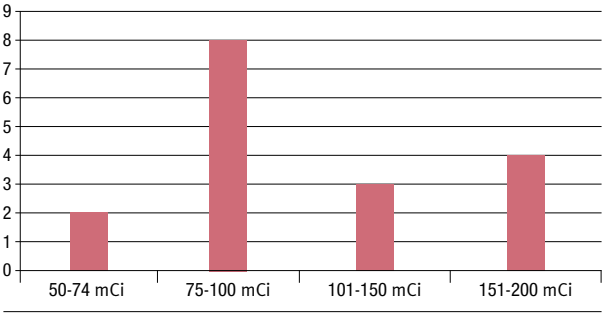
The patients were reevaluated 9–12 months after ablation by a follow-up neck ultrasound and measurement of suppressed and stimulated serum thyroglobulin. Follow-up diagnostic whole-body scan was performed in selected patients. Yearly follow-up for clinical re-evaluation included neck ultrasound, suppressed thyroglobulin levels, and additional workup for patients with positive findings were also conducted.

Ablation was considered successful when the stimulated thyroglobulin level was < 1 ng/ml and neck ultrasonography was negative, defined by the absence of suspicious findings in the thyroid bed and the absence of suspicious lymph nodes 6–12 months after ablation. The hospital's ethics committee approved the study design and conduct.

## RESULTS

During the period 2005–2011, 17 patients with thyroid cancer, after thyroidectomy, received radioiodine therapy with

**Figure 1.** RAI dose used. The bars represent the number of patients treated at the specified dose




$^{131}I$ using rhTSH. Of these, 13 were females (76.4%) and 4 were males (23.5%). Sixteen had undergone a total thyroidectomy and one a near-total thyroidectomy. Lymph node dissection was performed in patients with evidence of lymph node involvement.

According to the histological diagnosis, 14 patients (82.33%) were diagnosed with papillary carcinoma, 1 (5.88%) with mixed papillary/follicular carcinoma, 1 (5.88%) with Hurthle cell carcinoma, and 1 (5.88%) was diagnosed with less differentiated carcinoma (tall cell carcinoma). According to disease staging (using criteria of the American Joint Committee on cancer), 15 patients were in stage I (88.3%), 1 was categorized as stage II (5.88%), and 1 as stage III (5.88%).

Prior to the ablation, thyroglobylin antibodies were detected in 4 (23.5 %) of 17 patients. Stimulated thyroglobylin at ablation was > 1 ng/ml in 5 patients (29.4%). None of the patients showed an adverse reaction to rhTSH or to ablative RAI and none was hospitalized for the ablation. All the patients received 10 days of sick leave after the ablation.

Ablation was successful (stimulated thyroglobylin < 1 ng/ml and negative neck ultrasound) in 15 of 17 patients (88.2%). One of the patients was lost to follow-up. One patient had the rhTSH stimulated radioiodine therapy as the second RAI. A year before the current treatment with rhTSH she received ablative radioiodine therapy without thyroid replacement, after total thyroidectomy. At the follow-up whole-body scan that was performed 6 months later, a residual uptake in the thyroid bed was noted. The patient underwent a second operation with removal of thyroid cancer cells followed by ablation. The patient's thyroglobulin was > 300 ng/ml prior to ablation. She received 176 mCi. At the final whole-body scan performed 18 months after ablation with rhTSH, the neck ultrasound was normal and the thyroglobulin was < 0.2 ng/ml.

Four of the patients who presented with positive thyroglobulin antibodies were included in the final analysis of the study. One of the patients, at final follow-up 32 months after

RAI = radioactive iodine

ablation, had a negative neck ultrasound and no findings on the diagnostic whole-body scan. Another patient, who also had positive Tg-Ab initially, at the final follow-up 12 months after ablation had negative antibodies and no findings on neck ultrasound and diagnostic whole-body scan. A third patient, at final follow-up 22 months after ablation, had negative Tg-Ab and clear neck ultrasound. The fourth patient, who initially presented with positive Tg-Ab, was the one who was lost to follow-up. The only patient with no remission after rhTSH radioiodine ablation had received two previous RAI doses. The patient was categorized as $T_xN_1M_x$ and received 200 mCi. The stimulated thyroglobulin at the final follow-up, 25 months after ablation, was 4.3 ng/m. This patient therefore does not meet the strict criteria of a low risk patient. Since this patient was treated with the intent to ablate with rhTSH, he was added to the study.

## DISCUSSION

The benefits of postoperative radioiodine administration in terms of recurrence and survival have not been clearly shown in patients with low risk thyroid cancer after complete surgical resection [20-22]. Because of the unclear degree of benefit, any therapeutic radioiodine intervention should be minimal. Until recently this procedure required L-T4 withdrawal for 3–4 weeks, resulting in acute and intense hypothyroidism in some cases [10]. Furthermore, an activity of 3.7 GBq (100 mCi) $^{131}$I is still commonly prescribed to these patients, despite the known risk of adverse effects [11,15].

Thus, there is growing concern that the risks inherent in iatrogenic hypothyroidism and radio toxicity may outweigh the eventual benefits of ablation in patients at low risk for recurrence [8,9,12]. Therefore, measures that minimize these risks are desired. These include preparation with rhTSH to prevent hypothyroidism, and the use of low $^{131}$I activity to reduce the adverse effects of radioiodine. Doubts regarding the efficacy of this approach have dispersed with the advent of studies such as the present one demonstrating the effectiveness of this approach. In patients at low risk of recurrence after total thyroidectomy, control assessment after ablation consists of measurement of stimulated thyroglobulin, Tg-Ab and neck ultrasonography. Diagnostic whole-body scan is not recommended [6,7,23].

In our study, ablation using rhTSH and different doses of $^{131}$I activity (8 patients, 47.06%, received < 100 mCi) was successful in 88.2%. This success rate is consistent with the results of a number of studies performed in the same period as ours [16-18]. Two recent prospective randomized studies, performed in the UK [17] and France [16], demonstrated comparable results using either high or low dose (30 mCI) with and without rhTSH. Additionally, lower radiotoxicity has been associated with the use of rhTSH versus hypothyroidsm [11]. For these reasons, the use of low $^{131}$I activity with rhTSH is associated with lower risk and should be the preparation of choice in cases where the benefit is questionable. It is therefore possible that similar results would have been obtained in our patients with low risk of recurrence using low dose of radioiodine.

Tg-Ab = thyroglobulin antibodies

## CONCLUSIONS

The study shows that the use of rhTSH instead of thyroid hormone withdrawal for the postoperative ablation of thyroid remnants in well-differentiated thyroid cancer resulted in an excellent outcome during a median of 25 months follow-up. Thus, this approach can be adopted in low risk and near-total thyroidectomy patients as the treatment of choice for this indication.

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## Capsule

### Mycobacteria manipulate macrophage recruitment through coordinated use of membrane lipids

The evolutionary survival of *Mycobacterium tuberculosis* depends on its ability to invade the host, replicate, and transmit infection. At its initial peripheral infection site in the distal lung airways, *M. tuberculosis* infects macrophages, which transport it to deeper tissues. How mycobacteria survive in these broadly microbicidal cells is an important question. Cambier et al. show in mice and zebrafish that *M. tuberculosis*, and its close pathogenic relative *Mycobacterium marinum*, preferentially recruit and infect permissive macrophages while evading microbicidal ones. This immune evasion is accomplished by using cell surface-associated phthiocerol dimycoceroserate (PDIM) lipids to mask underlying pathogen-associated molecular patterns (PAMPs). In the absence of PDIM, these PAMPs signal a Toll-like receptor (TLR)-dependent recruitment of macrophages that produce microbicidal reactive nitrogen species. Concordantly, the related phenolic glycolipids (PGLs) promote the recruitment of permissive macrophages through a host chemokine receptor 2 (CCR2)-mediated pathway. Thus, the authors identified coordinated roles for PDIM, known to be essential for mycobacterial virulence, and PGL, which (along with CCR2) is known to be associated with human tuberculosis. These findings also suggest an explanation for the longstanding observation that *M. tuberculosis* initiates infection in the relatively sterile environment of the lower respiratory tract, rather than in the upper respiratory tract, where resident microflora and inhaled environmental microbes may continually recruit microbicidal macrophages through TLR-dependent signaling.

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Eitan Israeli

## Capsule

### Muc5b is required for airway defense

Respiratory surfaces are exposed to billions of particulates and pathogens daily. A protective mucus barrier traps and eliminates them through mucociliary clearance (MCC). However, excessive mucus contributes to transient respiratory infections and to the pathogenesis of numerous respiratory diseases. *MUC5AC* and *MUC5B* are evolutionarily conserved genes that encode structurally related mucin glycoproteins, the principal macromolecules in airway mucus. Genetic variants are linked to diverse lung diseases, but specific roles for MUC5AC and MUC5B in MCC, and the lasting effects of their inhibition, are unknown. Roy et al. (show that mouse Muc5b (but not Muc5ac) is required for MCC, for controlling infections in the airways and middle ear, and for maintaining immune homeostasis in mouse lungs, whereas Muc5ac is dispensable. Muc5b deficiency caused materials to accumulate in upper and lower airways. This defect led to chronic infection by multiple bacterial species, including *Staphylococcus aureus*, and to inflammation that failed to resolve normally. Apoptotic macrophages accumulated, phagocytosis was impaired, and interleukin-23 (IL-23) production was reduced in *Muc5b*–/– mice. By contrast, in mice that transgenically overexpress *Muc5b*, macrophage functions improved. Existing dogma defines mucous phenotypes in asthma and chronic obstructive pulmonary disease as driven by increased MUC5AC, with MUC5B levels either unaffected or increased in expectorated sputum. However, in many patients, MUC5B production at airway surfaces decreases by as much as 90%. By distinguishing a specific role for Muc5b in MCC, and by determining its impact on bacterial infections and inflammation in mice, these results provide a refined framework for designing targeted therapies to control mucin secretion and restore MCC.

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