Published in final edited form as:
Endocr Pract. 2013 ; 19(1): 139–148. doi:10.4158/EP12244.RA.

POTENTIAL USE OF RECOMBINANT HUMAN THYROTROPIN IN THE TREATMENT OF DISTANT METASTASES IN PATIENTS WITH DIFFERENTIATED THYROID CANCER

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Abstract

Objective—In order to effectively treat differentiated thyroid cancer (DTC) with radioiodine (RAI) it is necessary to raise serum TSH levels either endogenously by thyroid hormone withdrawal (THW) or exogenously by administration of recombinant human TSH (rhTSH). The goal of this review is to present current data on the relative efficacy and side effects profile of rhTSH-aided versus THW-aided RAI therapy for the treatment of patients with distant metastases of DTC.

Methods—We have searched the PubMed database for articles including the keywords "rhTSH", "thyroid cancer", and "distant metastases" published between January 1, 1996 and January 7, 2012. As references, we used clinical case series, case reports, review articles, and practical guidelines.

Results—Exogenous stimulation of TSH is associated with better quality of life because it obviates signs and symptoms of hypothyroidism resulting from endogenous TSH stimulation. The rate of neurological complications after rhTSH and THW-aided RAI therapy for brain and spine metastases is similar. The rate of leukopenia, thrombocytopenia, xerostomia, and pulmonary fibrosis is similar after preparation for RAI treatment with rhTSH and THW. There is currently a controversy regarding RAI uptake in metastatic lesions after preparation with rhTSH versus THW,

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DISCLOSURE
The authors have no multiplicity of interest to disclose.

with some studies suggesting equal and some superior uptake after preparation with THW. Analysis of available retrospective studies comparing survival rates, progression free survival, and biochemical and structural response to a dosimetrically-deterrnined dose of RAI shows similar efficacy after preparation for therapy with rhTSH and THW.

Conclusion—The rhTSH stimulation is not presently approved by the FDA as a method of preparation for adjunctive therapy with RAI in patients with metastatic DTC. Data on rhTSH compassionate use suggest that rhTSH stimulation is as equally effective as THW as a method of preparation for dosimetry-based RAI treatment in patients with RAI-avid metastatic DTC.

INTRODUCTION

Well differentiated thyroid cancer is the fastest increasing cancer in both men and women with incidence rates increasing from 2004 by 5.5% yearly in men and 6.6% per year in women. An estimated 56,460 new cases of thyroid cancer are expected to be diagnosed in the U.S. in 2012. The 5-year survival rate is nearly 100% for localized disease, 96% for loco-regional disease, and 56% for thyroid cancer presenting with distant metastases (1). The routine management of patients with differentiated thyroid cancer (DTC) presenting with distant metastases consists of thyroidectomy with or without lymph node dissection, as appropriate, followed by therapy with radio-iodine (RAI) (2). American Thyroid Association (ATA) guidelines underscore the main goals of administration of RAI: (1) remnant ablation (to facilitate detection of recurrent disease and initial staging), (2) adjuvant therapy (to decrease risk of recurrence and disease-specific mortality by destroying suspected, but unproven metastatic disease), or (3) RAI therapy (to treat known persistent disease). Administration of RAI requires TSH stimulation, which may be achieved by two possible methods: (1) L-T4 withdrawal (THW) to provoke endogenous TSH elevation, or (2) exogenous stimulation with recombinant human TSH (rhTSH). The rhTSH glycoprotein is produced by transfection with plasmids containing the alpha and beta sequences of TSH in a genetically modified Chinese hamster ovarian cell line. It is characterized by lower glycosylation and a higher sialylation levels compared to endogenous TSH, which is responsible for three to four times lower affinity for the TSH receptor but has a longer half-life (3-8). The standard optimal dose of rhTSH for diagnostic and; therapeutic procedures in patients with well differentiated thyroid cancer is 0.9 mg intramuscularly on 2 consecutive days. After injection, median peak concentrations of TSH (124- 132+/89 mIU/mL) are reached in 10 hours (range: 3 to 24 hours) and decline to 17+/−7 rnIU/mL at 72 hours after the second injection (7). Hepatic and renal metabolism of rhTSH results in a half-life of approximately 25 ± 10 hours. There are large individual variations in serum TSH concentration achieved after rhTSH, which are associated with age, weight, height, body surface area, body mass index (BMI), and lean and fat body mass (9-13). Endogenous stimulation of TSH achieved by THW provides less intense but more durable TSH elevation (14).

The rhTSH was approved by the European Medicines Agency (EMEA) in 2005 for the ablation of remnant thyroid tissue in low-risk patients who have undergone total/near total thyroidectomy and by the U.S. Food and Drug Administration (FDA) in 2007 for RAI treatment in patients without evidence of distant metastases (15). Use of rhTSH for

adjunctive therapy of metastatic disease is not FDA and EMEA approved and the efficacy data in this group of patients are derived from the studies based on the rhTSH Compassionate Use Program (TCUP). A potential advantage of using rhTSH-aided treatment is to obviate the signs and symptoms of hypothyroidism that might be poorly tolerated by elderly individuals and patients with medical comorbidities.

The goal of this review is to present current data on the relative efficacy and side effects profile of rhTSH-aided versus THW-aided RAI therapy for the treatment of patients with distant metastases of DTC.

Compassionate Use Program

The TCUP is dedicated to individuals with (1) coincidental hypothalamic-pituitary disorders that preclude the ability to elevate endogenous TSH after THW; (2) sufficient tumor bulk to produce levels of thyroid hormone inhibiting the proper elevation of TSH after THW; and (3) comorbidities, making induction of hypothyroidism medically contraindicated (16). One of the first reports of the off-label use of rhTSH was provided by Rudavsky and Freeman in 1997. They presented the case report of clinical and biochemical improvement after rhTSH-aided RAI therapy with 515 mCi of RAI in a 54-year-old man with widespread metastases to the lungs and bones (17). Since then, there has been growing evidence of successful use of adjunctive rhTSH-aided RAI therapy in patients with metastatic thyroid cancer (18-23). The summary of these case series are presented in Table 1. The summary of the outcome of many of these cases indicated that approximately 65% of patients obtained either partial remission (36%), disease stabilization (27%), or rarely, complete remission (2%) (24). Although promising, these studies do not provide comparative data on the efficacy of exogenous versus endogenous TSH stimulation used as a preparation for treatment of metastatic thyroid cancer with RAI.

Efficacy of rhTSH-Aided Versus THW-Aided RAI Treatment

RAI kinetics—Use of rhTSH is associated with more rapid whole body clearance of RAI, resulting in a lower total body, bone marrow, and gastrointestinal radiation exposure for a given administered activity (25-28). However, there are contradictory data regarding the RAI uptake within metastatic lesions. One of the first large studies comparing the effects of preparation for diagnostic whole body scan (WBS) with rhTSH versus THW was performed by Haugen et al (29). The study group consisted of 229 patients who underwent diagnostic WBS and serum thyroglobulin (Tg) measurements after administration of rhTSH and again after THW in each patient. Among the study group, 49 patients (22%) had metastatic disease, of which 39 patients (80%) had concordant WBS after rhTSH and THW preparation, 2 (5%) had superior rhTSH scans, and 8 (16%) had superior withdrawal scans. There was no significant difference in the number of superior rhTSH or THW scans in the study group.

A study by de Keizer et al used lesion dosimetry to assess radiation absorbed dose in 16 patients with metastatic or recurrent RAI-avid DTC prepared for RAI therapy with rhTSH. The tumor radiation dose was highly variable, with a median of 26.3 Gy (range: 1.3 to 368 Gy), and the median effective half-life was 2.7 days (range: 0.5 to 6.5 days) (30).

There are case reports describing superior RAI uptake after preparation with rhTSH compared to prior preparation with THW, specifically in a patient with concomitant secondary hypothyroidism (31) or in patients with large tumor burden producing thyroid hormones sufficient to suppress endogenous TSH (32). On the other hand, there are some case reports and case series suggesting inferior rhTSH properties compared to endogenous TSH stimulation in regards to RAI uptake in metastatic lesions. Teieb et al and Driedger et al described less radioiodine uptake after rhTSH-aided treatment than after THW in patients who were first treated with THW-aided and then rhTSH-aided RAI therapy (33-34). Dosimetric evaluation performed by Potzi et al revealed that of four patients presenting with metastatic thyroid cancer, all had less uptake of 123-1 after rhTSH stimulation than after THW. The median half-life in tumor tissue was longer after withdrawal (39.8 hours) then after rhTSH stimulation (39.8 hours versus 2l.9 hours, respectively). Furthermore, the cumulative dose in metastatic tissue was lower after rhTSH than during hypothyroidism, with considerable variations between individual lesions (35). Freudenberg et al (36) retrospectively compared the mean lesion dose of administered RAI activity between patients prepared for 124-I positron emission tomography/computed tomography (124I-PET/CT) either with rhTSH (n = 27) or THW (n = 36). They did not observe any statistically significant differences in mean lesion dose of administered RAI between rhTSH and THW groups (30.6 Gy/GBq versus 51.8 Gy/GBq, respectively; $P = .1667$). However, a subanalysis focused on within a patient comparison revealed a 2.9- to 10-fold higher mean lesion dose of administered RAI after THW than after rhTSH.

A similar observation was found by Van Nostrand et al in a study comparing RAI in 24 patients prepared for diagnostic whole body scan (I31-I-WBS) and 124-I-PET-CT with rhTSH and 16 patients prepared with THW (37). The proportion of patients with positive foci detected either by 131-I-WBS or 124-I-PET was significantly higher for the THW group compared to the rhTSH group (63% versus 4%, $P<.02$ and 63% versus 29% $P<.03$, respectively). Moreover, the number of metastatic foci detected after preparation with THW was significantly higher than after preparation with rhTSH. One of the strengths of this study was similar baseline characteristics of patients from both groups, including baseline Tg levels. However, one cannot exclude differences in tumor burden, differentiation, and location of metastases potentially affecting RAI avidity. Therefore, only large, well-controlled, prospective non-inferiority studies comparing the preparation with rhTSH and TWH with the patient being their own control should be used to compare RAI uptake in metastatic lesions after the preparation with rhTSH and THW. However, there is another important clinical question that needs to be addressed: does RAI uptake correlate with the biological response to RAI therapy?

Response to Treatment with RAI

One of the first reports comparing the response to rhTSH-aided and THW-aided RAI therapy in patients with distant metastases was provided by Jarzab et al (38). The authors compared the early radiological, clinical, and biochemical response after rhTSH-aided 131-1 treatment to outcomes seen after prior withdrawal-aided therapy in the same patients. They concluded that 52% of patients had identical outcomes after endogenous or exogenous TSH stimulation, 27% actually achieved a superior response to rhTSH-aided treatment, and 16%

had a superior response after THW-aided treatment. Although having the patients serve as their own historical controls is an attractive model, this method of comparison introduces some potential bias. Thus, results of the second intervention may be influenced by factors related to the earlier treatment, such as different radiation activity, number of prior courses of radioiodine, different time interval between the courses of treatment, and tumor progression over time (35).

Rosario et al (39) documented a similar response to RAI therapy in a group of 275 high-risk patients with DTC of whom 77 were prepared for RAI treatment with rhTSH and 198 patients with THW. Among the study group, there were 4 with distant micropulmonary metastases (rhTSH group: n = 1; THW group: n = 3). Two patients obtained complete remission: 1 after preparation with rhTSH and 1 after receiving THW-aided RAI therapy. Tuttle et al (40) showed very similar data in a retrospective review of the clinical outcomes of 84 thyroid cancer patients in whom RAI-avid lesions outside the thyroid bed were first identified at the time ofRAI remnant ablation. THW- and rhTSH-stimulated RAI ablation had similar efficacy in eliminating RAI-avid locoregional metastases (42/60, 70% of rhTSH; and 10/16,63% of THW; $P = .65$) and pulmonary metastases (3/4, 75% of rhTSH; and 1/4, 25% of THW; $P = .41$) Both of the above mentioned studies included a relatively small number of patients with distant metastases diagnosed incidentally in postablation WBS. A larger cohort of patients with metastatic disease was analyzed in the most recent study from the Sloan-Kettering group (41). The authors assessed a short-term (at 2 years) and long-term (at median 9 years) response to rhTSH-aided and THW-aided therapy in a group of 1586 patients, of which 111 presented with distant metastases discovered at the time of RAI ablation at posttreatment WBS. Among patients with distant metastases,65 were prepared for RAI ablation with THW and 46 with rhTSH. There were no differences in either short-term or long-term response to RAI therapy in this subgroup of patients.

The studies mentioned above were not specifically designed to compare the relative efficacy of rhTSH-aided and THW-aided therapy in patients with distant metastases of thyroid cancer. The data on patients with widespread disease were provided as subgroup analyses of patients for whom distant metastases were detected incidentally on postablation WBS. There are two retrospective studies specifically comparing rhTSH-aided and THW-aided RAI therapy in patients with distant metastases of thyroid cancer. Tala et al assessed 175 patients with RAI avid distant metastases of thyroid cancer who were treated after preparation with rhTSH (n = 5S) or THW (n = 35) or a combination of both methods (n = 82) (42). The baseline characteristics of the study groups were comparable; there were no statistically significant differences between the three groups in terms of age, gender, histological breakdown, distribution of distant metastases, size of lung metastases, and presence of multiple bone metastases. The median follow-up was significantly longer in the THW-only group (6.9 years) and in patients who received initial doses prepared with THW followed by rhTSH (6.9 years) compared to the rhTSH-only group (3.4 years; $P<.05$). The number of RAI doses administered as well as the cumulative administered activity was higher in patients treated with THW followed by rhTSH than in either the TWH-only or rhTSH-only groups (median: 967 mCi versus 522 mCi versus 40S mCi, respectively; $P<.05$). There was no significant difference in overall survival between patients receiving RAI treatments with

TWH-only, rhTSH-only, or initial treatments with TWH followed by subsequent treatments with rhTSH stimulation (*P* = .80). A multivariate analysis that included age at the time of diagnosis, gender, histology of the primary tumor, presence of bone metastases, and method of preparation demonstrated that the only variable significantly associated with a survival difference was age of the patients at the time of diagnosis. Adequate serial cross-sectional imaging was available to retrospectively evaluate a structural response to therapy in 24 patients from the THW-only group and 43 patients from the rhTSH-only group. Response to therapy assessed at the last follow-up visit was similar between the groups. No structurally identifiable disease was present at sites of previous RAI-avid metastatic lesions in 17% of the THW-only patients and 19% of the rhTSH-only patients (*P* = .70). Structural disease progression was seen in 54% of the THW-only and 46% of the rhTSH-only patients (*P* = . 60). The remaining 29% in the THW-only and 35% in the rhTSH-only cohorts did not demonstrate a clinically significant change {n the size of the RAI-avid structural lesions (*P* = .14).

Similar observations were found by our group in a study that included 56 patients with RAI-avid distant metastases of DTC treated with either rhTSH-aided (n = 15) or THW-aided RAI (n = 41) and followed for 72 ± 36.2 months (43). The strength of this study was the inclusion of patients with RAI-avid disease who were prepared for the treatment either exclusively with rhTSH or THW, thus enabling the clear distinction between these two methods of TSH stimulation. Moreover, the comparison of the relative efficacy of rhTSH-aided versus THW-aided RAI treatment was justified by the relatively equivalent tumor burden documented by the similar baseline dimensions of target lesions (6.4 em versus 4.S em, respectively; *P* = .41), baseline Tg values (6995 ng/mL versus 5544 ng/mL, respectively; *P* = .83), similar distribution of patients with micro- and macro-pulmonary metastases (67% versus 63%, *P* = .54, and 13% versus 15% *P* = .64, respectively), bone lesions (53% versus 29%, respectively; *P* = .09), and atypical metastases to the brain (0% versus 2%, respectively; *P* = .73) and the liver/kidney (13% versus 2%, respectively; P = . 61). Patients in the rhTSH group were older than the THW group (mean: 62 years versus 49 years, respectively; *P* = .01) and received lower cumulative RAI activity (256 mCi versus 416 mCi, respectively; *P* = .03), which was more frequently based on dosimetric calculations (80% versus 46%, respectively; P = .024). Other treatment modalities applied during the follow-up period, such as external beam radiation therapy, additional surgical excision of metastatic lesions, and treatment of patients with osseous metastases with zoledronic acid were similar between the study groups. We found a similar biochemical response to RAI between the groups. Tg decreased after treatment in 79% of patients treated with rhTSH-aided RAI and 70% of patients treated with THW-aided RAI (*P* = .42). Notably, the treatment efficacy was also assessed by RECIST criteria for response to treatment (44) and when adjusted by age, the rates of complete response (CR), stable disease (SD), progressive disease (PD), and progression free survival (PFS) were not significantly different between the groups. The only independent risk factor for no response to treatment and presentation with PD was age (hazard ratio [HR] 1.06 and 95% confidence interval [CI] 1.02-1.11; *P* = .008). Age was also the only independent factor affecting PFS (HR 1.04 for each year and 95%CI 1.02-1.07; *P* = .001) (43).

A summary of the above mentioned studies is presented in Table 2. There are several important limitations of the above studies that must be considered. Studies by Tala et al and by our group exclusively included patients with RAI-avid metastatic disease. In addition, the majority of patients analyzed by Tala et al and by our group were treated with dosimetrically-determined RAI activity, warranting therapy with the highest tolerated RAI activity that did not exceed 200 rad to the bone marrow. Therefore, the results of these studies cannot be directly translated to the empirical approach for determining therapeutic RAI activities. An important additional confounder when comparing outcomes after RAI therapy for metastatic disease is that the conclusion that there is no difference in outcome between patients receiving a preparation with rhTSH compared to THW may in fact be that they are equally unsuccessful and characterized by a very low complete remission rate. The reason for this might be due to insufficient radioiodine uptake or insufficient residence time within individual lesions to deliver any significant radiation absorbed dose.

The relative efficacy of an rhTSH versus THW preparation for RAI treatment of patients with metastatic disease needs to be assessed not only for efficacy, but also for safety and the side effects profile.

Safety Profile of rhTSH Versus THW-Aided RAI Therapy

Administration of rhTSH is well-tolerated, with mild, transient fever, nausea, and/or headaches occurring in a minority of patients (45). A number of studies emphasized that exogenous stimulation of TSH is associated with better quality of life because it obviates the signs and symptoms of hypothyroidism resulting from endogenous TSH stimulation. Duntas and Biondi (46) focused on the side effects of both methods of TSH stimulation and pointed out that the short-term hypothyroidism after LT4-withdrawal severely impairs quality of life, deranges lipid profile, and may be hazardous for patients with underlying cardiovascular diseases, especially in elderly individuals. Schroeder et al (47) presented a multicenter study that included 228 patients undergoing diagnostic follow-up evaluations for thyroid cancer and found that the quality of life significantly declines after THW, which can be abrogated by rhTSH.

Nevertheless, the safety profile needs to be assessed separately for patients with widespread disease. The rhTSH has been advocated in patients with brain or spinal metastases to avoid chronic endogenous TSH stimulation of neoplastic tissue, which could predispose a patient to tumor expansion (48,49). On the other hand, peak values of TSH after rhTSH are significantly higher than after withdrawal, and thus there is a potential increased risk of tumor swelling after rhTSH. There have been case reports of an association of the use of rhTSH with neurological complications in patients with metastases to the brain, spine, or vertebrae. Vergas et al described hemiplegia due to hemorrhage in a brain metastasis (48). Robbins et al described neurological side effects after both methods of TSH stimulation in a patient with multiple bone and brain metastases (49). The patient developed sudden onset of hemiparesis during THW withdrawal as well as confusion, ataxia, dysphagia, headache, and papilledema after subsequent rhTSH preparation for RAI ablation. The complications were found to be associated with increased edema surrounding the brain metastasis. Jarzab et al reported that 2 of 4 patients who experienced rapid tumor progression after previous L-

thyroxine withdrawal also experienced this complication after rhTSH-aided treatment (35). Among 55 patients with central nervous system (CNS) metastases who were enrolled in the TCUP, four developed complications, including hemiparesis, hemiplegia, or headache, which were attributed to edema or focal hemorrhage within the tumor (50). One patient with metastasis to the optic nerve developed acute visual loss 24 hurs after rhTSH administration.

There are case reports and case series describing respiratory failure in patients with widespread metastases to the lungs, which is most likely caused by stimulation and rapid swelling of the metastatic lesions by the rhTSH (51,52). Braga et al described respiratory distress and dysphonia in patients with locally advanced disease after rhTSH induced an increase in the size of the tumor mass (49). There have also been multiple case reports describing a decrease in bone pain at a metastatic site after rhTSH injection (53). A temporal relationship between the injection of rhTSH and the development of acute symptoms strongly suggests a direct effect of TSH on the development of inflammatory edema surrounding the tumor. Although the precise mechanism is not known, a vascular effect, followed by edema, has been proposed to be the mechanism responsible for acute tissue reactions after rhTSH stimulation. Desideri et al observed that supraphysiological concentrations of rhTSH promote activation of vascular endothelial cells and platelets, most likely through enhanced oxidative stress (54). The acute increase in serum TSH levels after rhTSH injection leads to an acute impairment of endothelium-dependent vasodilatation and to a significant decrease in total antioxidant power (55,56) Although controlled studies are not feasible, expert opinion holds that glucocorticoid coverage should be provided in patients with cerebral or spinal metastases to mitigate the risk of tumor swelling and neurologic emergency (44,48).

Jarzab et al described thyrotoxicosis after rhTSH-aided treatment in a patient with massive functional bone and soft tissue metastases who was treated successfully with beta blockers only. Berg et al described development of severe ophthalmopathy in a patient with disseminated thyroid cancer and no previous autoimmune thyroid disease. The ophthalmopathy occurred after the treatment with retinoic acid to induce RAI uptake, followed by rhTSH-aided administration of RAI (57).

Our group compared potential RAI-induced side effects in patients with distant metastases of thyroid cancer prepared for the treatment with either rhTSH or THW (43). The rates of leukopenia, thrombocytopenia, xerostomia and restrictive pulmonary disease after RAI were not significantly different between rhTSH-aided and THW-aided administration.

CONCLUSION

The rhTSH stimulation is not presently approved by the FDA as a method of preparation for adjunctive therapy with RAI in patients with metastatic DTC. Data on rhTSH compassionate use suggest that rhTSH stimulation is equally effective as THW as a method of preparation for dosimetry-based RAI treatment in patients with RAI-avid metastatic DTC. The availability of randomized studies is hampered by the relative number and heterogeneity of patients with metastatic thyroid cancer that are seen at any given medical center. Clearly,

there is a necessity to address the following questions in randomized, controlled prospective clinical studies:

1. The relative efficacy and side effect profile of rhTSH-aided versus THW-aided RAI therapy of metastatic DTC with empirically- and dosimetrically-determined RAI doses.
2. A noninferiority study based on a comparison of RAI uptake in metastatic lesions after preparation with rhTSH and TWH with the patient being their own control, controlled with lesion dosimetry.
3. The optimal steroid coverage prior to exogenous and endogenous TSH stimulation in patients with large tumor burden and/or bone metastases.

Acknowledgments

Portions of these data have been published previously (43).

Abbreviations

BMI	body mass index
DTC	differentiated thyroid cancer
RAI	radioiodine
rhTSH	recombinant human thyroid stimulating hormone
TSH	thyroid stimulating hormone
TWH	thyroid hormone withdrawal

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Table 1

Case Reports and Case Series Describing the Efficacy of TCUP Program of rhTSH-Aided RAI Treatment for Metastatic Thyroid Cancer

Reference	Number of patients	Age	Sex	Location of metastases	131-I activity	Outcome
17	1	54	M	bones, lungs	515 mCi	Disease stabilization
18	2	56	F	pituitary gland	200 mCi	Disease stabilization
19	1	61	F	vertebral spine	200 mCi, 3 months later repeat 200 mCi	3 months after first dose clinical improvement, less 131I uptake shown in WBS
20	1	46	F	liver	65 mCi, 6 months later 297 mCi	6 months after 1st treatment significant reduction in size of liver metastases
16	115	59	F 60 M 55	lymph nodes 39.1%, lungs 39.1%, bones 29.6%, spinal 20% mediastinum 14.8%, brain 9.6%, liver 6.1%	No data	**Clinical response** Clinical status 12 months after treatment improved 24.3% no change 54.1%, worsened 21.6% **Biochemical response** Serum Tg 12 months after treatment decreased/undetectable 72.7%, increased 27.3%
22	12	48-75	F 6 M 6	lungs, bones, lymph nodes	2.7-3 mCi/kg	Decrease in serum Tg level in 50% of patients, not clinically relevant
23	11	15-82	F 6 M 5	lungs, bone, brain	27-200 mCi	5/11 patients – progression (including death 3/5) 6/11 – decreased or stabilized tumor burden
33	1	28	F	lungs	100 mCi (previously THW-aided 1528 mCi)	Superiority of THW in detection of RAI uptake in lungs metastases
34	2	71 and 32	F	Case 1- bones Case 2- locoregional disease, lungs	Case 1 7 courses of THW –aided treatment with 200 mCi 2 courses of rhTSH aided treatment with 200 mCi, 2 courses of THW aided treatment with 150mCi Case 2 2 courses of THW-aided treatment with 200 mCi 6 courses of rhTSH-aided treatment with 200 mCi 1 course of THW-aided treatment with 200 mCi	Superiority of THW in detection of RAI uptake in lungs metastases

Abbreviations: DTC = differentiated thyroid cancer; mCi = RAI = radioiodine; rhTSH = recombinant human thyroid stimulating hormone; THW = thyroid hormone withdrawal; WBS = whole body scan

Table 2

Comparison of Relative Efficacy and Side Effect Profile Between rhTSH and THW Preparation for RAI Treatment of Metastatic Thyroid Cancer

Reference	Design	rhTSH # patients with distant metastases	THW # patients with distant metastases		Location of distant metastases	Outcome
38	Retrospective observational - patients served as their own historical controls	54	54		Lungs, mediastinum, bones, brain, soft tissue	52% similar outcomes after rhTSH versus THW 27% superior response to rhTSH 16% superior response to THW
39	Subgroup analysis of a retrospective study comparing rhTSH vs THW-aided RAI therapy in high-risk patients (n = 275)	1	3		Lung micro-metastases	Complete response in 1/1 patients in rhTSH group and 1/3 patients in THW group
40	Subgroup analysis of a retrospective study comparing rhTSH versus THW-aided RAI therapy in high-risk patients (n = 84)	4	4		Lung micro-metastases	Complete response 3/4 in rhTSH and 1/4 of THW group (P = .41)
41	Subgroup analysis of a retrospective study comparing rhTSH versus THW-aided RAI therapy (n = 586)	46	65		Lung metastases	Short term response (at 2 years) rhTSH versus THW Excellent 20.9% versus 6.2% (P = NS) Acceptable 14% versus 12.3% (P = NS) Incomplete 65.1% versus 81.5% Long-term response rhTSH versus THW No evidence of disease 23.3% versus 16.1% (P = NS) Persistent disease 76.7% versus 83.9% (P = NS)
42	Retrospective comparison of survival after preparation for RAI therapy of metastatic thyroid cancer with rhTSH-only, THW-only, and rhTSH + THW	rhTSH-only 58	THW -only 35	rhTSH+ THW 82	Lungs, bones	No difference in 5 years survival between rhTSH-only, THW-only, and rhTSH + THW group (P = .80)
43	Retrospective comparison of biochemical and structural response (by RECIST criteria) and side-effects profile of rhTSH vs THW-aided therapy for metastatic DTC	15	41		Lungs, bones, brain, kidney	**Biochemical response** rhTSH versus THW Tg decrease in 79% versus 70% of patients (P = .42). **RECIST criteria response** rhTSH versus THW Complete response 7% versus 12%, P = .48, Stable disease 73% versus 56%, P = .20, Progressive disease 20% versus 32%, P = .31 **Complications** rhTSH versus THW

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Reference	Design	rhTSH # patients with distant metastases	THW # patients with distant metastases	Location of distant metastases	Outcome
					Leukopenia 30% versus 28%, *P* = .61, thrombocytopenia 10% versus 0%, *P* = .37 Xerostomia 0% versus 12%, *P* = .20 Restrictive pulmonary disease 0% versus 2%, *P* = .73

Abbreviations: DTC = differentiated thyroid cancer; RAI = radioiodine; RECIST = response evaluation criteria in solid tumors; rhTSH = recombinant human thyroid stimulating hormone; THW = thyroid hormone withdrawal