Treatment of Metastatic Thyroid Cancer with Radioiodine Following Preparation by Recombinant Human Thyrotropin

57

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Introduction

Complete eradication of metastatic thyroid carcinoma is difficult to achieve. This challenge is attributed to (1) the reduction in iodine uptake by thyroid cancer cells, (2) the relatively slow and unpredictable rate of progression, and (3) the generally high quality of life (QOL), even in patients with widely metastatic disease. Furthermore, relatively few studies have identified reliable predictors of the progression rate, the pattern of metastatic spread, or the sensitivity to ^{131}I therapy. Patients and their physicians often continue to administer large amounts of ^{131}I to lesions that appear iodine-avid, even in the absence of previous tumor responses. A common rationalization for this approach is that tumor progression would have been worse if another dose of ^{131}I had not been administered.

To compound this dilemma, considerable evidence suggests that thyrotropin (TSH) is a progression factor for metastatic thyroid carcinoma. Therefore, the standard management approach employs constant suppression of this pituitary hormone. Unfortunately, TSH is also the only known activator of the sodium-iodide symporter (NIS), which must be stimulated to deliver the optimal amount of ^{131}I. For many years, it has been the standard of care to withdraw patients from thyroid hormone in order to elevate endogenous TSH production, allowing TSH stimulation and possible cancer cell proliferation for 6–8 weeks. In vitro and in vivo studies provide evidence for thyroid cancer growth under TSH stimulation, and clinical examples of tumor expansion and progression have been documented in this setting [1–3].

Numerous clinicians have tried to attenuate the clinical symptoms of hypothyroidism by reducing the time of thyroid hormone withdrawal (THW) or by using triiodothyronine (T3) for a few weeks to minimize the hypothyroid state. These strategies all rely on the assumption that maximum radioiodine uptake, by neoplastic thyroid cells, occurs when the serum TSH has risen above the 25–30-mU/mL range. There is remarkably little evidence that indicates this assumption is true, despite its widespread acceptance within the community of thyroid specialists.

The advent of clinical-grade recombinant human TSH (rhTSH) provided an opportunity to examine the possibility that short-term elevations in serum TSH (i.e., 3–4 days) might enable a comparable activation of the NIS [4] in thyroid cancer tissue, without the need for prolonged TSH stimulation, which might result in disease progression. rhTSH-assisted treatment is usually given with patients taking full therapeutic doses of thyroxine (T4) following a low-iodine diet. A reduced whole-body radiation load is an additional theoretical advantage of the rhTSH approach, considering the known reduced renal iodine clearance that exists in hypothyroidism [5]. Finally, in our personal experience with thousands of thyroid cancer survivors, there is a reluctance to repeatedly withdraw from T4, because of its negative effect on their QOL [6–8]. Many patients simply choose to forgo the possible benefit of radioiodine therapy simply because they want to avoid hypothyroidism.

Immediately after the preliminary results from the phase II testing of rhTSH were announced, clinicians began requesting access to rhTSH for "unusual" patients who could not produce TSH endogenously or who were too unstable to undergo THW. Through a compassionate need program supported by the Genzyme Corporation and sanctioned by federal agencies, rhTSH (Thyrogen®) was made available to physicians on a case-by-case basis in April 1995.

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Case Reports (Table 57.1)

The first evidence that rhTSH could be used to stimulate ^{131}I uptake in metastatic lesions was presented at the annual meeting of the American Thyroid Association in November 1996 [9]. All four patients in this preliminary report remained on TSH suppressive doses of T4 throughout testing and therapy. Uptake of ^{131}I into metastatic lesions was demonstrated on post-therapy scans in all four patients. The initial published report on rhTSH-assisted ^{131}I therapy of metastatic thyroid carcinoma was by Rudavsky and Freedman [10]. These physicians also showed that rhTSH could substitute for endogenously produced TSH and stimulate the uptake of ^{131}I into lung and bone metastases in one patient. Their patient received 515 mCi of ^{131}I 24 h after the second of two daily 0.9-mg injections of rhTSH. Within 2 weeks, the patient had a substantial reduction in bone pain related to his metastases. His serum thyroglobulin (Tg) level fell from 7,800 ng/mL to 1,924 ng/mL over a 4-months interval. Subsequent to this report, many clinicians and investigators began to apply this approach to selected patients. Chiu et al. [1] administered 200 mCi of ^{131}I following two 0.9-mg doses of rhTSH to treat brain metastases in a patient with a tall-cell variant of papillary thyroid carcinoma and demonstrated uptake of the isotope into the lesions.

Adler et al. [2] reported that rhTSH could stimulate uptake of a therapeutic dose of ^{131}I into the brain, spine, and lung metastases. One patient had central TSH deficiency. Improvement in the lung metastases was observed in one patient. Colleran and Burge [11] reported on the use of rhTSH for a patient whose TSH level did not elevate following 7 weeks of THW, despite being clinically hypothyroid. Magnetic resonance imaging (MRI) of the pituitary revealed an empty sella. rhTSH was then used to stimulate ^{131}I uptake. Rotman-Pikielny et al. [12] used rhTSH to assist ^{131}I therapy in a patient with functioning hepatic metastases, which prevented an elevation of TSH after THW. A partial reduction in liver metastases was found 6 months after therapy.

Perros [3] reported on a patient with unstable angina who sustained a myocardial infarction following THW in preparation for radioiodine therapy for follicular thyroid carcinoma. rhTSH was then used to prepare the patient for ^{131}I administration, without any adverse cardiovascular events, on two different occasions. Risse et al. and Masiukiewicz et al. [13, 14] both reported on the use of rhTSH to assist in ^{131}I therapy of patients with hypopituitarism from thyroid cancer involvement of the pituitary gland. Vargas et al. [15] also reviewed a patient with thyroid cancer involving the pituitary region. Unfortunately, in this case, rapid expansion of the lesion following rhTSH was associated with the onset of hemiplegia. After 4 days, the patient received 304 mCi of ^{131}I. A follow-up MRI scan 2 years later documented a reduction in the size of the pituitary mass.

Mazzaferri and Kloos [16] described a patient with papillary thyroid cancer and end-stage renal failure who could not tolerate hypothyroidism. Following two doses of rhTSH, the patient was treated with ^{131}I, and the post-therapy scan revealed uptake in lung metastases that was not seen on chest X-ray. Robbins et al. [17] reported a patient with follicular thyroid cancer who developed rapid expansion of a previously undiagnosed brain metastasis associated with hemiplegia after two rhTSH injections. The patient demonstrated good uptake of ^{131}I in lung, bone, and central nervous system lesions. This patient was treated on two subsequent occasions with the assistance of rhTSH and glucocorticoids and had no neurologic complications. Aslam and Daly [18] reported on a 62-year-old man treated with radioactive iodine for widely metastatic papillary thyroid cancer that was

Table 57.1 Individual case reports of rhTSH as preparation for radioiodine therapy

Author	Metastatic sites	131i(mCi)	Side effects	Outcome
Rudavsky	Lung, bone	515	Vomiting	PR
Chiu	Brain	200	NA	NA
Adler	Brain, lung, bone	434–506	Bone pain	PR
Colleran	Neck	150	NA	NA
Perros	Neck	135, 141	None	PR
Risse	Pituitary	0	None	Not treated
Masiukiewicz	Pituitary	200	NA	NA
Vargas	Brain	304	Hemiplegia	PR
Mazzaferri	Lung	100–140	NA	PR
Robbins	Brain	154	Papilledema	PR
Rotman	Liver	65	Nausea	PR
Aslam	C-spine, neck, mediastinum	209	NA	NA
Serafini	Orbit	207	NA	NA
Goffman	Lung, neck	157	Vomiting, dyspnea	PR

PR partial response, *NA* not available

enabled by rhTSH. Serafini et al. [19] reported on a woman with papillary thyroid cancer who was unable to tolerate hypothyroidism because of severe generalized malaise. On multiple occasions, she refused to be withdrawn from thyroid hormone, and rhTSH was used to prepare her for a therapeutic dose of ^{131}I. The post-therapy scan revealed radioiodine uptake in the thyroid bed region and disclosed a new metastatic lesion in her left orbit. Finally, Goffman et al. [20] analyzed a patient with diffuse lung metastases who was considered too ill to undergo THW as preparation for ^{131}I treatment. After two rhTSH injections, she developed moderate swelling of her neck lesions and dyspnea. She then received 157 mCi of ^{131}I; 2 days later, she developed severe respiratory failure, necessitating oxygen, steroids, and antibiotics. She gradually improved, and her serum Tg level declined. The sudden deterioration in pulmonary function was thought to be most likely the result of lesional edema, partly owing to the direct effect of rhTSH. Although these reports describe a diverse set of patients and circumstances, they have established that following rhTSH:

1. Serum TSH is reliably elevated considerably higher than 30 mIU/L.
2. Uptake of radioiodine is routinely demonstrated on post-therapy scans.
3. Although rhTSH is generally well-tolerated, large metastatic lesions can rapidly swell, causing neurological, respiratory, or painful events.
4. The vast majority of patients experience no symptoms of hypothyroidism.
5. Evidence of partial response to radioiodine or stabilization of disease is often realized.

However, individual case reports do not provide the full perspective of the possible risks and benefits of this approach that become evident in larger standardized trials.

Larger Series: Initial Results (Table 57.2)

From Wurzburg, Germany, Luster et al. [21] reported their observations in ten patients with advanced metastatic thyroid carcinoma who were treated with ^{131}I after rhTSH preparation, according to a standard protocol. Patients were offered this option because of the inability to produce sufficient TSH or because of a medical contraindication to hypothyroidism. Each patient received two daily 0.9-mg rhTSH injections, and the therapeutic administration of ^{131}I was given on the third day. T4 therapy was continued throughout the procedure. Those with brain or spinal cord metastases received high-dose steroids to prevent lesion edema. At follow-up (a mean of 4.3 months), three patients had died of progressive disease. Six of the eight surviving patients had evidence of partial responses, as indicated by reductions (at least 30 % lower than baseline) in serum Tg, and the other two were stable. No major adverse events occurred; however, headache ($n=2$), bone pain ($n=1$), fever ($n=1$), and rash ($n=1$) were reported. The authors concluded that this approach was a reasonable alternative to THW in selected patients.

Mariani et al. [22] administered ^{131}I to eight thyroid cancer survivors after preparation with rhTSH, which was administered as two 0.9-mg injections per day, and the ^{131}I was administered on day 3. Post-therapy scans showed considerable radioiodine uptake in residual disease in seven of the eight patients, but no long-term follow-up data was available to analyze its efficacy. Lippi et al. from Pisa, Italy, [23] used rhTSH-assisted ^{131}I therapy for 12 patients who had differentiated thyroid carcinoma and residual metastatic disease. They used two 0.9-mg injections of rhTSH for a 4-mCi diagnostic whole-body scan (WBS), then two more injections of rhTSH within 1 week to prepare for ^{131}I therapy, which was given 24 h following the last rhTSH injection. Based on published data suggesting that blood clearance rates of iodine were 50 % slower in hypothyroid patients, they doubled their usual activity administered to compensate. Serum TSH levels rose to over 100 mIU/L in all patients. The post-therapy WBS showed radioiodine uptake into metastatic lesions in all as well. Despite relatively advanced disease and previous high doses of ^{131}I, four of ten evaluable patients had a reduction in their serum Tg. Although this approach was well-tolerated, two patients had swelling and pain in bone lesions, similar to their past experience when withdrawn from T4. As in other reports, nausea and fever in low levels were also present. The authors concluded that rhTSH-assisted treatment of metastatic thyroid carcinoma was a safe method to administer ^{131}I, preventing the debilitating effects of hypothyroidism. Berg et al. [24] also investigated the safety and efficacy of rhTSH-treated ^{131}I in 11 frail thyroid cancer patients. Patients remained on T4 and were placed on a low-iodine diet for the 2 weeks prior to therapy. After two daily 0.9-mg injections of rhTSH, the patients each received approximately 108 mCi of ^{131}I. Of the 11 patients, 8 were being treated for metastatic disease. Five of the eight patients showed partial response to the therapy, two showed no response, and one is under surveillance. The rhTSH was well tolerated, with the exception of two patients who developed lesional swelling, one with nausea and the other with bone pain. No serious adverse events occurred. The authors concluded that rhTSH-assisted ^{131}I was safe and feasible in frail elderly patients and that it offered a means to reasonable palliative therapy for those with widely metastatic disease.

De Keizer et al. [25] applied this same strategy in 16 patients who underwent 19 rhTSH-administered ^{131}I treatments for metastatic disease. All patients had total thyroidectomy with radioiodine remnant ablation and were

Table 57.2 Reports of larger series of patients who received rhTSH-assisted therapy

Author	rhTSH schedule	131I administered	Side effects	Outcomes
Luster	0.9 mg IM 48 and 24 h prior	27–200 mCi	Headache, bone pain	PR: 5
				POD: 5
Mariani	0.9 mg IM 48 and 24 h prior	NA	Mild nausea, malaise	NA
Lippi	0.9 mg IM four doses prior	100 MBq/kg	Bone pain, nausea, fever	PR: 4
				Stable: 2
				POD: 4
Berg	0.9 mg IM 48 and 24 h prior	108 mCi	Nausea, bone pain	PR: 5
				NR: 2
De Keizer	0.9 mg IM 48 and 24 h prior	200 mCi	None	PR: 3
				Stable: 2
				POD: 6
Jarzab	0.9 mg IM 48 and 24 h prior	100–200 mCi	Bone pain, lesion edema,	CR: 1
			Paresthesiae, rash	PR: 12
				Stable: 19
				POD: 15

CR complete response, *PR* partial response; *stable* stable disease, *POD* progression of disease, *NR* no response, *IM* intramuscular

being treated for residual cancer. Patients were on a low-iodine diet and received two daily 0.9-mg injections of rhTSH, then ^{131}I on day 3. The radiation to individual lesions was estimated by post-therapy scanning techniques. Tumor response was solely based on changes in serum Tg. In 11 evaluable treatments, a partial Tg response occurred in 27 %, stable disease in 18 %, and progression of disease was seen in 55 %. None of those whose disease progressed received a lesion dose of more than 30 Gy. The treatments were well tolerated, with only one patient showing spinal cord compression that responded to corticosteroid administration. The authors thought that this approach was reasonable for those with advanced disease who were not good candidates for THW.

The largest report yet on this strategy is from Jarzab et al. [26]. They used rhTSH-assisted ^{131}I therapy in 54 patients who, with a few exceptions, had a total thyroidectomy and radioiodine remnant ablation. Only 31 of the patients had radioiodine-avid metastases. Those with nonfunctional metastases were given retinoic acid prior to the rhTSH to determine if they could reinduce radioiodine avidity. All patients received twice-daily 0.9-mg rhTSH injections, followed by ^{131}I on day 3 (median, 100 mCi; range, 100–250 mCi). They were not placed on low-iodine diets. The patients who qualified for this trial had a large amount of residual cancer that was considered at risk for growth during a prolonged THW preparation. A total of 18 patients were considered to have insufficient endogenous TSH production. In 49 patients, the serum TSH at the time of treatment was significantly higher after rhTSH than in previous THW treatments (mean, 190 mIU/L vs 70 mIU/L). Bone pain occurred in 25 % of those with known bone metastases. Tumor edema in the neck was seen in three patients, tachycardia in five, and a rash occurred in two. Of 47 evaluable patients at 6-month follow-up, these investigators found 1 who had a complete response to ^{131}I treatment, 12 (26 %) had partial responses, 19 (40 %) had stable disease, 15 (32 %) had progression of disease, and 5 patients died. Of the subset ($n=20$) with non-radioiodine-avid disease following retinoids, 2 had partial responses, 11 had stable disease, and 7 had progression. In 34 patients, there was a 46 % reduction in the median serum Tg; however, this did not have statistical significance. There were 44 patients who had a previous THW-assisted ^{131}I therapy, allowing outcomes to be compared between the two methods of preparation, where patients served as their own controls. The early outcomes were found to be identical in 52 %, better after rhTSH in 32 %, and inferior following rhTSH in 16 %, compared to preparation by THW. The authors concluded that rhTSH-administered ^{131}I therapy of metastatic thyroid cancer was safe and as equally effective as THW.

Robbins et al. [27] published a retrospective experience of rhTSH-assisted RAI therapy in patients with metastatic thyroid cancer from the USA and Canada. All 115 of these patients were judged unable to produce TSH or were too medically unstable to be withdrawn from thyroid hormone. Formal evaluations were done every 3 months up to 1 year. At the 1-year time point, 73 % of the patients had decreased or undetectable serum Tg levels; overall cancer-related symptoms were judged to be improved in 24 % and stable in another 54 %. Only 2 of the 115 patients were felt to have suffered a serious adverse event related to rhTSH. Overall, many of these patients, who had no other means of receiving radioiodine therapy, benefited by the ability to use rhTSH as a preparation for radioiodine.

In aggregate, these larger series provide a clear sense that rhTSH preparation can stimulate radioiodine uptake in meta-

static lesions, that the approach is generally safe, that many patients actually benefit from additional radioiodine treatment, and that steroid pretreatment should be considered in any lesions of the bone, pleura, or the central nervous system, to prevent sudden swelling. These reports also show that partial responses and/or disease stabilization is the most common short-term outcome.

Larger Series: Intermediate-Term Outcomes

Tala et al. [28] published a retrospective study on overall survival in a cohort of 175 thyroid cancer patients who were treated with high-dose radioiodine for lung and/or bone metastases. Radioiodine was administered following THW only in 35 patients; 82 patients had their initial radioiodine treatment following THW and all subsequent treatments following rhTSH preparation, while 58 of the patients received all of their radioiodine treatments following rhTSH preparation. rhTSH-prepared patients received an average of four injections of 0.9 mg rhTSH in the 2 weeks prior to a therapeutic dose of radioiodine. These patients also received the largest safe dose of ^{131}I based on formal dosimetry. After a median of 5.5 years of follow-up, there were no significant differences in overall survival among the three groups. Overall 5-survival was in the 75–80 % range. Most recently, Klubo-Gwiezdzinska et al. [29] reported a retrospective study on 56 thyroid cancer survivors who had distant metastases. Forty one patients received dosimetry-based amounts of radioiodine following THW and 15 following rhTSH preparation. Clinical features were comparable between the groups. After a mean of 72 months of follow-up, they found no differences between the two groups in rates of complete response, stable disease, or progression-free survival. Rates of adverse effects of the radioiodine were also similar between the two groups. They concluded that similar benefits occurred regardless of the method of preparation for radioiodine treatment.

Summary

The international use of rhTSH to prepare thyroid cancer patients for high-dose ^{131}I therapy of metastatic disease is growing. Given the small number of patients who die each year of thyroid cancer, it is unlikely that any federal agencies will support research analyzing the rhTSH preparation vs. THW preparation. Second, it is unlikely that any single center has sufficient patients to answer the many questions that have been raised. Therefore, it is time for leaders in the field to develop a set of guidelines regarding the appropriate use of this approach and design multicentered trials to quantify the safety and efficacy of rhTSH preparation in comparison to the traditional method of thyroid hormone withdrawal.

Issues that need to be carefully addressed include:

1. What are the optimum rhTSH doses and schedules for rhTSH-assisted ^{131}I therapy? Some studies utilize four 0.9-mg injections just prior to therapy, whereas others use only two.
2. Should strict low-iodine diets be routinely employed and should patients continue taking T4 immediately preceding the administration of ^{131}I?
3. Uniform criteria should be established to define complete and partial responses, stability, and progression of disease. A consensus on this point among the leaders in the field would be valuable, as research on this approach moves forward.
4. It is clear that radioiodine clearance from blood and bodily tissues is not the same in the hypothyroid state when compared to the slightly hyperthyroid state. The differences between blood and lesional clearance should be more carefully defined so that investigators can agree whether to adjust the therapeutic administered activity of ^{131}I. The use of ^{124}I dosimetry with PET/CT scanning may enable the determination of the exact amount of radiation that can be delivered to a specific lesion.
5. Additional studies examining longer monitoring periods (5–10 years) will be necessary before concluding that rhTSH preparation is comparable to thyroid hormone withdrawal as an adjunct to radioiodine therapy in patients with distant metastases.
6. The incidence of adverse effects should be prospectively studied in a randomized controlled trial of rhTSH preparation vs. T4 withdrawal. The evidence that repeated episodes of prolonged serum TSH elevations may foster tumor progression is only referred to anecdotally in the literature.

References

1. Chiu AC, Delpassand ES, Sherman SI. Prognosis and treatment of brain metastases in thyroid carcinoma. J Clin Endocrinol Metab. 1997;82:3637–42.
2. Adler M, Macapinlac HA, Robbins RJ. Radioiodine treatment of thyroid cancer with the aid of recombinant human thyrotropin. Endocr Pract. 1998;4:282–6.
3. Perros P. Recombinant human thyroid-stimulating hormone (rhTSH) in the radioablation of well-differentiated thyroid cancer: preliminary therapeutic experience. J Endocrinol Invest. 1999;22:30–4.
4. Dai G, Levy O, Carrasco N. Cloning and characterization of the thyroid iodide transporter. Nature. 1996;379:458–60.
5. Villabona C, Sahun M, Roca M, et al. Blood volumes and renal function in overt and subclinical primary hypothyroidism. Am J Med Sci. 1999;318:277–80.

6. Cohen O, Dabhi S, Karasik A, Zila ZS. Compliance with followup and the informative value of diagnostic whole-body scan in patients with differentiated thyroid carcinoma given recombinant human TSH. Eur J Endocrinol. 2004;150:285–90.
7. Reiners C, Lassmann M, Luster M. Recombinant human thyrotropin: safety and quality of life evaluation. J Endocrinol Invest. 2012;35(6 Suppl):30–5.
8. Klubo-Gwiezdzinska J, Burman KD, Van Nostrand D, et al. Potential use of recombinant human thyrotropin in the treatment of distant metastases in patients with differentiated thyroid cancer. Endocr Pract. 2012;27:1–26.
9. Robbins R, Macapinlac H, Yeung H, Larson S. 131-Iodine therapy of metastatic thyroid cancer with the aid of human recombinant TSH. Thyroid. 1996;6:S1–6.
10. Rudavsky AZ, Freeman LM. Treatment of scan-negative, thyroglobulin positive metastatic thyroid cancer using radioiodine 131I and recombinant human thyroid stimulating hormone. J Clin Endocrinol Metab. 1997;82:11–4.
11. Colleran KM, Burge MR. Isolated thyrotropin deficiency secondary to primary empty sella in a patient with differentiated thyroid carcinoma: an indication for recombinant thyrotropin. Thyroid. 1999;9:1249–52.
12. Rotman-Pikielny P, Reynolds JC, Barker WC, et al. Recombinant human thyrotropin for the diagnosis and treatment of a highly functional metastatic struma ovarii. J Clin Endocrinol Metab. 2000;85:237–44.
13. Risse JH, Grunwald F, Bender H, et al. Recombinant human thyrotropin in thyroid cancer and hypopituitarism due to sella metastasis. Thyroid. 1999;9:1253–6.
14. Masiukiewicz US, Nakchbandi IA, Stewart AF, Inzucchi SE. Papillary thyroid carcinoma metastatic to the pituitary gland. Thyroid. 1999;9:1023–7.
15. Vargas GE, Uy H, Bazan C, et al. Hemiplegia after thyrotropin alfa in a hypothyroid patient with thyroid carcinoma metastatic to the brain. J Clin Endocrinol Metab. 1999;84:3867–71.
16. Mazzaferri EL, Kloos RT. Using recombinant human TSH in the management of well-differentiated thyroid cancer: current strategies and future directions. Thyroid. 2000;10:767–78.
17. Robbins RJ, Voelker E, Wang W, et al. Compassionate use of recombinant human thyrotropin to facilitate radioiodine therapy: case report and review of literature. Endocr Pract. 2000;6:460–4.
18. Aslam SN, Daly RG. Use of recombinant human thyrotropin in a complicated case of metastatic papillary thyroid carcinoma. Endocr Pract. 2001;7:99–101.
19. Serafini AN, Clauss RP, Levis-Dusseau S. Protocol for the combined diagnostic and therapeutic use of recombinant human thyroid stimulating hormone. Clin Nucl Med. 2003;28:14–7.
20. Goffman T, Ioffe V, Tuttle M, et al. Near-lethal respiratory failure after recombinant human thyroid-stimulating hormone use in a patient with metastatic thyroid carcinoma. Thyroid. 2003; 13:827–30.
21. Luster M, Lassmann M, Haenscheid H, et al. Use of recombinant human thyrotropin before radioiodine therapy in patients with advanced differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2000;85:3640–5.
22. Mariani G, Ferdeghini M, Augeri C, et al. Clinical experience with recombinant human thyrotrophin (rhTSH) in the management of patients with differentiated thyroid cancer. Cancer Biother Radiopharm. 2000;15:211–7.
23. Lippi F, Capezzone M, Angelini F, et al. Radioiodine treatment of metastatic differentiated thyroid cancer in patients on L-thyroxine, using recombinant human TSH. Eur J Endocrinol. 2001;144:5–11.
24. Berg G, Lindstedt G, Suurkula M, Jansson S. Radioiodine ablation and therapy in differentiated thyroid cancer under stimulation with recombinant human thyroid-stimulating hormone. J Endocrinol Invest. 2002;25:44–52.
25. de Keizer B, Brans B, Hoekstra A, et al. Tumour dosimetry and response in patients with metastatic differentiated thyroid cancer using recombinant human thyrotropin before radioiodine therapy. Eur J Nucl Med Mol Imaging. 2003;30:367–73.
26. Jarzab B, Handkiewicz-Junak D, Roskosz J, et al. Recombinant human TSH-aided radioiodine treatment of advanced differentiated thyroid carcinoma: a single-centre study of 54 patients. Eur J Nucl Med Mol Imaging. 2003;30:1077–86.
27. Robbins RJ, Driedger A, Magner J, et al. Recombinant human thyrotropin-assisted radioiodine therapy for patients with metastatic thyroid cancer who could not elevate endogenous thyrotropin or be withdrawn from thyroxine. Thyroid. 2006;16:1121–30.
28. Tala H, Robbins R, Fagin JA, et al. Five-year survival is similar in thyroid cancer patients with distant metastases prepared for radioactive iodine therapy with either thyroid hormone withdrawal or recombinant human TSH. J Clin Endocrinol Metab. 2011;96:2105–11.
29. Klubo-Gwiezdzinska J, Burman KD, Van Nostrand D, et al. Radioiodine treatment of metastatic thyroid cancer: relative efficacy and side effect profile of preparation by thyroid hormone withdrawal versus recombinant human thyrotropin. Thyroid. 2012;22:310–7.