Recombinant Human Thyroid-Stimulating Hormone Versus Thyroid Hormone Withdrawal in the Identification of Metastasis in Differentiated Thyroid Cancer with ^{131}I Planar Whole-Body Imaging and ^{124}I PET

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Various studies have compared the detection of functioning residual thyroid tissue after thyroidectomy using radioiodine whole-body (WB) imaging following preparation of patients with injections of recombinant human thyroid-stimulating hormone (rhTSH) and thyroid hormone withdrawal (THW). However, metastases may have radiopharmacokinetics different from normal thyroid tissue. The objective of this study was to evaluate these 2 methods of patient preparation for the detection of metastases from differentiated thyroid cancer (DTC) using ^{131}I WB imaging and ^{124}I PET. **Methods:** A prospective study approved by the institutional review board was conducted at Washington Hospital Center from 2006 to 2010 recruiting patients who had DTC, were suspected of having metastasis from DTC (e.g., elevated thyroglobulin level without thyroglobulin antibodies, positive results on recent fine-needle aspiration, suspected enlarging mass, and abnormal findings suggesting metastasis on a diagnostic study) and were referred for ^{131}I WB dosimetry. All patients subsequently underwent both ^{131}I WB imaging and ^{124}I PET performed using the same preparation. All foci of uptake identified on these scans were categorized in a masked manner by consensus of 2 physicians in the following manner: 1, definite physiologic uptake or artifact; 2, most likely physiologic uptake or artifact; 3, indeterminate; 4, most likely locoregional metastases in the neck bed; 5, most likely distant metastases; or 6, definite distant metastases. Foci categorized as 4, 5, and 6 were considered positive for functioning metastases. **Results:** Of 40 patients evaluated, 24 patients were prepared with rhTSH and 16 with THW. No statistical difference was noted between the 2 groups for any of the parameters evaluated, including serum thyroglobulin. The percentages of patients with positive foci detected on the rhTSH ^{131}I and THW ^{131}I WB scans were 4% (1/24) and 63% (10/16), respectively ($P < 0.02$). The number of foci detected on the rhTSH ^{131}I and THW ^{131}I WB scans were 2 and 58, respectively ($P < 0.05$). When ^{124}I PET was used for imaging, the percentages of patients with foci detected on the rhTSH and THW scans were 29% (7/24) and 63% (10/16), respectively ($P < 0.03$). The number of foci detected on the rhTSH and THW scans were 17 and 117, respectively ($P < 0.03$). **Conclusion:** Significantly more foci of metastases of DTC may be identified in patients prepared with THW than in patients prepared with rhTSH.

Key Words: thyroid cancer; recombinant human thyroid stimulating hormone; thyroid hormone withdrawal; ^{131}I; ^{124}I

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Radioiodine is important for both the imaging and the treatment of differentiated thyroid cancer (DTC). However, for metastases of DTC to take up radioiodine, the thyroid tissue must first be stimulated by thyroid-stimulating hormone (TSH). This can be achieved either by withdrawing the patient's thyroid hormone, thereby stimulating production of the patient's endogenous TSH, or by having the patient remain on thyroid hormone and receive 2 or 3 intramuscular injections of recombinant human thyroid-stimulating hormone (rhTSH). Unfortunately, preparation by thyroid hormone withdrawal (THW) will result in the patient becoming hypothyroid, and for a period of 2 or 3 wk the patient's quality of life might be significantly reduced. During this interval of withdrawal, patients have a reduction in 5 of 8 quality-of-life domains such as physical functioning, vitality, social functioning, and mental health, and patients may also lose significant productivity, time from work, and earnings (*1*). However, this reduction in quality of life can be avoided if rhTSH is used instead of THW. Although rhTSH has been shown to be as effective as THW for the preparation of the patient for the initial diagnostic radioiodine scans as well as the initial ^{131}I ablation of remnant thyroid tissue (*1,2*), the only commercial product of rhTSH (Thyrogen; Genzyme Corp.) approved by the Food and Drug Administration in the United States and the European Medicine Agency in Europe is not currently approved for use in patients who have evidence of any metastases or

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distant metastases. Because metastases may have radiopharmacokinetics significantly different from those of normal remnant thyroid tissue (*3*), a comparison of these 2 methods of patient preparation (THW vs. rhTSH) in the detection of functioning locoregional and distant metastases is important. Although an earlier publication has compared the radiation absorbed dose to metastases after preparation with THW and rhTSH (*4*), publications evaluating the detection of foci of radioiodine uptake are all based on a limited number (n = 1–4) of patients (*5–8*).

The objective of this study was to compare these 2 methods of patient preparation in terms of the detection of metastatic foci in a group of patients that had a high suspicion of having metastases of DTC. To our knowledge, this study is also unique because not only ^{131}I planar whole-body (WB) scans but also ^{124}I PET scans were used in the evaluation.

MATERIALS AND METHODS

The prospective study, performed from 2006 to 2010 at Washington Hospital Center, recruited patients who had DTC, had evidence strongly suggestive of metastasis from DTC (e.g., elevated serum thyroglobulin level, positive results on recent fine-needle aspiration, suspected enlarging mass, abnormal findings suggesting metastasis on a diagnostic study) and were referred to our clinic for ^{131}I WB dosimetry. Demographics were tabulated for all patients and included age, sex, thyroglobulin level, TSH level, urine iodine level, type of cancer, number of radioiodine therapies, total prescribed activity of therapeutic ^{131}I, and indications. The patients were prepared with either THW or rhTSH on the basis of the clinical order from the patient's referring endocrinologist. Those patients referred for THW discontinued their long-acting thyroid hormone medication, levothyroxine, for 4–6 wk and discontinued their short-acting thyroid hormone medication for 2–3 wk before dosing for imaging. Those patients referred for rhTSH stimulation received an injection of rhTSH (0.9 mg) intramuscularly on 2 consecutive days, with radioiodine administration on the next day. All the patients underwent both ^{131}I WB scans and ^{124}I PET scans. Patients were also instructed to follow a low-iodine diet for 2 wk before the dosing and during the period of scanning. All patients subsequently underwent ^{124}I PET scans using the same method of preparation. The imaging protocols for ^{131}I planar WB scans and ^{124}I PET/CT scans have been summarized in Table 1 and have previously been described (*9,10*). All foci of uptake on each of the scans were categorized in a masked manner by consensus of 2 physicians using the following criteria: 1, definite physiologic uptake or artifact; 2, most likely physiologic uptake or artifact; 3, indeterminate; 4, most likely locoregional metastases in the neck bed; 5, most likely distant metastases; or 6, definite distant metastases. Foci categorized as grade 4, 5, or 6 were considered positive for functioning metastases.

This study was approved by the institutional review board, and all patients gave informed consent.

RESULTS

Forty patients were evaluated. Twenty-four were prepared with rhTSH, and 16 were prepared with THW. The demographics of the patients are shown in Table 2. No statistical difference was noted between the 2 groups regarding age, sex, thyroglobulin level, TSH level, urine iodine level, type of cancer, number of therapies, total prescribed activity of therapeutic ^{131}I, or indications (not listed in the table). All patients had at least 1 prior therapy; 12 of 14 patients pre-

TABLE 1
Techniques for Image Acquisition

Parameter	^{131}I WB planar	^{124}I PET/CT
Prescribed activity	74 MBq (2 mCi) of ^{131}I, with a range of 69.2–81.4 MBq (1.87–2.2 mCi)	62.9 MBq (1.7 mCi)
Images obtained at...	48 h after administration of ^{131}I	48 hours after administration of ^{124}I
Type of system	ADAC Genesys	GE Advance Nxi
	Dual-head WB scanner	Emission scans, 5 min/bed position
	Speed, 4 cm/min; ^{131}I, 364 keV, 20% window	Transmission scans, 2.5 min/bed position
		Processing: reconstruction with ordered-subset expectation maximization (4.3-mm isotropic pixels) with segmented attenuation correction
	Siemens E-cam	Philips Gemini time of flight 64
	Dual-head WB scanner	Emission scans, 4 min/bed position
	Speed, 4 cm/min; ^{131}I, 364 keV, 20% window	CT attenuation scans, 120 kV and 30 mAs
		Processing: reconstruction with ordered-subset expectation maximization time of flight with segmented attenuation correction using the CT data
	Searle	
	Single-head planar and pinhole scanner with an MIE computer	
	Aperture, 6 mm; 1,200 s (20 min) duration; ^{131}I, 364 keV, 20% window	

TABLE 2
Patient Demographics

Parameter	THW	rhTSH	*P*
Mean age ± SD (y)	53 ± 18.7	53 ± 14.0	
Sex (*n*)			
Male	4	11	Not significant
Female	12	13	Not significant
Mean thyroglobulin ± SD (ng/mL)	652 ± 1,319	534 ± 1,092	Not significant
Mean TSH ± SD (μIU/L)	43 ± 37	66 ± 67	Not significant
Mean urine iodine ± SD (μg/dL)	206.7 ± 238	157 ± 160	Not significant
Type of cancer (*n*)			
Papillary	9	16	Not significant
Papillary–follicular variant	4	2	Not significant
Follicular	2	2	Not significant
Hürthle cell	1	1	Not significant
Tall cell	0	1	Not significant
Insular	0	1	Not significant
Poorly differentiated	0	1	Not significant
More than one radioiodine therapy (*n*)	14/16	21/24	Not significant
Mean no. of prior therapies + SD	2 ± 1.2	2.22 ± 0.95	Not significant
Mean total GBq + SD	18.6 ± 9.9	19.9 ± 9.4	Not significant

pared with THW had at least 2 prior therapies, and 21 of 24 patient prepared with rhTSH had at least 2 prior therapies. The percentages of patients having positive foci detected on the rhTSH ^{131}I and THW ^{131}I scans were 4% (1/24) and 63% (10/16), respectively ($P < 0.02$). The number of positive foci detected on the rhTSH ^{131}I and THW ^{131}I scans were 2 and 58, respectively ($P < 0.05$). The percentages of patients having positive foci detected on the rhTSH ^{124}I and THW ^{124}I scans were 29% (7/24) and 63% (10/16), respectively ($P < 0.03$), and the number of positive foci detected on the rhTSH ^{124}I and THW ^{124}I scans were 17 and 117, respectively ($P < 0.03$).

DISCUSSION

This study reports the largest series of patients who have undergone evaluation for lesion detection of metastatic DTC after preparation with either THW or rhTSH with both ^{131}I planar WB images and ^{124}I PET.

Our prospective study strongly suggests that more metastatic foci of DTC were detected on radioiodine scans after preparation with THW than with rhTSH injections. Furthermore, ^{124}I PET scans detected more foci than did ^{131}I planar WB scans.

Driedger et al. (*6*), Taïeb et al. (*7*), and Hung et al. (*8*) have published case reports (2, 1, and 1 patients, respectively) in which preparation with THW was compared with rhTSH. THW appeared superior in the detection of metastatic foci in all 4 of these patients. Potzi et al. (*5*) evaluated 4 patients who underwent scanning after preparation with both THW and rhTSH, and again THW was superior to rhTSH.

In comparing our data with other reports that evaluated preparation with THW and rhTSH, our data are most consistent with those of Freudenberg et al. (*4*) but not consistent with the data of Klubo-Gwiezdinska et al. (*11*) or Tala et al. (*12*). In the study of Freudenberg et al. (*4*), their endpoint was the estimation of the radiation absorbed dose to the metastatic foci after THW and rhTSH preparation. They reported that the mean radiation absorbed dose for the lesions identified in a group of patients ($n = 27$) prepared with rhTSH was only 60% of the radiation absorbed dose to lesions in another group of patients ($n = 36$) prepared with THW. However, this difference was not statistically different. Klubo-Gwiezdinska et al. (*11*) from our institution evaluated patient outcomes from the ^{131}I therapy as their endpoint for comparison. They reported that patients who had metastatic DTC achieved comparable benefit from their ^{131}I treatment whether prepared with rhTSH or THW. Likewise, Tala et al. (*12*) were unable to demonstrate any difference in the 5-y survival of patients with distant metastases who were prepared with injections of rhTSH relative to those patients prepared with THW. At this time, we cannot explain the difference between the results of the present study, other imaging studies (*5–8*), and the study of Freudenberg et al. (*4*) versus the outcome studies of Klubo et al. (*11*) and Tala et al. (*12*). However, the latter were both retrospective studies with a relative short duration of follow-up, and these studies were not noninferiority studies. Thus, an absence of evidence that there was a difference is not evidence that the outcomes are the same. Another possible explanation is that although the preparation with THW relative to rhTSH injections may result in the superior uptake of ^{131}I and ^{124}I for lesion detection and even in a high radiation absorbed dose, the difference in uptake does not result in a difference in radiation absorbed dose to the metastases and thus in a different therapeutic effect. Further controlled prospective noninferiority studies are warranted.

Our study has several potential limitations. First, although this was a prospective study, our patients were not randomized as to the method of preparation. This decision was made by the referring endocrinologist, whose criteria were subjective and not systematically recorded. Accord-

ingly, there may have been a bias between the 2 groups. However, there was no statistical difference between the 2 groups regarding age, sex, thyroglobulin level, urine iodine level, type of histology, or indications on the order form. A prospective study in which each patient is studied using both methods of preparation is warranted.

Another limitation of our study is that we included in our analysis foci of uptake in the thyroid bed. Although these foci were most likely locoregional disease, one cannot completely exclude normal remnant tissue that had not been successfully ablated. However, we believe the inclusion of these foci was appropriate because all patients had prior ^{131}I ablation, and 35 of 40 patients had at least 2 prior treatments with ^{131}I. Thus, any radioiodine activity in the thyroid bed more than likely represented local regional disease and not untreated normal functioning thyroid remnant tissue. Second, the total mean prescribed activity was 18.6 and 19.9 GBq (504 and 539 mCi) in the THW and rhTSH groups, respectively. Finally, on the basis of previous publications (*1*), the detection of normal functioning thyroid remnant tissue after preparation with rhTSH was comparable to that after preparation of THW, and thus the inclusion of foci in the thyroid bed area that were in fact normal functioning thyroid remnant tissue would bias the results toward the 2 preparations being equal—not different. Thus, exclusion of any true normal functioning thyroid remnant tissue would most likely accentuate the differences between the 2 methods of preparation.

Nevertheless, why should the detection of metastases after preparation with THW be superior to the preparation with rhTSH? This has not yet been determined. However, as Zanotti-Fregonara et al. (*3*) have noted, the function of normal thyroid tissue may be biologically distinct from that of metastases, and metastases may have reduced ability to take up iodine. Of course, this is why thyroid cancer typically appears hypofunctioning in an otherwise normal thyroid gland. Because of this reduced ability to take up iodine, metastases may require a more prolonged period of TSH stimulation of the sodium-iodide symporter, and preparation with THW may provide a longer and more profound period of TSH stimulation of the sodium-iodide symporter than would 2 injections of rhTSH. Because of the longer period of TSH stimulation, THW could result in greater uptake in the foci and thus better detection and potentially greater radiation absorbed dose to the tumor per gigabecquerel (mCi) of ^{131}I administered (*3*).

CONCLUSION

In patients diagnosed with DTC and in whom distant metastases is suspected, ^{131}I WB and ^{124}I PET scans obtained after THW identified significantly more foci of metastasis than scans obtained after rhTSH injections. Until more data become available, physicians should be cautious in using rhTSH for patient preparation before diagnostic scanning for the detection of DTC or treating distant metastases secondary to DTC with ^{131}I. The use of rhTSH is appropriate for patients who cannot tolerate hypothyroidism or increase their endogenous TSH because their metastases are producing significant thyroid hormone.

DISCLOSURE STATEMENT

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