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ORIGINAL ARTICLE

Lesion dose in differentiated thyroid carcinoma metastases after rhTSH or thyroid hormone withdrawal: ^{124}I PET/CT dosimetric comparisons

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Abstract
Purpose Renal radioiodine excretion is ~50% faster during euthyroidism versus hypothyroidism. We therefore sought to assess lesion dose/GBq of administered ^{131}I activity (LDpA) in iodine-avid metastases (IAM) of differentiated thyroid carcinoma (DTC) in athyreotic patients after recombinant human thyroid-stimulating hormone (rhTSH) versus after thyroid hormone withdrawal (THW).

Methods We retrospectively compared mean LDpA between groups of consecutive patients (N=63) receiving ^{124}I positron emission tomography/computed tomography (^{124}I PET/CT) aided by rhTSH (n=27) or THW (n=36); we prospectively compared LDpA after these stimulation methods within another individual. Data derived from serial PET scans and one CT scan performed 2–96 h post-^{124}I ingestion. A mixed model analysis of covariance (ANCOVA) calculated the treatment groups' mean LDpAs adjusting for statistically significant baseline intergroup differences: non-IAM were more prevalent, median IAM count/patient lower in cervical lymph nodes and higher in distant sites, median stimulated thyroglobulin higher, mean cumulative radioiodine activity greater and prior diagnostic scintigraphy more frequent in the rhTSH patients.
Results Mean LDpAs were: rhTSH group (n=71 IAM), 30.6 Gy/GBq; THW group (n=66 IAM), 51.8 Gy/GBq. The difference in group means (rhTSH less THW), −21.2 Gy/GBq, was statistically non-significant (p=0.1667). However, the 95% confidence interval of that difference (−51.4 to +9 Gy/GBq) suggested a trend favouring THW. The within-patient comparison found 2.9- to 10-fold higher LDpAs under THW.
Conclusion We found some suggestions, but no statistically significant evidence, that rhTSH administration results in a lower radiation dose to DTC metastases than does THW. A large, well-controlled, prospective within-patient study should resolve this issue.

Keywords Differentiated thyroid carcinoma · Metastases · Recombinant human TSH · Thyroid hormone withdrawal · Lesion dose per administered activity · ^{124}I positron emission tomography/computed tomography

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Introduction

Radioiodine therapy (RIT) with ^{131}I is a mainstay in the treatment of iodine-avid metastases of differentiated thyroid carcinoma (DTC). To optimise RIT, it is considered necessary to elevate serum thyroid-stimulating hormone (TSH) to compensate for sodium-iodide symporter (NIS) defects in DTC cells [1–3]. In athyreotic patients, such serum TSH elevation traditionally has been attained endogenously, through several weeks of thyroid hormone withdrawal (THW). However, clinical hypothyroidism frequently ensues, leading to important morbidity, with markedly reduced quality of life and ability to perform daily living, work, academic and leisure activities [4–7]. Additionally, THW-related hypothyroidism may exacerbate concomitant cardiovascular, psychological and other conditions [8].

Recombinant human TSH (rhTSH) was developed to elevate serum TSH exogenously, allowing patients to continue on thyroid hormone and to avoid THW-related hypothyroid morbidity [9]. rhTSH has undergone Phase 3 clinical study [10] and received regulatory approval in Europe and North America as an adjunct to the administration of large radioiodine activities for thyroid remnant ablation.

However, although rhTSH has been applied "off-label" safely and sometimes with efficacy in hundreds of patients to aid RIT of iodine-avid metastatic DTC [11, 12], the drug has not undergone Phase 3 study for this indication. Additionally, only limited data have been published on lesional radioiodine kinetics under rhTSH stimulation. Publications to date comprise three individual case reports [13–15] and two small studies [16, 17].

Radioiodine kinetics, and particularly the lesion dose after rhTSH versus after THW, are of clinical interest for two reasons. First, the markedly faster (by ~50%) renal excretion of radioiodine under euthyroid conditions compared to hypothyroid conditions [18, 19] raises the possibility that the radiation dose delivered by a given ^{131}I activity could differ appreciably between the two TSH stimulation methods. Second, use of an effective radioiodine activity is especially important in the RIT of metastatic disease, the DTC setting with, at least theoretically, the most marked NIS defects and the greatest downside to diminished efficacy.

We therefore sought, through a retrospective analysis, to compare the DTC lesion dose after rhTSH versus under THW in a large series of patients with metastatic DTC, employing ^{124}I positron emission tomography/computed tomography (^{124}I PET/CT), a relatively accurate and a clinically useful dosimetric method [20]. We also applied ^{124}I PET/CT to conduct a prospective within-patient comparison in an additional individual from the Hanover University School of Medicine (MHH); we present a case report of this comparison.

Materials and methods

Patients

The retrospective study included all consecutive DTC patients (N=63) seen from 1 January 2004 through 31 December 2006 at a tertiary referral centre, the University Hospital of Essen, fulfilling two criteria. First, the patients had one or more radioiodine-avid DTC neck lymph node metastases or distant metastases, or both. Second, the patients underwent ^{124}I PET/CT dosimetry before a planned RIT for treatment of unresectable disease, and in some cases, also for thyroid remnant ablation. Only data from each patient's first ^{124}I PET/CT imaging were used in this analysis. However, more than 40% of patients in either treatment group had received their first ^{124}I PET/CT examination when no longer RIT-naïve, i.e. before a second or subsequent RIT (Table 1).

The study population was made up of two types of DTC patients routinely receiving pre-RIT ^{124}I PET/CT dosimetry at our centre: (1) those with histologically confirmed advanced disease, namely pT4, pN1 or cM1 status [21] and (2) selected other "high-risk" individuals, e.g. those with unfavourable histology or under 19 years old. All patients or their parents or guardians gave written informed consent for ^{124}I PET/CT dosimetry and for analysis and publication of related data.

Treatment groups

Based on their TSH preparation method for ^{124}I PET/CT, the 63 patients eligible for the present analysis were retrospectively divided into an "rhTSH group" (n=27) or a "THW group" (n=36). Those in the rhTSH group were on thyroid hormone therapy, which had been started 2 days after thyroidectomy. They ingested ^{124}I 24 h after the second of two consecutive daily intramuscular injections of rhTSH (Thyrogen®, Genzyme Corporation, Cambridge, MA, USA), 0.9 mg. Patients in the THW group ingested ^{124}I following at least 4 weeks without thyroid hormone, after their serum TSH levels first were measured at ≥25 mIU/l.

The criteria for choosing rhTSH versus THW were subjective, case by case and not systematically recorded. Our clinical impression is that rhTSH was most often prescribed due to high risks of tumour progression during prolonged TSH elevation or of concomitant illness exacerbation due to hypothyroidism. However, in some patients, the indication for rhTSH was avoidance of hypothyroid morbidity in order to preserve the ability to work or study.

Table 1 Selected patient, disease, treatment and imaging characteristics

Characteristic	rhTSH group (n=27)	Endogenous TSH group (n=36)	p, rhTSH vs endogenous TSH group, statistical test
Female, % (n)	44.4% (12)	55.6% (20)	0.383, Pearson's χ^2 test
Age at ^{124}I PET/CT dosimetry, years, mean±SD	53.5±19.4	46.1±18.7	0.132, t test
Height, cm, mean±SD	168.9±10.0	168.1±13.5	0.809, t test
Weight, kg, mean±SD	77.5±18.0	80.8±17.9	0.474, t test
Histology type, % (n)			
Papillary	59.3% (16)	80.6% (29)	0.064, Pearson's χ^2 test
Follicular	40.7% (11)	19.4% (7)	
Unfavourable subtypes[a], % (n)	11.1% (3)	11.1% (4)	1.00, Fisher's exact test
T[b], % (n)			0.220, Fisher's exact test
T1	14.8% (4)	11.1% (4)	
T2	14.8% (4)	5.6% (2)	
T3	25.9% (7)	13.9% (5)	
T4	44.4% (12)	69.4% (25)	
N[b], % (n)			0.393, Pearson's χ^2 test
N0	18.5% (5)	27.8% (10)	
N1	81.5% (22)	72.2% (26)	
M[b], % (n)			0.215, Pearson's χ^2 test
M0	37.0% (10)	52.8% (19)	
M1	63.0% (17)	47.2% (17)	
Patients with non-iodine-avid metastases, % (n)	66.7% (18)	41.7% (15)	0.049, Pearson's χ^2 test
Iodine-avid lesions, number per patient by site, median (range)	(n of iodine-avid metastases=71)	(n of iodine-avid metastases=66)	Wilcoxon rank sum tests
Any	2 (1–5)	2 (1–12)	0.676
Cervical lymph nodes	1 (0–4)	1 (0–3)	0.043
Distant sites	1 (0–12)	0 (0–3)	0.015
Thyroid remnant			
Patients without remnant, % (n)	46.2% (12)	33.3% (12)	0.306, Pearson's χ^2 test
Total remnant volume, ml[c], median (range)	<0.1 (<0.1–4.0)	0.8 (<0.1–2.5)	0.350, Wilcoxon rank sum test
Stimulated serum Tg, µg/l, median (range)	152.0 (0.0–16400.0)	9.2 (0.0–6465.0)	0.009, asymptotic Wilcoxon rank sum test
Serum TSH, mIU/l, median (range)	141.9 (101.0–463.0)	83.4 (24.7–250.0)	<0.001, asymptotic Wilcoxon rank sum test
Urinary iodine excretion, µg/l, median (range)	100.0 (50.0–142.0)	110.0 (37.0–148.0)	0.171, t test
Timing of ^{124}I PET/CT dosimetry, % (n):			0.825, Pearson's χ^2 test
Before first RIT	55.6% (15)	58.3% (21)	
Before subsequent RIT	44.4% (12)	41.7% (15)	
Cumulative activity, GBq, mean±SD	9.5±13.4	2.8±15.0	0.019, Welch t test
Prior dxWBS scans/patient, median (range)	0 (0–6)	0 (0–2)	0.039, asymptotic Wilcoxon rank sum test

CT computed tomography, *dxWBS* diagnostic whole-body scintigraphy, *IIT* iterative image thresholding, *PET* positron emission tomography, *rhTSH* recombinant human TSH, *RIT* radioiodine treatment, *SD* standard deviation, *Tg* serum thyroglobulin

[a] Unfavourable subtypes included the tall cell, diffuse sclerotic and oncocytic variants of papillary DTC and the Hürthle cell variant of follicular DTC

[b] According to the 5th edition of the Union Internationale Contre le Cancer staging system [21]

[c] Calculated based on the total volume of all remnants by either ultrasonography, CT or PET IIT [29]

^{124}I PET/CT dosimetry protocol—University of Essen (retrospective study)

We described our ^{124}I PET/CT dosimetry protocol in detail elsewhere [20, 22]. Briefly, we obtained whole-body ^{124}I PET data 4, 24, 48, 72 and 96 h and ^{124}I PET/CT data 25 h post-oral administration of 24±3 MBq of highly purified ^{124}I from our cyclotron [23, 24]. We gave these low ^{124}I activities to avoid potential "stunning," i.e. impairment of therapeutic radioiodine uptake due to incomplete treatment or other biological effects of the tracer activity. In our hands, these activities obtain sufficient signal to noise ratios [25].

We used a Biograph Emotion Duo combined PET/CT scanner for the 25-h imaging and an ECAT EXACT HR+ PET scanner for all other imaging (both models from Siemens Medical Solutions, Hoffman Estates, IL, USA). Whole-body emission data were acquired by scanning from head to thigh in three-dimensional mode using five to eight bed positions for 5 min each. CT scans were performed with 130 kVp tube voltage, 160 mAs, 5-mm slice width and 1.6 pitch, without contrast agent. For image reconstruction of the corrected emission data, we employed Fourier rebinning attenuation-weighted ordered subsets expectation maximisation at 2 iterations and 8 subsets with a 5-mm post-reconstruction Gaussian filter and attenuation image segmentation. We used CT data to correct for PET/CT scan attenuation.

^{124}I PET/CT dosimetry protocol—MHH (case report of within-patient comparison)

^{124}I PET/CT dosimetry methods for the within-patient comparison were essentially similar to those for the retrospective study, except that scanning was performed at MHH (although the same scanner models were used as at Essen), and except that PET was performed 4, 12, 24 and 48 h and CT approximately 24 h post-^{124}I administration.

Lesion dose per administered activity (LDpA) calculation

Using the ^{124}I PET data, we determined the so-called LDpA, that is, the lesion dose that would be obtained with administration of 1 GBq of ^{131}I, according to the formula:

$$LDpA = \frac{\Delta}{\rho \cdot V} \cdot \frac{\widetilde{C}}{A_{tr}}$$

where Δ denoted the equilibrium dose constant for non-penetrating radiation for ^{131}I, 0.11 (Gyg)/(MBqh) [26], ρ denoted the gland mass density assuming the value of water (1 g/ml) and V denoted the lesion volume in ml. $\widetilde{C}$ represented the cumulative activity of ^{131}I, obtained using the time-activity curves of the serial ^{124}I PET scans corrected with the measured recovery coefficient [27]. A_{tr} represented the tracer activity upon capsule administration. The self-irradiation absorbed dose of the ß-particles was calculated using the Medical Internal Radiation Dose formula [28], omitting effects at the lesion border. The penetrating absorbed dose, i.e. γ-rays, was ignored since the lesion volumes were small.

Lesion volumetry

For volumetry of each lesion, we chose the method among the CT component of the ^{124}I PET/CT, ultrasonography (US) or a novel PET iterative thresholding (ITM) technique [29] that best visualised the given lesion; these three modalities are listed in descending order of the frequency with which they were applied. US was performed by experienced operators on a Sonoline Elegra system using previously described methods [30]; a 7.5L40 small part transducer at a frequency of 8 MHz was used for neck imaging and a convex array 4C1 transducer at a frequency of 3 MHz was used for abdominal imaging. The ITM method was developed and validated using ^{18}F-fluorodeoxyglucose PET as well as ^{124}I PET and using phantoms as well as DTC metastases and other tumours≥0.7 ml on CT [29]. The average absolute deviation between measurements obtained with ITM and those obtained with CT has been documented elsewhere as ~9% for lesions 0.8–7.5 ml (n=31) and ~15% for lesions >7.5 ml (n=8) [29].

Statistics

For patient, disease, treatment and imaging characteristics, we generated baseline statistics, including, as applicable, the frequency, the median and range (minimum-maximum), and the mean±standard deviation (SD). We statistically compared intergroup differences in the baseline values using Pearson's χ^2 test for dichotomous variables or, when dichotomous variables had a small number of expected frequencies, Fisher's exact test. We applied the t test to statistically compare intergroup differences in variables having homogeneous variances and following an approximately Gaussian distribution. For variables having heterogeneous variances and following a Gaussian distribution, Welch's t test was computed. The asymptotic Wilcoxon rank sum test was used to compare variables with a skewed distribution. For all comparisons of baseline values, $p<0.05$ was considered statistically significant.

The calculation of the mean LDpA for each treatment group comprised the LDpAs of all lesions in the group that were defined as iodine-avid according to previously described criteria [31]. Since patients varied in their number of iodine-avid lesions, this approach meant that the calculation included more lesions from some individuals than from others. This situation could potentially introduce bias; however, our statistical model attempted to mitigate against such bias (see below). Moreover, we felt that using the mean, median, minimum or maximum LDpA for each patient would be an arbitrary choice that also could potentially introduce bias and beyond that, would obscure the actual dosimetric situation of many lesions.

As its primary statistical analysis, the study tested whether the mean LDpAs of the rhTSH group and the THW group were equivalent. For this purpose, a (1-2α) confidence interval (CI) of the difference between those means (mean rhTSH group LDpA − mean THW group

LDpA) was computed using a mixed model analysis of covariance (ANCOVA). Included in the model was the fixed factor, treatment group (rhTSH or THW) and possible covariables adjusting for the patient, disease, treatment or imaging characteristics found to differ significantly between the groups, except for biochemical variables (TSH, thyroid hormones) related to the difference in preparation methods. Most patients had more than one metastasis. Thus, repeated measurements existed and to account for them, the patients were included in the model as the random factor. The type I error, α, was set to 2.5%, resulting in a 95.0% CI. We performed all statistical calculations on SPSS for Windows, release 15.0.1 (SPSS Inc., Chicago, IL, USA, 2006) or on SAS for Windows Release 9.1 (SAS Institute, Inc., Cary, NC, USA, 2003).

Results

Patient and ^{124}I PET characteristics

Table 1 shows selected patient, disease, treatment and imaging characteristics for the rhTSH and THW groups. These groups did not differ statistically with respect to gender, height, weight, age at the study ^{124}I PET/CT, distributions of DTC histology classifications or T, N or M classifications, number of iodine-avid lesions per patient, proportion of patients without visible thyroid remnant, median total thyroid remnant volume, urinary iodine excretion or proportion of patients undergoing ^{124}I PET/CT before versus after their first RIT. The groups also did not differ significantly according to prevalence of anti-thyroglobulin (Tg) antibody seropositivity, interval between diagnosis of metastatic DTC and ^{124}I PET/CT or ^{124}I activity (data not shown).

However, six statistically significant differences between the groups suggested that the rhTSH patients tended to have more advanced disease than did the THW patients (Table 1). Namely, non-iodine-avid metastases were more than half again as prevalent in the rhTSH group as in the THW group. Additionally, the median number of iodine-avid cervical lymph node metastases per patient was lower, but the median number of iodine-avid distant metastases was higher in the rhTSH patients. Further, median stimulated serum Tg was over 16 times as high, and median prior cumulative radioiodine activity was over 3 times as high in the rhTSH group as in the THW group. Lastly, the rhTSH group tended to have received more diagnostic whole-body scintigraphy (dxWBS) scans than had the THW group.

As expected given the exogenous TSH administration and uninterrupted thyroid hormone therapy in the rhTSH patients but not the THW patients, the rhTSH group had significantly higher serum TSH (Table 1), free triiodothyronine and free levothyroxine concentrations (data not shown). However, in no patient did free triiodothyronine or free levothyroxine reach thyrotoxic levels (data not shown).

LDpA

Table 2 presents the results of the primary analysis, a mixed model ANCOVA addressing the treatment groups' mean LDpAs and the differences between these values. To adjust the estimated treatment effect for the statistically significant intergroup differences in patient, disease, treatment or imaging characteristics, the model factored in the prevalence of non-iodine-avid metastases, the median lesion counts/patient for cervical lymph node or distant metastases, the median stimulated serum Tg value, the mean cumulative prior ^{131}I activity and the median number of prior dxWBS scans.

As seen in Table 2, the mean LDpA computed by the mixed model ANCOVA for the rhTSH group was under 60% of that of the THW group. Nonetheless, the difference between the group mean LDpAs was not statistically significant. However, 85% of the CI, i.e. 51.4 Gy/GBq of the 60.4 Gy/GBq total, encompassed differences favouring THW.

Prospective within-patient comparison, MHH

Table 3 presents selected biochemical, ^{124}I PET and dosimetric variables for a 78-year-old woman at the MHH participating in a prospective within-patient comparison of LDpAs on ^{124}I PET/CT under rhTSH stimulation versus under THW stimulation. This comparison was conducted under an experimental protocol that was approved by the MHH Ethics Committee, and the patient provided written informed consent to participate.

The patient had pT4b N0 M1 disease according to the 5th edition of the Union Internationale Contre le Cancer staging system [21]. After total thyroidectomy, she received four THW-aided RITs totalling 44.4 GBq to ablate thyroid remnant (first RIT) or to treat pulmonary metastases (all four RITs). Throughout this patient's course, thoracic CT showed small lung metastases, which decreased in size after each RIT, remaining stable at the smaller sizes between therapies. Six days after her most recent RIT (7.4 GBq given 5 months before study entry), post-therapy whole-body scintigraphy revealed local recurrence on the left side of the thyroid bed and pathological uptake in the left adrenal gland. Shortly before study entry, neck US showed the same local recurrence, while FDG PET was slightly positive at this site and the left adrenal gland. The patient's most recent Tg measurement (THW-aided and performed 3 months before study entry) was 226.6 μg/l. At the time of

Table 2 Mean LDpAs by treatment group: mixed model ANCOVA[a]

Variable	Estimated means from the mixed model ANCOVA[a]		Difference in means (rhTSH group − THW group)	95% CI, difference in means	*p* value
	rhTSH group (n=27 patients, 71 iodine-avid metastases)	THW group (n=36 patients, 66 iodine-avid metastases)			
LDpA, Gy/GBq	30.6	51.8	−21.2	−51.4 to 9.0	0.1667

ANCOVA analysis of covariance, *CI* confidence interval, *LDpA* lesion absorbed dose in Gy per GBq of administered ^{131}I activity, *rhTSH* recombinant human TSH, *THW* thyroid hormone withdrawal

[a] Adjusted for the following baseline factors that statistically differed between the treatment groups: prevalence of non-iodine-avid metastases, median number per patient of iodine-avid cervical lymph node metastases, median number per patient of iodine-avid distant metastases, median stimulated serum thyroglobulin, mean prior cumulative radioiodine activity and median number of prior dxWBS scans

study entry, she was on suppressive thyroid hormone therapy (serum TSH <0.1 mU/l).

After two consecutive IM injections of rhTSH, 0.9 mg, she ingested 27.7 MBq ^{124}I and underwent ^{124}I PET/CT as described in the "Materials and methods" section. The patient began THW the day after the last rhTSH-aided PET scan at 48 h following the rhTSH injection. After approximately 4 weeks off thyroid hormone, when her TSH measured 96.91 mIU/l, she ingested 32.4 MBq ^{124}I. She received ^{124}I PET/CT at the same time points, performed according to the same methods and by the same operators as she had after rhTSH administration.

As seen in Table 3, the LDpA for this individual's local recurrence was tenfold higher and the mean LDpA for her distant metastases nearly threefold higher after THW than after rhTSH administration.

Figure 1 compares ^{124}I PET/CT images for the patient under rhTSH stimulation (a, c) versus under THW stimulation (b, d). As seen in the figures, THW-aided scans (using 32.4 MBq ^{124}I) provided superior image quality with respect to a cervical metastasis (Fig. 1a, b) and unlike the rhTSH-aided scans (using 27.7 MBq ^{124}I), visualised the adrenal gland metastasis (Fig. 1c, d).

Table 3 Selected biochemical, ^{124}I PET and dosimetric variables for a 78-year-old woman from the Hanover University School of Medicine undergoing prospective within-patient comparison of LDpA after rhTSH versus after THW

Variable	After rhTSH	After THW
Serum Tg, μg/l	147.8	316.0
Serum TSH, mU/l	>150	97
Urinary iodine, μg/g creatinine	80	57
^{124}I activity, MBq	27.7	32.4
LDpA, Gy/GBq for local recurrence	1.5	15.0
LDpA, Gy/GBq for distant metastases	4.0	11.6

CT computed tomography, *LDpA* lesion absorbed dose in Gy per GBq of administered ^{131}I activity, *PET* positron emission tomography, *rhTSH* recombinant human TSH, *THW* thyroid hormone withdrawal

Discussion

The present retrospective study and within-patient comparison aimed to apply ^{124}I PET/CT, the state-of-the-art method of measuring radioiodine kinetics in DTC [20], to answer an important clinical question: does use of rhTSH as a stimulation method for ^{131}I treatment of iodine-avid DTC metastases deliver an equivalent radiation dose to such lesions as does THW? As noted in the "Introduction" section, there is a paucity of published data on this issue using any dosimetric method. In our retrospective comparison, we sought to capitalise on data from a relatively large group of patients, while our within-patient comparison had the advantages of being prospective and controlled.

Taken together, the results of our work were suggestive: rhTSH delivered appreciably lower doses than did THW in both our retrospective study (Table 2) and our within-patient comparison (Table 3). However, in the retrospective study, the primary end-point was non-significant despite multiple significant intergroup differences in baseline patient characteristics indicating more advanced, poorer prognosis and more pretreated disease in the rhTSH group. Additionally, the prospective within-patient comparison involved only a single individual and hence must be considered anecdotal. Therefore, at the end of the day, the present study must be regarded as inconclusive. Nonetheless, we believe that our data provide a useful input to clinical decision making until such time as data from a large, prospective, within-patient lesion dose comparison become available.

Our observations of lower tumoural radiation doses per GBq of administered activity after rhTSH than after THW agree with the findings of the only previously published comparison of lesional radiation dose under the two TSH stimulation methods, a small pilot study by Pötzi et al. [17]. That prospective investigation included four patients with ten metastases in total (seven lung, two bone and one cervical), who served as their own controls. The investigators measured kinetics with ^{123}I scintigraphy/single photon emission CT. Because of uncertainties surrounding

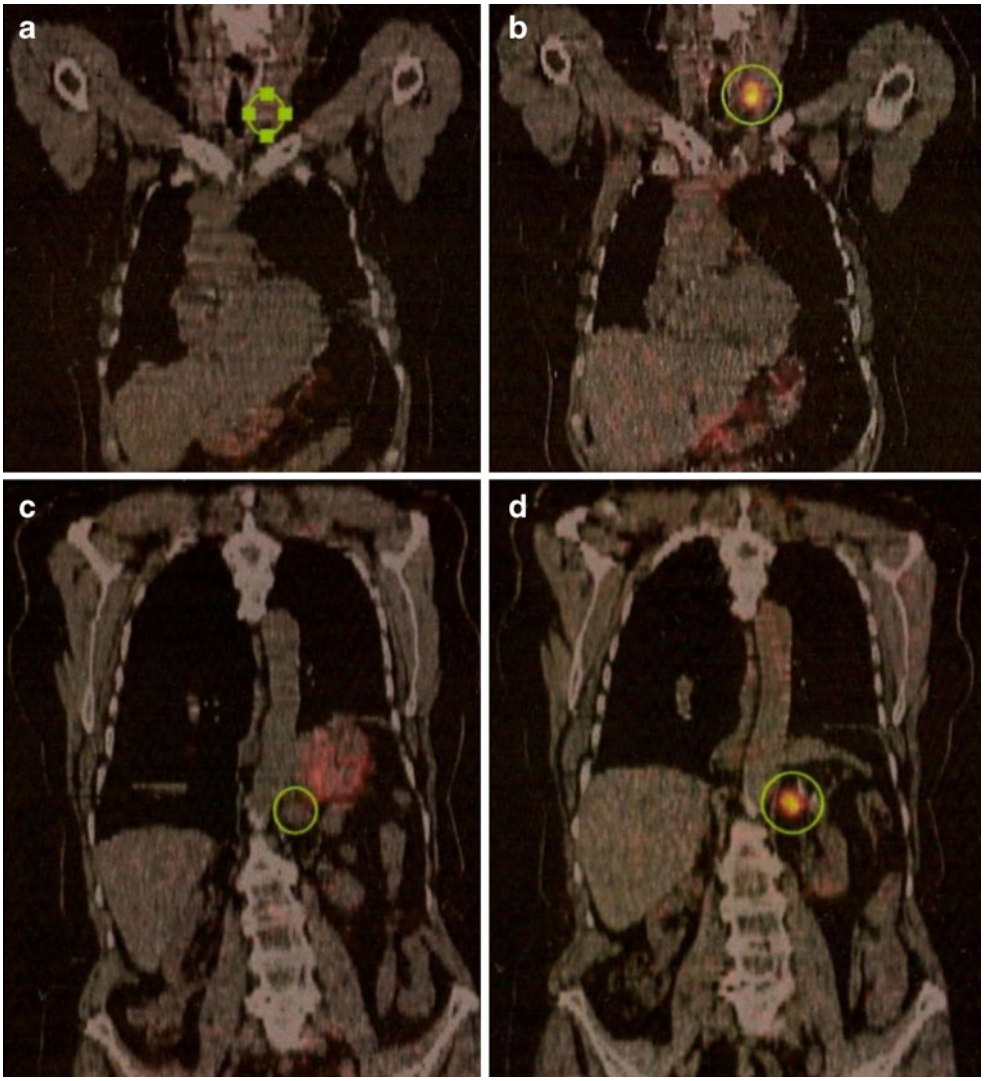

Fig. 1 ^{124}I PET/CT images of the MHH patient at 24 h after ^{124}I administration: iodine uptake in a cervical metastasis is substantially lower after rhTSH stimulation (**a**) than after THW (**b**). An iodine-avid adrenal gland metastasis is not visible after rhTSH (**c**) but visible after THW (**d**)

volumetry of metastases, especially small lesions, Pötzi and coworkers chose to use lesion cumulative activity in μCi*h as a surrogate marker for lesion dose. They found that in all ten lesions the cumulative activity was higher after THW than after rhTSH administration; the mean±SD (median) activities were 5.6±13.7 μCi*h (1.3 μCi*h) with rhTSH versus 9.5±26.3 μCi*h (3.4 μCi*h) with THW, and this difference was statistically significant ($p<0.05$).

One may speculate about factors that might contribute to our observations of lower LDpAs with rhTSH administration than with THW. As noted above, in our retrospective study, one such factor may be later-stage disease in the rhTSH patients than in their THW counterparts. The significantly different profiles of the treatment groups were unsurprising given the lack of formal treatment group inclusion criteria inherent in the retrospective nature of this study. Our mixed model ANCOVA that calculated the group mean LDpAs did adjust for six statistically significant differences between the groups in variables related to the advanced disease itself or to greater prior radioiodine exposure. Nonetheless, this adjustment may not have fully compensated for a more unfavourable outlook in the rhTSH patients. For example, the adjustment did not factor in their far greater proportion of lesions affecting the bone (41.4 vs 9.1%), which a large study [32] has shown to be significantly associated with poor radiation responsiveness. Nor did our analysis factor in the rhTSH group's older age and greater prevalences of N1 or M1 disease, i.e. nodal or distant metastases at diagnosis, and of follicular histology. While these differences did not attain statistical significance, they still may have been biologically and clinically relevant.

Another potential explanatory factor for the lower mean LDpAs with rhTSH than with THW is the contrasting characteristics of the two stimulation methods: the TSH elevation achieved with rhTSH is sharper but much shorter lived than that attained by THW [33]. More protracted TSH stimulation might result in enhanced DTC cell expression

or trafficking of NIS, which might lead to higher radioiodine uptake. Studies correlating the level of NIS on DTC cell surfaces with the area under the curve of TSH elevation are needed to investigate this possibility.

Of note, we have reported elsewhere [34] that in a retrospective comparison rhTSH and THW groups did not differ statistically with respect to thyroid remnant dose per GBq of administered activity which, indeed, was numerically higher with rhTSH. That finding dovetails with observations of ablation success rates that were not statistically different, i.e. healthy thyroid cell eradication rates, for the two methods in all seven clinical studies [7, 10, 35–39] comparing rhTSH-aided ablation when the radioiodine was given at the indicated 24 h after the second rhTSH injection against THW ablation.

Moreover, the large retrospective study of Tuttle et al. [38] noted low medium-term DTC recurrence rates that were not statistically different in rhTSH and THW ablation groups, both of which were overwhelmingly M0. This observation awaits confirmation in longer-term follow-up. However, the finding of Tuttle et al. suggests that at the micrometastatic level large radioiodine activities may have similar antitumour efficacy, presumably reflecting similar radiation doses, when aided by either TSH stimulation method. NIS might be sufficiently abundant on healthy thyroid remnant cell surfaces or even DTC micrometastatic cell surfaces that the difference (if any) between rhTSH and THW in their degree of NIS stimulation remains subclinical in these settings. In macrometastatic DTC cells with presumably greater NIS deficiencies, the difference in stimulation might be clinically apparent. It should be noted that rhTSH is not indicated for thyroid remnant ablation in patients with evidence of distant metastasis at the time of the procedure.

It has been speculated that “cold iodine” from continued thyroid hormone therapy might interfere with therapeutic radioiodine uptake [36, 40]. However, in our retrospective study, the treatment groups did not differ statistically in median urinary iodine excretion. Moreover, in neither that study nor our within-patient comparison did urinary iodine excretion levels ever exceed the 150 μg/l level widely considered to reflect clinically relevant iodine excess. Similarly, urinary iodine excretion did not differ significantly in the rhTSH phase versus the THW phase of the Pötzi et al. study [17].

We found wide inter- and intra-patient variation in tumour dose with either stimulation method, including lesions with a very low LDpA precluding safe and effective RIT. This observation was in line with our earlier results [20] and those of others performing post-therapeutic dosimetry using ^{131}I aided by rhTSH [16] or pre-therapeutic dosimetry using ^{124}I aided by THW [41] or by an unspecified stimulation method [42]. These findings highlight the need to individualise radioiodine activities and therapeutic modalities for patients with advanced DTC, and the value of ^{124}I PET/CT in helping to do so [20].

The present study and within-patient comparison have certain limitations besides those mentioned earlier. First, because small numbers of lesions at a given site in a given treatment group not infrequently precluded meaningful statistical analyses, our retrospective study did not compare the mean LDpAs of the TSH stimulation methods by site of metastasis. This could diminish generalisability to specific patient types.

Second, ^{124}I PET/CT is influenced by a variety of physical and radiobiological uncertainties that can lead to an error margin of up to 30%, as we have discussed in greater depth elsewhere [25]. However, these uncertainties may be presumed to similarly affect both treatment groups in the retrospective study and both phases of the within-patient comparison, given that essentially identical ^{124}I PET/CT methodology was applied under rhTSH and THW stimulation. We have not assessed methodology-related error rates in euthyroidism versus hypothyroidism, however.

Lastly, though in the retrospective study mean ^{124}I activities did not differ statistically between the treatment groups, in the within-patient comparison a 17% larger activity was given with THW than with rhTSH (Table 3; no statistical test performed). However, this discrepancy is unlikely to have influenced the LDpA findings in that comparison, since our methodology normalises that variable to the administered activity.

It is worth noting that based on the data in our retrospective study the mean LDpA after rhTSH, 30.6 Gy/GBq, would be sufficiently high that treatment with a typical empirical fixed 7.4 GBq activity would deliver 226 Gy to an “average metastasis”, well above the 80–100 Gy that is widely considered to be effective. However, based on the data in our within-patient comparison, the subject would receive adequate lesion doses of 86–111 Gy with THW, but insufficient lesion doses of 11–30 Gy with rhTSH. These estimates suggest that if our findings regarding relative LDpAs between rhTSH and THW are borne out, differences in this variable might have little clinical relevance in many, but not all instances.

In conclusion, we found some suggestions, but no statistically significant evidence, that rhTSH stimulation may result in a lower radiation dose to advanced DTC lesions per GBq of administered activity than does THW stimulation. A large, well-controlled, prospective, within-patient study is needed to resolve the clinically important question of whether lesion doses significantly differ between the two TSH stimulation methods. Until data from such a study become available, we suggest reserving rhTSH-aided treatment of metastatic DTC to patients who

are at high risk of tumour progression under THW or unable to tolerate THW, or to cases in which it is essential to preserve baseline abilities to work or study despite RIT.

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