Thyroid Uptake and Effective Half-Life of Radioiodine in Thyroid Cancer Patients at Radioiodine Therapy and Follow-Up Whole-Body Scintigraphy Either in Hypothyroidism or Under rhTSH

Robin Bacher, Melanie Hohberg, Markus Dietlein, Markus Wild, Carsten Kobe, Alexander Drzezga, and Matthias Schmidt

Department of Nuclear Medicine, University Hospital of Cologne, Cologne, Germany

Adjuvant radioiodine therapy (RITh) for differentiated thyroid carcinoma is performed either with thyroid hormone withdrawal or with administration of recombinant human thyroid-stimulating hormone (rhTSH). Heterogeneous results have been obtained on the impact of the method of patient preparation on thyroid uptake and whole-body effective half-life. A higher radiation exposure using thyroid hormone withdrawal for several weeks compared with rhTSH was reported in prior studies. It was the aim to examine whether these findings are reproducible in a modern protocol with a short interval between surgery and RITh. **Methods:** A retrospective study was performed on patients admitted for adjuvant RITh for differentiated thyroid carcinoma at the University Hospital of Cologne over a 5-y period from 2010. Dose rate measurements were analyzed for 366 patients, and subgroup analyses were performed for papillary thyroid cancer ($n = 341$) and follicular thyroid cancer ($n = 25$) patients, sex, length of hypothyroidism, and normal versus decreased glomerular filtration rate (GFR). **Results:** The median interval between surgery and RITh was 18 d for thyroid hormone withdrawal and 25 d for rhTSH ($P < 0.01$). The mean thyroid uptake was 4.2% ± 1.8% for the 300 hypothyroid patients versus 3.8% ± 1.6% ($P = 0.12$) for the 66 rhTSH patients. Whole-body half-life in the hypothyroid group was significantly longer at 19.3 ± 7.7 h versus 16.4 ± 4.6 h in the rhTSH group ($P < 0.01$). Results were predominantly influenced by data from the largest subgroup, that is, female papillary thyroid cancer patients. Within this group, whole-body half-life was significantly shorter in the rhTSH treatment arm. Duration of hypothyroidism and a decrease in GFR less than 60 mL/min/1.73 m^2 significantly influenced results, with an increased whole-body half-life occurring in the hypothyroid group. When patients returned for whole-body scintigraphy, thyroid, half-life, and whole-body half-life were significantly shorter in the rhTSH groups, resulting in a low thyroid and remaining-body dose. **Conclusion:** With a shortening of the time between surgery and adjuvant RITh, thyroid uptake is not significantly changed but whole-body half-life becomes longer in the hypothyroid group. Radiation exposure for most patients is not significantly different. However, patients with a hypothyroid phase of more than 4 wk, and in particular those with a decreased GFR, experience higher radiation exposure.

Key Words: differentiated thyroid carcinoma; radioiodine therapy; dosimetry; thyroid uptake; effective half-life; recombinant human thyroid-stimulating hormone

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In Germany, adjuvant radioiodine therapy (RITh) is given after thyroidectomy for differentiated thyroid cancer, except for papillary microcarcinomas, with the aim of improving disease-specific survival (*1*). International guidelines vary in their recommendations with regard to RITh. The British (*2*) and American Thyroid Association (*3*) guidelines are more restrictive, whereas Italian (*4*) and French (*5*) guidelines are generally in favor of RITh. Over the years, the time interval set between thyroidectomy and RITh has become shorter. Currently, RITh is often given 2–3 wk after surgery (*1*). Previous studies found differences in radiation exposure between patients treated in hypothyroidism versus rhTSH (*6–15*). The aim was to retrospectively examine thyroid uptake and effective half-life in patients with a shorter time interval between surgery and RITh, thus reflecting current therapeutic standards. A further aim was to characterize thyroid uptake and effective half-life during whole-body scintigraphy performed 6–9 mo after RITh for response assessment.

MATERIALS AND METHODS

Patients

From January 1, 2010, to December 31, 2014, 424 patients with a histopathologically confirmed diagnosis of differentiated thyroid cancer after total thyroidectomy underwent RITh at the University Hospital of Cologne. Patients with known metastases or with an initial activity of more than 4,000 MBq of radioiodine ($n = 23$), patients with a latency period between surgery and RITh of more than 4 mo ($n = 2$), and patients with an uptake in the thyroid bed of more than 10% (rated as incomplete surgery, $n = 33$) were excluded. Finally, 366 patients were analyzed (341 papillary thyroid carcinoma [PTC] and 25 angioinvasive follicular thyroid carcinoma [FTC] patients) from which 339 patients returned for whole-body scintigraphy 6–9 mo after initial treatment. Patients were prepared with a low-iodine diet.

Laboratory Values: Hypothyroidism Versus rhTSH

Thyroid-stimulating hormone (TSH), free T4, free T3, thyroglobulin, and thyroglobulin antibodies were measured in hypothyroid patients before administration of radioiodine (Immulite 2000; Diagnostic Products). In the hypothyroid group, no levothyroxine was given after

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For correspondence or reprints contact: Matthias Schmidt, Oberarzt, Arzt für Nuklearmedizin, FEBNM, Klinik und Poliklinik für Nuklearmedizin, Universitätsklinikum Köln, Department of Nuclear Medicine, University Hospital of Cologne, Kerpener Strasse 62, 50937 Köln/Cologne, Germany.
E-mail: matthias.schmidt@uk-koeln.de
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histopathologic diagnosis of differentiated thyroid carcinoma whereas in the rhTSH group levothyroxine was initially administered and only withheld for a short time of usually 8 d (3 d before rhTSH injection until day 2 after radioiodine application). When returning for whole-body scintigraphy after 6–9 mo, most patients received rhTSH with an interruption of levothyroxine for 8 d. To achieve hypothyroidism patients stopped levothyroxine 5 wk before radioiodine application and had intermittent liothyronine in weeks 2 and 3.

At initial adjuvant RITh, 300 patients were treated in hypothyroidism and 66 patients under rhTSH. The decision for hypothyroidism or rhTSH was based on physician counseling and patient preferences. Elder patients and especially those with comorbidities were preferentially prepared with rhTSH. For response assessment, whole-body scintigraphy was almost exclusively done under rhTSH ($n = 312$), whereas only 27 patients were admitted in hypothyroidism.

Dosimetry and Calculations

Postradioiodine whole-body uptake was measured immediately after radioiodine application and then twice daily every 12 h using a calibrated scintillation counter (ISOMED 2101; MED Nuklear-Medizintechnik Dresden GmbH) with a distance of 4.5 m between the patient and the instrument, ensuring that count rate losses due to dead-time effects of the scintillation counter were negligible. For thyroid measurements, the patient was positioned behind a whole-body lead plate with a hole for neck exposure only while the remaining body was shielded behind the lead plate. Calculations of the cumulated activity and effective half-life for the thyroid and whole body were based on these measurements. For this purpose, a numeric integration was performed for the period of the inpatient stay and a calculated extrapolation for the period thereafter.

The thyroid dose was calculated using the following formula (*16*):

$$D[Gy] = \tilde{A}[MBq*d]*E/M[g]$$

where E = 2.808 Gy*g/(MBq*d). A mass of 1 g was assumed for the remnant thyroid M[g]. The average absorbed energy per unit of mass deposited in the target organ (index k) was then calculated as a product of the cumulated activity ($\tilde{A}_h$) and the corresponding S value ($S_{(h\leftarrow k)}$):

$$D_{(k\leftarrow h)} = \tilde{A}_h * S_{(k\leftarrow h)}.$$

This equation was used for calculating the absorbed dose in the whole body and remaining body:

$$D_{(WB)} = \tilde{A}_{WB} * S_{(WB\leftarrow WB)},$$

where WB is whole-body, RB is remaining body, and T is thyroid:

$$D_{(RB)} = \tilde{A}_{RB} * S_{(WB\leftarrow WB)} + \tilde{A}_T * S_{(WB\leftarrow T)},$$

where the cumulated activity of the remaining body is defined as $\tilde{A}_{RB} = \tilde{A}_{WB} - \tilde{A}_T$. The therapeutically achieved half-life was estimated from measurements of thyroid and whole-body uptake estimated from readings taken from at least 5 points of uptake. Time–activity curves were generated for calculation of thyroid and whole-body half-life and cumulated activity.

Parameters analyzed were radioiodine activity (MBq) given to the patients, thyroid uptake (%), thyroid half-life (h), thyroid cumulated activity (MBq*d), and thyroid residence time (h) as well as whole-body half-life (h), whole-body cumulated activity (MBq*d) and whole-body residence time (h), and remaining-body dose (mGy). Results were calculated for patients in hypothyroidism versus rhTSH application. As we saw only 25 patients with angioinvasive FTC, calculations were focused on the predominant group of PTC patients. Subgroups included patients of younger versus older age, duration of the hypothyroid period (≤4 vs. >4 wk) and glomerular filtration rate (GFR) (<60 vs. ≥ 60 mL/min 1.73 m^2). GFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula (*17*). IBM SPSS Statistics (64-bit) was used for statistical analysis. Data are expressed as mean ± SD and 25–75 percentiles in brackets. Groups were compared using the Mann–Whitney test, and the level of significance was set at 0.05. The institutional review board approved this retrospective study, and the requirement to obtain informed consent was waived.

RESULTS

Adjuvant RITh

Patient characteristics are given in Table 1, and these parameters did not differ between groups. Patients in hypothyroidism had a mean TSH greater than 30 mU/L (25 percentile 31.1mU/L – 75 percentile 60.4mU/L). The mean TSH in FTC patients was higher than in PTC patients (63.2 [28.9–87.7] mU/L vs. 51.4 [31.6–60.0] mU/L). Patients under 60 y of age had a higher TSH than those of ≥ 60 y (52.8 [32.0–63.2] vs. 45.9 [29.3–48.5] mU/L). TSH increased over time without levothyroxine: TSH was 47.6 (31.0–54.8) mU/L in hypothyroid patients off levothyroxine for ≤4 wk whereas TSH was 75.9 (41.6–112.7) mU/L in patients who were without levothyroxine for >4 wk. GFR had no influence on TSH increase: TSH was 55.7 (29.9–69.6) mU/L in patients with GFR < 60 mL/min/1.73 m^2, and TSH was 52.1 (33.0–61.2) mU/L in patients with GFR ≥ 60 mL/min/1.73 m^2.

Table 2 provides dosimetric results for all patients. The median interval between surgery and adjuvant radioiodine was 18 d in the hypothyroid and 25 d in the rhTSH group ($P < 0.001$).

TABLE 1
Patient Characteristics

Characteristic	Hypothyroid, *n* (%*)	rhTSH, *n* (%*)	*P*
Sex (female/male)	216 (82.4)/84 (80.8)	46 (17.6)/20 (19.2)	0.71
Age (<60/≥60 y)	244 (83.3)/56 (76.7)	49 (16.7)/17 (23.3)	0.19
Histology (PTC/FTC)	281 (82.4)/19 (76.0)	60 (17.6)/6 (24.0)	0.42
T (T ≤ T2/>T2)	229 (83.3)/70 (78.7)	46 (16.7)/19 (21.3)	0.32
N (N0/N1)	203 (79.0)/81 (88.0)	54 (21.0)/11 (12.0)	0.06

*Row wise.

TABLE 2
Dosimetric Results for All Patients

Parameters of iodine kinetics	Hypothyroid (n = 300)	rhTSH (n = 66)	P
Activity (MBq)	3,417 ± 599	3,284 ± 728	0.34
Thyroid uptake (%)	4.2 ± 1.8	3.8 ± 1.6	0.12
Thyroid half-life (h)	30.6 ± 15.0	30.1 ± 14.6	0.86
Thyroid cumulated activity (MBq*d)	287 ± 209	250 ± 192	0.08
Thyroid residence time (h)	2.1 ± 1.5	1.9 ± 1.3	0.26
Thyroid dose (Gy)	801 ± 587	702 ± 540	0.09
Whole-body half-life (h)	19.3 ± 7.7	16.4 ± 4.6	≤0.01
Whole-body cumulated activity (MBq*d)	1,695 ± 547	1599 ± 498	0.31
Whole-body residence time (h)	11.9 ± 3.3	11.8 ± 3.4	0.64
Remaining-body dose (mGy)	90 ± 30	86 ± 27	0.36

No significant differences in dosimetric results were found except with regard to whole-body half-life. However, the whole-body half-life was less than 1 d in both groups and therefore resulted in no statistically significant differences in radiation exposure.

The largest subgroup were PTC patients (Table 3). Whole-body half-life was significantly shorter for female rhTSH patients, and less than 1 d in both male and female PTC patients. This did not result in any significant differences in thyroid or whole-body cumulated activities. The difference was more pronounced in patients younger than 60 y of age and less in patients aged 60 y or older, with a higher thyroid uptake in hypothyroid patients younger than 60 (P = 0.07), probably due to the higher TSH in patients under 60 y. Neither thyroid nor remaining-body dose were significantly different. In the male PTC group, the mean remaining-body dose was 92 mGy for hypothyroid and 91 mGy for rhTSH patients whereas in the female PTC group, values were 89 and 85 mGy, respectively ($P > 0.05$).

When analyzing duration of hypothyroidism, a long period of at least 4 wk between surgery and adjuvant RITh was associated with a significantly longer whole-body half-life in the hypothyroid in comparison to the rhTSH group (Table 4).

A reduced GFR had pronounced effects on the results. In hypothyroid patients with a GFR < 60 mL/min/1.73m^2, whole-body half-life was significantly different between groups and whole-body cumulated activity was significantly higher in the hypothyroid group, resulting in a higher remaining-body dose with a mean value of 127 mGy in the hypothyroid versus 87 mGy in the rhTSH group. Thus, renal function significantly influenced thyroid uptake and remaining-body dose (Table 5).

Response Evaluation with Whole-Body Scintigraphy

Patients treated under hypothyroidism had a mean TSH > 30 mU/L: PTC patients had a TSH of 79.3 (47.4–110.9) mU/L and 1 FTC patient had a TSH of 83.9 mU/L. Patients younger than 60 y had a higher TSH than those who were older (83.2 [49.2–111.8] vs. 49.2 [27.4–60.0] mU/L).

Almost all patients had their examination for response evaluation under rhTSH, and only 27 patients (26 PTC and 1 FTC) were admitted in hypothyroidism. For the whole group and for PTC patients, values differed significantly between hypothyroidism and rhTSH with significantly lower values in the rhTSH group despite a slight, nonsignificant elevation of applied activity (Table 6). This was seen in both male and female PTC patients.

TABLE 3
Dosimetric Results for Male and Female PTC Patients

	Male PTC patients			Female PTC patients		
Parameters of iodine kinetics	Hypothyroid (n = 79)	rhTSH (n = 16)	P	Hypothyroid (n = 202)	rhTSH (n = 44)	P
Activity (MBq)	3,480 ± 515	3,586 ± 441	0.19	3,382 ± 644	3,161 ± 791	0.04
Thyroid uptake (%)	4.9 ± 2.0	4.1 ± 1.3	0.14	3.9 ± 1.7	3.6 ± 1.7	0.32
Thyroid half-life (h)	38.1 ± 19.9	32.3 ± 15.5	0.22	28.0 ± 12.0	29.6 ± 14.7	0.57
Thyroid cumulated activity (MBq*d)	406 ± 284	298 ± 180	0.21	242 ± 152	225 ± 169	0.19
Thyroid residence time (h)	2.9 ± 2.1	2.0 ± 1.1	0.16	1.8 ± 1.1	1.8 ± 1.3	0.68
Thyroid dose (Gy)	1,139 ± 797	836 ± 505	0.21	674 ± 427	630 ± 475	0.22
Whole-body half-life (h)	22.7 ± 11.6	18.0 ± 6.6	0.06	18.1 ± 5.1	15.9 ± 3.7	0.01
Whole-body cumulated activity (MBq*d)	1,859 ± 557	1,754 ± 350	0.53	1,622 ± 527	1,547 ± 548	0.46
Whole-body residence time (h)	12.9 ± 3.4	11.8 ± 2.0	0.23	11.6 ± 3.1	11.9 ± 3.9	0.86
Remaining-body dose (mGy)	92 ± 28	91 ± 20	0.95	89 ± 30	85 ± 30	0.45

TABLE 4
Dosimetric Results for PTC Patients with More Than 4-Week Hypothyroidism in Comparison to rhTSH PTC Patients

Parameters of iodine kinetics	Hypothyroid (*n* = 31)	rhTSH (*n* = 60)	*P*
Activity (MBq)	3,298 ± 714	3,274 ± 736	0.79
Thyroid uptake (%)	4.5 ± 1.8	3.7 ± 1.6	0.07
Thyroid half-life (h)	38.0 ± 19.9	30.3 ± 14.8	0.05
Thyroid cumulated activity (MBq*d)	351 ± 272	244 ± 174	0.07
Thyroid residence time (h)	2.6 ± 2.0	1.8 ± 1.2	0.09
Thyroid dose (Gy)	985 ± 763	685 ± 488	0.07
Whole-body half-life (h)	21.6 ± 12.8	16.5 ± 4.7	0.02
Whole-body cumulated activity (MBq*d)	1,682 ± 530	1,602 ± 508	0.54
Whole-body residence time (h)	12.3 ± 2.7	11.9 ± 3.5	0.34
Remaining-body dose (mGy)	85 ± 28	87 ± 28	0.88

DISCUSSION

This retrospective analysis produced 2 main results. First, with shortening of the time between thyroidectomy and adjuvant RITh, the use of rhTSH resulted in a significantly shorter whole-body half-life. However, the mean absolute difference was only 2.9 h, and this did not translate into significant differences in the remaining-body dose. Nevertheless, in patients with more than 4 wk between surgery and RITh and particularly in those with a low GFR, remaining-body dose was significantly lower in the rhTSH group. Diminished GFR is a key factor, with significant influence on radiation exposure, and accordingly, patients with a GFR < 60 mL/min/1.73 m^2 in hypothyroidism had a significantly higher radiation exposure than did the group treated under rhTSH. Second, whole-body scintigraphy for response assessment is associated with low radiation exposure and currently in our clinic done almost exclusively with rhTSH.

Table 7 compiles publications comparing the effect of hypothyroidism and rhTSH on whole-body dose, half-life, or residence time (*6–15*). Most publications are based on studies with a limited number of patients. Our retrospective analysis comprises the largest number of patients analyzed so far and only the studies of Menzel et al. (*6*) and Remy et al. (*10*) analyzed more than 200 patients. The age group is comparable in all studies analyzing patients with a mean age in the late 40s or 50s.

In comparison to previously published studies, our patients had a rather short time interval between surgery and adjuvant RITh of 18 d. Only in the study of Grenfell et al. (*15*) was this interval within the same range, and they found no differences in whole-body half-life between the rhTSH and hypothyroidism groups. TSH values in the literature show that these are usually much higher than the commonly accepted threshold of 30 mU/L. Former prospective randomized controlled trials had longer hypothyroid intervals of several weeks (*18,19*).

Most studies report lower whole-body radiation exposure in the rhTSH versus hypothyroid group (*6–14*). Comparison of these publications reveals considerable differences in methodology, especially in the methods for measuring thyroid uptake and effective half-life. Both parameters, thyroid uptake and effective half-life, are key determinants of radiation exposure. Carvalho et al. (Portuguese Oncology Institute, Lisbon, Portugal) used a radiation detector to measure whole-body retention at a distance of 1 m 48 h after radioiodine application (*12*). No serial measurements were performed (*12*). Ravichandran et al. used sequential measurements with a digital autoranging β-γ survey instrument at

TABLE 5
Dosimetric Results for Hypothyroid PTC Patients with GFR ≥ Versus < 60 mL/min/1.73m^2 in Comparison to rhTSH PTC Patients

Parameters of iodine kinetics	Hypothyroid normal GFR (*n* = 227)	rhTSH (*n* = 60)	*P*	Hypothyroid low GFR (*n* = 20)	rhTSH (*n* = 60)	*P*
Activity (MBq)	3,385 ± 634	3,274 ± 736	0.36	3,508 ± 512	3,274 ± 736	0.23
Thyroid uptake (%)	4.1 ± 1.8	3.7 ± 1.6	0.28	4.7 ± 1.5	3.7 ± 1.6	0.02
Thyroid half-life (h)	31.2 ± 15.5	30.3 ± 14.8	0.73	27.2 ± 8.3	30.3 ± 14.8	0.76
Thyroid cumulated activity (MBq*d)	277 ± 195	244 ± 174	0.14	311 ± 171	244 ± 174	0.06
Thyroid residence time (h)	2.0 ± 1.5	1.8 ± 1.2	0.37	2.1 ± 1.1	1.8 ± 1.2	0.16
Thyroid dose (Gy)	774 ± 548	685 ± 488	0.17	873 ± 481	685 ± 488	0.06
Whole-body half-life (h)	19.4 ± 8.0	16.5 ± 4.7	≤0.01	19.0 ± 4.5	16.5 ± 4.7	0.02
Whole-body cumulated activity (MBq*d)	1,619 ± 473	1,602 ± 508	0.89	2,325 ± 807	1,602 ± 508	≤0.01
Whole-body residence time (h)	11.6 ± 2.8	11.9 ± 3.5	0.88	15.7 ± 4.7	11.9 ± 3.5	≤0.01
Remaining-body dose (mGy)	86 ± 25	87 ± 28	0.94	127 ± 45	87 ± 28	≤0.01

TABLE 6
Dosimetric Results for Whole-Body Scintigraphy

Parameters of iodine kinetics	Hypothyroid (n = 27)	rhTSH (n = 312)	P
Activity (MBq)	403 ± 88	412 ± 83	0.11
Thyroid uptake (%)	4.8 ± 3.5	3.6 ± 5.2	≤0.01
Thyroid half-life (h)	15.0 ± 2.6	12.5 ± 3.1	≤0.01
Thyroid cumulated activity (MBq*d)	18 ± 9	14 ± 12	≤0.01
Thyroid residence time (h)	1.1 ± 0.5	0.8 ± 0.7	≤0.01
Thyroid dose (Gy)	51 ± 27	39 ± 23	≤0.01
Whole-body half-life (h)	13.6 ± 3.7	11.5 ± 4.0	≤0.01
Whole-body cumulated activity (MBq*d)	197 ± 69	169 ± 74	0.01
Whole-body residence time (h)	11.6 ± 3.1	9.9 ± 4.2	≤0.01
Remaining-body dose (mGy)	11 ± 4	10 ± 3	0.01

1 m in the air providing μSv/h (*11,13*). Grenfell et al. (Royal Adelaide Hospital, Australia) took serial measurements in μSv/h at a distance of 1 m (*15*). Hänscheid et al. (Würzburg, Germany) combined whole-body probe measurements, scintigraphic whole-body imaging, and blood sampling (*8*). One important aspect of the study of Hänscheid et al. was that the variability of the results increased with a lowering of the distance between patient and measurement device. The advantage of our methodology is that the selected distance of 4.5 m between patient and detector minimizes count rate losses due to dead-time effects of the scintillation counter. In addition, our results are fairly robust with regard to minimal differences in patient positioning, which may occur in the course of serial measurements. Other authors used blood samples or calculated a red-marrow absorbed dose, which we did not do in our retrospective analysis (*8,9,14*).

Absolute values for whole-body half-life differ in the literature. Ravichandran et al. reported about 16.45 h in the hypothyroidism group versus 12.35 h in the rhTSH group (*11,13*). Our values for whole-body half-life were longer with 22.7 ± 11.6 h for hypothyroid male and 18.1 ± 5.1 h for hypothyroid female patients whereas in the rhTSH group values were 18.0 ± 6.6 h for male and 15.9 ± 3.7 h for female patients. However, Ravichandran et al. also reported a whole-body half-life of 22 h in a previous cohort of patients, which compares well with our data (*11*).

It is well established that thyroid half-life is longer than whole-body half-life, as the thyroid stores thyroid hormones. In male hypothyroid patients, thyroid half-life was 38.1 ± 19.9 h whereas in the rhTSH group it was 32.3 ± 15.5 h. Ravichandran et al. measured 48.2 h in 8 rhTSH patients (*11,13*). Current developments in radioiodine therapy for differentiated thyroid cancer decrease the administered activity. Lower ^{131}I activity could potentially be used especially in hypothyroid patients aiming to achieve comparable thyroid doses as in the rhTSH group and resulting in a more balanced residual body dose.

Iodine kinetics are influenced by the method of patient preparation: a higher renal clearance of radioiodine under rhTSH reduces the mass of radioiodine available for transport into thyroid tissue. This may explain why thyroid uptake was lower in the

TABLE 7
Literature Compilation of Dosimetric Studies Examining Iodine Kinetics in Hypothyroid and rhTSH Patients

First author and year of publication	THW/rhTSH (n)	Age THW/ rhTSH (y)	Latency OP-RIT (d)*	THW TSH (mU/L)	Body dose, half-life or residence time	Thyroid dose, half-life or residence time
Menzel 2003 (*6*)	163/64	50/57	≥28	Ø~50	rhTSH < THW	?
Sisson 2003 (*7*)	87/10	44/?	?	Ø117	rhTSH < THW	?
Hänscheid 2006 (*8*)	33/29	?/?	?	Ø84	rhTSH < THW	rhTSH > THW
Vaiano 2007 (*9*)	29/17	46/52	≥28	?	rhTSH < THW	rhTSH > THW
Remy 2008 (*10*)	218/36	48/44	≥35	Ø69	rhTSH < THW	?
Carvalho 2012 (*12*)	50/50	50/48	≥56	Ø59	rhTSH < THW	?
Ravichandran 2014 (*13*)	81/22	?/?	≥35	?	rhTSH < THW	rhTSH < THW
Grenfell 2015 (*15*)	31/19	49/48	21 (median)	?	rhTSH = THW	?
Guo 2015 (*14*)	9/6	41/58	≥28	?	rhTSH < THW	?
Ravichandran 2016 (*32*)	28/14	?/?	≥28	Ø88	rhTSH < THW	?
Data presented in this publication	281/60	46/51	18 (median)	Ø51	rhTSH = THW	rhTSH = THW

*Or if not reported, time of L-T4 withdrawal.
THW = thyroid-hormone withdrawal; OP–RIT = time between surgery and radioiodine therapy (d).

rhTSH group. However, the differences we observed, like those of Hänscheid et al. (*8*), were not statistically significant. Our findings are supported by compartment model calculations. For a given transfer coefficient, the maximal uptake and the residence time in the target tissue depend almost linearly on the blood residence time, which is inversely proportional to the renal clearance (*8*). Other parameters such as ingestion of stable iodine may also influence uptake. In 1 levothyroxine molecule, the iodine atomic weight accounts for two thirds of the entire levothyroxine molecular weight. Thus, a daily dose of 100–150 μg of levothyroxine represents a daily intake of 70–100 μg of iodine (*14*). At least parts of iodine are made biologically available. Löffler et al. showed that urinary iodine excretion was significantly higher in patients under rhTSH and levothyroxine medication in comparison to hypothyroidism (*20*). The duration of pausing levothyroxine before radioiodine therapy should therefore influence thyroid uptake.

The absorbed dose to the remnant is difficult to calculate and any reported values must be interpreted with caution. The remnant volume cannot usually be measured precisely shortly after operation and calculations may assume volumes as small as 1 mL (*8*). Therefore, it was suggested to rather rely on mean residence time instead of remnant absorbed doses. Remnant residence time depends on both uptake and half-time and is proportional to the energy deposited in the remnant volume (*8*).

Diminished kidney function appears to be a key component for radiation exposure (*21–23*). Coura-Filho et al. reported on a significant GFR decrease from 94 ± 19 to 76 ± 16 mL/min/1.73 m^2 ($P = 0.009$) in 14 hypothyroid patients (TSH > 30 μIU/mL) while GFR was preserved under rhTSH with 91 ± 18 mL/min/1.73 m^2 at baseline and 93 ± 15 mL/min/1.73 m^2 after rhTSH (*21*). Hypothyroidism is known to decrease effective renal plasma flow and GFR (*22*). As the kidneys express thyroid-related genes, TSH may have a direct effect on kidney function (*23*).

In our study we used a short-term levothyroxine withdrawal (3 d before rhTSH injection until day 2 after radioiodine application) in the group that received rhTSH. The short-term levothyroxine withdrawal is used to reduce iodine intake (*20*). In an earlier group of patients, we did not observe the development of hypothyroidism within a few days of levothyroxine withdrawal. However, small influences on kidney function during short-term levothyroxine withdrawal cannot be excluded. Grenfell et al. failed to detect a significant difference in effective half-life between rhTSH and hypothyroidism (*15*). These authors found an effective half-life of 13.29 ± 6.29 h in hypothyroidism versus 11.51 ± 5.28 h under rhTSH ($P = 0.761$). Though effective half-life was longer in the hypothyroidism group, the difference was not statistically significant. This may be explained by the small patient group with 31 hypothyroid patients and 19 patients under rhTSH but it may also reflect the relatively short hypothyroid period. Most patients had a hypothyroid period of less than 3 wk. As an explanation for their findings, the authors assume that the decrease in renal clearance was less pronounced than that observed in other studies (*15*).

There are potential limitations due to our retrospective data analysis. Patients in the rhTSH group were about 9 y older than the patients treated in hypothyroidism. This may reflect the clinical decision to treat patients of increasing age preferentially with rhTSH due to comorbidities. A reduced kidney function was one aspect to use rhTSH. The rate of patients with a GFR < 60 mL/min was 8.1% in hypothyroid patients and thus slightly higher than the 5.7% in rhTSH-stimulated patients ($P = 0.545$). Patients with cardiac dysfunction or some psychiatric conditions are preferentially prepared with rhTSH (*24,25*).

It is generally agreed that the use of rhTSH provides a better quality of life in comparison to hypothyroidism (*26–28*). We did not measure quality of life in our patients, but from clinical experience it can be said that the avoidance of hypothyroidism provided a better quality of life. In addition, the injection of rhTSH is very well tolerated in almost all patients, and side effects are either nonexistent or negligible.

The use of rhTSH is associated with drug costs (*26*) but these are counterbalanced in the German DRG system. The costs of rhTSH may also be counterbalanced by reduced absence from work. rhTSH was associated with a significantly shorter hospital stay in our patients. However, its exact economic impact is difficult to ascertain as there are considerable differences in the healthcare systems between countries.

It is common practice in Germany to perform whole-body scintigraphy in combination with measurements of stimulated thyroglobulin for response assessment 6–9 mo after radioiodine therapy. Results of whole-body scintigraphy and stimulated thyroglobulin level determine response and prognoses, for example, excellent response is usually defined as a TSH-stimulated thyroglobulin of < 1 ng/mL in the absence of structural or functional evidence of disease (and in the absence of antithyroglobulin antibodies) and with no pathologic uptake on whole-body scintigraphy. In our patients, dosimetric results at whole-body scintigraphy were more favorable when using rhTSH, with a remaining-body dose as low as 10 mGy.

Worldwide, the use of whole-body scintigraphy is a controversial discussion. In our department, we do not rely on stimulated thyroglobulin measurements only because there are patients with iodine-avid metastases without measurable thyroglobulin. In our understanding, radioiodine therapy is done to eliminate iodine-concentrating thyroid remnants and metastatic tissue and the reason to perform whole-body scintigraphy is to demonstrate the absence of such tissue, especially the absence of iodine-avid metastases. The result is crucial to compare whole-body scintigraphy with subsequent examinations in the case of suspicion of recurrence. A newly iodine-avid lesion in comparison to previously normal findings indicates recurrence. Whole-body scintigraphy can be done with little radiation exposure currently. A low thyroglobulin level does not exclude the presence of iodine-avid metastases: in a recent publication Campennì et al. identified 82 of 570 (14.4%) patients with metastases at initial evaluation of whom 73 patients (90.2%) had thyroglobulin levels < 1 ng/mL (*29*). Nascimento et al. found disease persistence or recurrent disease in 8 of 242 (3.3%) with iodine-avid lesions despite a normal thyroglobulin level (*30*). Gonzales-Carvalho et al. showed that a complete omission of whole-body scintigraphy in the surveillance of differentiated thyroid carcinoma is justified once whole-body scintigraphy is negative and stimulated thyroglobulin is below the functional sensitivity (with no evidence of thyroglobulin antibodies), as patients showing this combination of test results especially 12 mo after radioiodine therapy show an at worst marginal risk of recurrence (*31*).

CONCLUSION

This retrospective analysis of 366 patients, comparing hypothyroidism with rhTSH for adjuvant RITh and whole-body scintigraphy, showed a significantly lower whole-body half-life for the rhTSH groups. The short whole-body half-life of less than 1 d in both groups resulted in roughly equal dosimetric results for the entire patient cohort. However, subgroups could be defined between which more differences emerged. Hypothyroidism of more than 4 wk and especially a decreased GFR resulted in higher radiation exposure in the hypothyroid versus rhTSH group. In our clinic, whole-body scintigraphy is currently almost exclusively done after rhTSH and was associated with a low thyroid- and remaining-body dose.

DISCLOSURE

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