

Iodine Biokinetics and Dosimetry in Radioiodine Therapy of Thyroid Cancer: Procedures and Results of a Prospective International Controlled Study of Ablation After rhTSH or Hormone Withdrawal

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Technical aspects and results of the dosimetric assessments of postoperative radioiodine ablation in the framework of an international, prospective, controlled, randomized, comparative study of the effectiveness of ablation therapy with 3.7 GBq ¹³¹I in differentiated thyroid cancer after stimulation with recombinant human TSH (rhTSH) or by thyroid hormone withdrawal (THW) are presented. **Methods:** Sixty-three patients were randomized after thyroidectomy to either the THW or the rhTSH group. Scintigraphic neck images were acquired starting 48 h after radioiodine administration to assess biokinetics in the thyroid remnant. The activity in blood samples was quantified and data from whole-body probe measurements and scintigraphic whole-body scans were combined to deduce retention curves in blood and whole body, respectively. The absorbed dose to the blood was calculated using a modified approach based on the formalism of the MIRD Committee of the Society of Nuclear Medicine. **Results:** The effective half-time in the remnant thyroid tissue was significantly longer after rhTSH than THW (67.6 ± 48.8 vs. 48.0 ± 52.6 h, respectively; $P = 0.01$), whereas the observed differences of the mean 48-h ¹³¹I uptakes ($0.5\% \pm 0.7\%$ vs. $0.9\% \pm 1.0\%$ after THW; $P = 0.1$) and residence times (0.9 ± 1.3 vs. 1.4 ± 1.5 h after THW; $P = 0.1$) between the rhTSH and THW groups were not statistically significant. The specific absorbed dose to the blood was significantly ($P < 0.0001$) lower after ad-

ministration of rhTSH (mean, 0.109 ± 0.028 mGy/MBq; maximum, 0.18 mGy/MBq) than after THW (mean, 0.167 ± 0.061 mGy/MBq; maximum, 0.35 mGy/MBq), indicating that higher activities of radioiodine might be safely administered after exogenous stimulation with rhTSH. **Conclusion:** Indication of an influence of the residence time of radioiodine in the blood on the fractional uptake into thyroid remnant was found. A novel regimen is proposed in which therapeutic activities to be administered are determined from the individual specific blood dose.

Key Words: differentiated thyroid cancer; radioiodine therapy; rhTSH; blood dose; dosimetry

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Radioiodine therapy has proven to be a safe and effective method in the treatment of patients with differentiated thyroid carcinoma (DTC). The target dose is the determinant for successful therapy, and the decisive parameters are the therapeutic activity and retention of radioiodine in the target volume.

There is no consensus on the activity of ¹³¹I to be administered. Usually 1.1–3.7 GBq (30–100 mCi) is prescribed for the first radioiodine therapy after thyroidectomy in newly diagnosed DTC patients to ablate the remaining glandular tissue. Higher amounts of ¹³¹I are given in subsequent therapies or in case of metastatic disease. Usually the activity is limited for safety to around 7.4 GBq (200 mCi).

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However, not uncommonly, a higher administered activity is desired to achieve higher tumor doses. To avoid serious complications, the commonly used dose concept published by Benua et al. (1) for radioiodine treatment of DTC restricts the blood dose to <2 Gy (200 rad). In their protocol, measurements of iodine retention in the blood and whole body with a tracer activity are required to estimate the blood dose before the radioiodine therapy. The method has been applied successfully (2–4).

The second important factor for the target dose is the iodine retention in the target tissue. The retention depends primarily on the degree of cell differentiation and normal physiologic functions of the tissue and is widely influenced by the thyroid-stimulating hormone (TSH) concentration in the blood and possibly by other parameters such as the individual iodine supply.

Recombinant human TSH (rhTSH, Thyrogen; Genzyme Corp.) has been developed for exogenous TSH stimulation in thyroid cancer patients remaining on thyroid hormone therapy. Clinical studies have shown that administration of rhTSH promotes radioiodine uptake and thyroglobulin production by thyroid cells with comparable efficacy to hypothyroidism for diagnosing residual or recurrent cancer (5). Furthermore, initial trials using rhTSH as a preparation for postoperative thyroid remnant ablation have been reported (6–11). The radiation dose to blood was found to be lower after stimulation with rhTSH than that in patients after thyroid hormone withdrawal (THW) (8,12), which most likely was due to the more rapid renal iodine clearance in euthyroidism. Additionally, longer effective half-times in thyroid remnants have been observed in euthyroidism (12). However, to our knowledge, only a few comparative dosimetric studies have been published.

We now report a prospective, randomized, controlled, multinational trial of postoperative radioiodine ablation of thyroid remnant tissue quantifying differences in iodine kinetics in euthyroidism after rhTSH stimulation and in the hypothyroid state after THW. The primary objective of the trial was to compare the effectiveness of the 2 regimens concerning thyroid remnant ablation (10). The protocol combines measurements with a γ -probe or survey meter with information gained from late scintillation camera imaging and blood sampling to calculate remnant residence times and blood doses, respectively, in ablation therapy of DTC.

In this work, the protocol and its technical aspects are introduced and the results of the dosimetric part of the study are described in detail (an Appendix to this article and supplemental Table 3 are available online only, at <http://jnm.snmjournals.org>). The findings may have impact on further strategies of radioiodine dosage and blood dose-dependent treatment.

MATERIALS AND METHODS

Design of Study

This randomized, controlled, open-label study involved 4 centers in Europe and 5 in North America (10). The protocol was

approved by each site's institutional review board and an independent ethics committee.

Sixty-six adult patients with newly diagnosed differentiated papillary or follicular thyroid carcinoma and recent surgery gave consent to participate in the study. Details regarding patient recruitment characteristics have been previously described (10). All patients underwent total or near-total thyroidectomy. Within 14 d after thyroidectomy, the patients were randomized to therapy while euthyroid after stimulation with rhTSH or while hypothyroid after THW. All patients were treated by radioiodine therapy with 3.7 GBq (100 mCi) ^{131}I without preceding diagnostic scanning and after a low-iodine diet for 2 wk.

Patients in the rhTSH group received levothyroxine therapy for 4–6 wk after thyroidectomy, until the serum TSH concentration was <5 mU/L. Then, 0.9 mg rhTSH (Thyrogen) was administered intramuscularly on 2 consecutive days. Radioiodine was administered 24 h after the second administration of rhTSH. Patients randomized to the THW group did not receive thyroid hormone therapy. Therapeutic radioiodine was administered after their endogenous serum TSH concentration was >25 mU/L. Levothyroxine therapy started after the last dosimetric measurements for these patients to have unvaried conditions during the investigation, although it may not be expected that an earlier beginning would significantly influence the iodine kinetics in the remnant and the remainder of the body.

Whole-body probe measurements and blood collections (2 mL whole-blood samples) were conducted 2, 6, 24, 48, 72–96, and 96–168 h after the administration of ^{131}I to obtain time–activity curves. Additionally, the patients underwent whole-body scanning and remnant neck imaging at 48, 72–96, and 96–168 h.

Operational Procedures

Calibrated probes or survey meters with a linear range up to a minimum of 100 $\mu\text{Gy/h}$ and a resolution of <0.1 $\mu\text{Gy/h}$ or corresponding counting rates were used for the probe measurements. All measurements for an individual patient were conducted with the same probe as conjugate (anterior and posterior) counts at a distance of 2 m using a reproducible measuring geometry. Every probe measurement of the patient was accompanied by measurements of a calibration standard and the actual background counting rate.

The well counters to quantify the blood activity concentrations at each site were calibrated for ^{131}I and quality checked with *in vitro* standards of well-known activities.

All scintillation camera images of the patient were acquired with the same dual-head camera system and the same set of high-energy ^{131}I collimators. The camera settings (width of the energy window, 15%; acquisition matrix, 256×256 for static neck images and $1,024 \times 256$ for whole-body scans; scan speed of whole-body acquisitions, 20 cm/min) were identical for all patients. Before the first imaging of every patient, the camera system was checked to meet the uniformity specifications of the National Electrical Manufacturers Association (13) and to be capable of measuring activities of 5% of the ablation activity linearly without major dead-time problems. The linearity check, basic sizing of the camera pixels, and assessment of the detection efficiency of the camera system were performed with identical sets of calibration sources in each site. A subset of the sources was always scanned together with the patient for quality control.

The data extraction was performed by drawing regions of interest (ROIs) at each site according to a dosimetry operational

manual with detailed instructions that was distributed to all participating centers before the beginning of the study. ROIs as indicated in Figure 1 were marked in the 48-h anterior images and then “flipped” to the posterior images and copied to the corresponding images of the later scans.

All data from the dosimetric measurements were transmitted from the study sites to the Dose Coordination Center (Würzburg), where the dosimetry results were determined centrally with the identical evaluation procedure for every patient.

Remnant Residence Time

The net remnant counting rates in the neck scans were converted to activity values using the scintillation camera detection efficiency as measured with the calibration sources and an attenuation correction according to a transmission factor of 0.3. Remnant uptake at nominal time points 48, 72–96, and 96–168 h was determined from the correspondent remnant activity and the administered activity. An exponential decay function was fit to the uptake values. The effective half-time in the remnant and the remnant residence time were deduced from the decay constant and the area under the curve, respectively.

Absorbed Dose to Blood

The absorbed dose to the blood was calculated with a modified method deduced from a procedure originally described by Thomas et al. (3), which hereafter is referred to as standard method. The approach is based on the formalism of the MIRD Committee of the Society of Nuclear Medicine. Published *S* values (14–16) were used to account for contributions of activity in the blood and the remainder of the body to the blood dose. A review of the underlying theory of blood dosimetry is provided in the Appendix (online).

Scintigraphic imaging is the most precise tool to quantify radioiodine in the remnant and the whole body. In contrast to diagnostic investigations, scintillation camera systems cannot be used to quantify the activity in a patient within the first hours after the administration of therapeutic ¹³¹I activities because of uncertainties introduced through dead-time characteristics. On the other hand, scintillation camera measurements are expected to be more precise at later time points when the whole-body activity is small. Therefore, the geometric mean values of the anterior and posterior

net counts of probe and camera measurements were combined to evaluate the decay curve of the activity in the whole body. The value obtained in the first probe count nominally 2 h after administration with no interim excretion was used to normalize all successive measurements to fraction of administered activity (activity at 2 h = 100%).

The time–activity functions used to calculate the residence times in the whole body and blood were assumed to be biexponential, unless the slowly decaying component was negligible, and were fit by minimizing χ^2 . The time–activity curves of the first patient treated according to the protocol are shown in Figure 2.

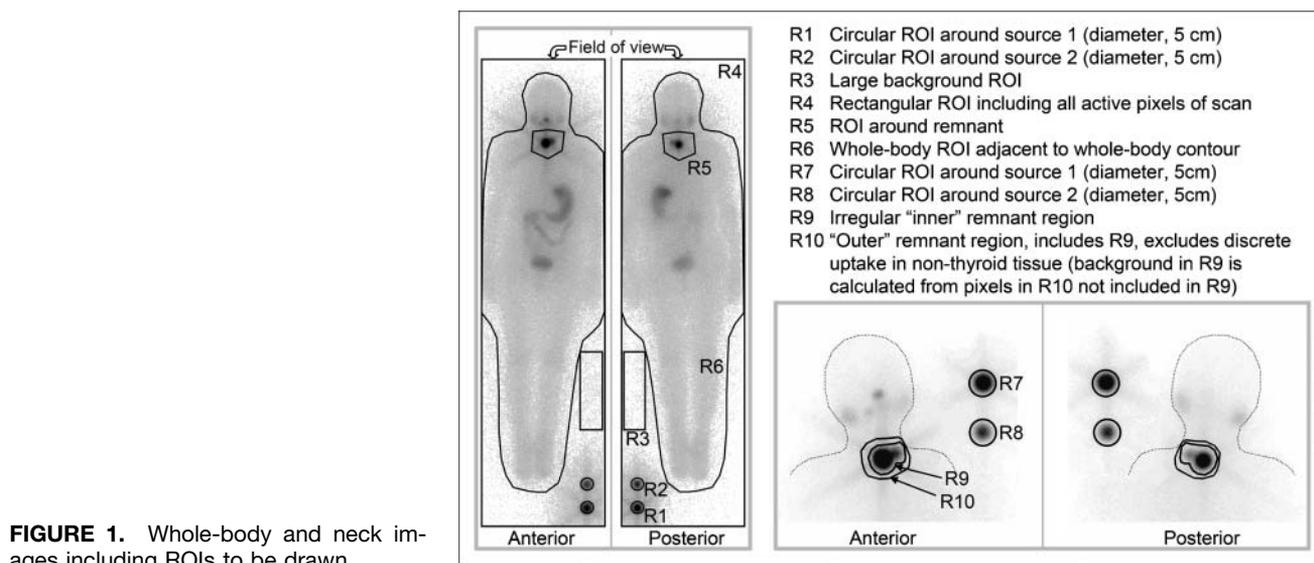
Statistical Evaluation

Differences between the 2 groups of patients were tested with the Wilcoxon rank test for statistical significance.

RESULTS

Sixty-three of 66 patients enrolled were randomized (33 rhTSH, 30 THW). The measurements of the iodine kinetics in the remnant were in compliance with the protocol in 62 patients (33 rhTSH, 29 THW). All patients had valid blood data, and 59 patients had complete and valid whole-body data (32 rhTSH, 27 THW). The other patients were excluded from the dosimetric assessment because of significant protocol violations, primarily due to technical problems during the measurements. One patient in the THW group showed distant metastases on the posttherapy whole-body scan. This patient was included in the dosimetric assessment.

The baseline TSH levels before therapy were 1.1 ± 1.3 mU/L (range, 0–4.8 mU/L) and 83.9 ± 51.2 mU/L (range, 25.5–254.6 mU/L) in the rhTSH and THW groups, respectively. The mean creatinine clearance was higher in the rhTSH group (143.5 ± 92.4 mL/min) than that in the THW group (92.4 ± 46.2 mL/min). No significant difference was observed in the groups with regard to the following parameters: age, sex, weight, height, body mass index, histologic tumor type, and TNM classification (10). The mean area of remnant tissue in the 48-h neck scan was $16.2 \pm$



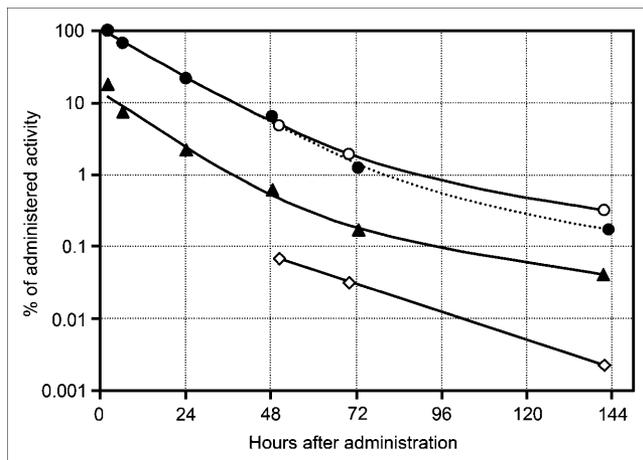


FIGURE 2. Activity in whole body (○, scintillation camera; ●, probe measurements), remnant (◇), and blood (▲) of the first patient treated according to the protocol as a function of time after administration.

10.4 cm² in the rhTSH group versus 18.8 ± 17.0 cm² in the THW group, indicating that remnant size was not significantly different in both populations.

The remnant ablation rate was 100% (10) according to the primary criterion prospectively defined in the study protocol that is, thyroid bed activity invisible or, if visible, <0.1% of the administered activity.

Mean values ± SD of iodine biokinetics in thyroid remnants after rhTSH and THW are listed in Table 1. The effective half-time in the remnant thyroid tissue was significantly longer after rhTSH than after THW ($P = 0.01$), whereas the observed differences of the mean 48-h ¹³¹I uptakes and residence times between the rhTSH and THW groups were not statistically significant ($P = 0.1$). The distributions of the observed 48-h uptakes, effective half-times, and residence times in thyroid remnants are shown in Figure 3.

The analysis of whole-body and blood radioiodine kinetics showed a lower uptake at 48 h and a lower mean residence time after rhTSH stimulation than after THW (Table 2). The mean specific absorbed doses to the blood were significantly lower ($P < 0.0001$) in the rhTSH group (0.109 ± 0.028 mGy/MBq after rhTSH and 0.167 ± 0.061 mGy/MBq after THW). The specific blood doses ranged

TABLE 1

Mean Values ± SD of Iodine Biokinetics in Remnants After rhTSH and THW

	rhTSH (n = 33)	THW (n = 29)	P
Remnant uptake at 48 h (%)	0.51 ± 0.70	0.91 ± 1.05	0.10
Effective half-time in remnant (h)	67.6 ± 48.8	48.0 ± 52.6	0.01
Remnant residence time (h)	0.86 ± 1.27	1.38 ± 1.51	0.11

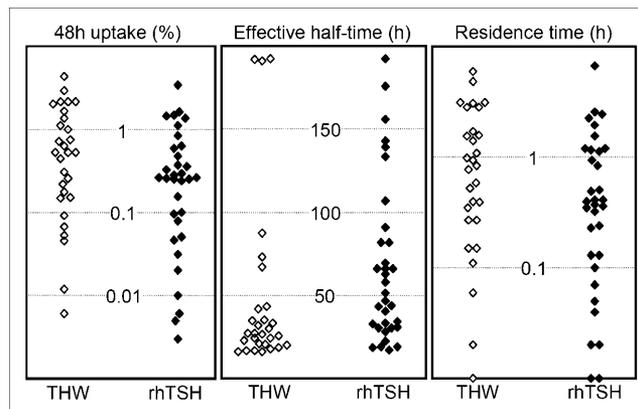


FIGURE 3. Remnant iodine kinetics in rhTSH group (◆) and THW group (◇).

from 0.064 to 0.18 mGy/MBq (0.24–0.67 rad/mCi) in the rhTSH group and from 0.088 to 0.35 mGy/MBq (0.33–1.30 rad/mCi) in the THW group. The distribution of the observed specific blood doses is presented in Figure 4.

A comparison of the blood dose values deduced with the standard procedure and the refined method (online Appendix, Eqs. 1 and 2, respectively) is listed in Table 2. The standard method underestimates the blood dose for most patients (mean, 5%; maximum, 21%) even for a 5-mm blood vessel radius (Table 2). This is attributed to the unaccounted contribution from the activity in distant blood. The dose estimates of the standard method for blood in smaller vessels are even lower as the S values account for the increasing fraction of radiation energy deposited outside the vessel. The values determined under the assumption of a blood vessel radius of 0.2 mm are about 35% lower than those calculated with the modified method. The refinement by the introduction of a mass-dependent S value results in blood dose corrections of 10% or more in 20% of the patients.

Residence times for individual patients and blood dose values determined with the standard procedure and the refined method are listed in Table 3 (online) for comparison.

DISCUSSION

The mode of TSH stimulation to prepare patients with DTC for postoperative radioiodine therapy, exogenously after rhTSH or endogenously after THW, clearly affects the iodine kinetics in both the thyroidal target tissue and the whole body. There are possible implications of the results of our study for clinical practice that should be considered.

The higher renal clearance of radioiodine in euthyroidism reduces the mass of iodide available for transport into thyroid tissue. Remnant uptake after 48 h was numerically less in the rhTSH group in this study, although the difference was not statistically significant. The assumption that a higher renal clearance reduces iodine uptake into the target tissue is supported by simple compartment model calculations. For a given transfer coefficient, the maximal uptake and the residence time in the target tissue depend almost

TABLE 2

Mean Values \pm SD of Iodine Biokinetics in Whole Body and Blood and Absorbed Doses to Blood After rhTSH and THW

	rhTSH	THW	P
Whole-body retention at 48 h (%)	6.9 \pm 5.7 (n = 32)	14.0 \pm 10.8 (n = 27)	0.0018
Whole-body residence time (h)	17.3 \pm 3.9 (n = 32)	24.1 \pm 7.8 (n = 27)	0.0002
Blood retention at 48 h (%)	0.78 \pm 0.78 (n = 33)	1.79 \pm 1.71 (n = 30)	0.0011
Blood residence time (h)	2.34 \pm 0.73 (n = 33)	3.53 \pm 1.63 (n = 30)	0.0004
Absorbed dose to blood (mGy/MBq)	(n = 32)	(n = 26)	<0.0001
Standard method, vessel radius: 0.2 mm	0.072 \pm 0.017	0.107 \pm 0.036	
Standard method, vessel radius: 5 mm	0.104 \pm 0.026	0.158 \pm 0.059	
Refined method	0.109 \pm 0.028	0.167 \pm 0.061	

Reduced numbers of patients with whole-body and blood dose data are due to technical failures during whole-body measurements.

linearly on the blood residence time $\tau_{\text{mL of blood}}$, which is inversely proportional to the renal clearance (17). If the lesion uptakes are normalized to $\tau_{\text{mL of blood}}$ for the individual patients, the difference between the rhTSH group and the THW group vanishes. Although the mean of the uncorrected 48-h uptake values is 78% higher in the THW group, it is only 6% higher after correction for the blood residence time. A Wilcoxon rank test to look for differences between the groups after the correction results in a *P* value = 0.40.

Other parameters might influence the uptake as well. Barbaro et al. (7) stopped thyroxine (T_4) medication 1 d before the first rhTSH injection to reduce the stable iodine pool and reported an ablation rate similar to that seen with THW after administration of 1.1 GBq (30 mCi) ^{131}I . With the same ablation activity, Pacini et al. (9) observed, without short-term withdrawal, a lower ablation rate in the rhTSH group. However, the radioiodine was given 48 h rather than 24 h after the second injection of rhTSH in this study; therefore, the results may not be comparable. In our study, the urinary iodine excretion was not significantly different in the 2 arms. The median urinary iodine levels in both groups were well below the approximately 20- $\mu\text{g/dL}$ threshold conventionally considered to have the potential for

interference with effective thyroid remnant uptake of radioiodine (10).

The concentration of stable iodine in the thyroid tissue might be another important factor that, to our knowledge, has not previously been discussed. In euthyroid patients, the thyroid remnant is not iodine depleted as it is after a longer period of THW associated with a continuous stimulation by an increased TSH level, leading to the excretion of organically bound iodine. Future studies of rhTSH may consider strategies aimed at an iodine depletion of the remnant before the therapy after rhTSH stimulation. A further prolonged THW some days earlier than that proposed by Barbaro et al. (7) would be possible without signs of clinical hypothyroidism.

The reduced uptake in euthyroid patients is partially compensated for by a significantly increased half-time in the target tissue. This might be explained by the favorable pattern of exogenous rhTSH stimulation producing a high, but promptly declining, peak of the TSH level. THW is characterized not only by a period of hypothyroidism before the therapy but also by a phase of a persistently high TSH level after the administration of radioiodine, which could promote release of organified radioiodine from thyroid remnant tissue, thus reducing the half-time.

The absorbed dose to the remnant of individual patients remains uncertain, as no validated method exists to determine exactly the mass of thyroid remnants after surgery. For this reason, we have not reported on radiation doses to the target tissue. As it can be expected that there is no significant difference between the distributions of postoperative thyroid remnant volumes in the groups with rhTSH and after THW, the mean residence times within the groups may serve as a suitable surrogate for the mean remnant absorbed doses. The remnant residence time, which is precisely measured, depends on both uptake and half-time and is proportional to the energy deposited in the remnant volume. In this study, the increased half-time in the rhTSH group does not fully compensate for the lower uptake, and the mean remnant residence time was longer in the THW group.

Other important points to be considered based on the results of our study are the effect of the use of rhTSH on the

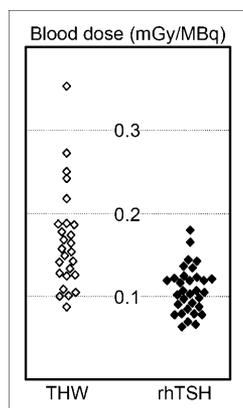


FIGURE 4. Specific blood dose values in rhTSH group (◆) and THW group (◇).

undesired radiation dose to the remainder of the body and whether rhTSH allows higher activities of radioiodine to be applied.

The higher renal clearance in euthyroidism causes a faster excretion of the activity and a significantly reduced radiation dose to the blood, indicating that the use of rhTSH in euthyroid patients reduces extrathyroidal exposure during radioiodine therapy. The actual absolute mean blood dose values after 3.7 GBq ^{131}I were 0.40 Gy in the group of euthyroid patients and 0.62 Gy in the THW group. The magnitude of these values is in good agreement with results from recent dosimetric studies and studies on biologic dosimetry (12,18–20). Watanabe et al. (18) demonstrated that radiation damage to lymphocytes in thyroid cancer patients after therapy with 3.7 GBq ^{131}I is equivalent to the effects observed after a mean external-irradiation dose of 0.45 Gy in vitro. The values published by other investigators range from 0.32 Gy (19) to 0.54 Gy (20).

A mean specific blood dose after stimulation with rhTSH that is more than twice as high as the value obtained in our study was reported by de Keizer et al. (11). The authors found mean absorbed doses to the blood of 1.69 ± 0.34 Gy after therapy with 7.4 GBq ^{131}I . In 4 of 17 treatments, the absorbed dose to the blood exceeded the limit of 2 Gy. The authors did not report any hematologic toxicity. However, some methodologic shortcomings (21) might have caused an overestimation of the blood dose values by de Keizer et al.

The observed blood residence times varied markedly, especially in the group of hypothyroid patients. The highest specific blood dose measured in this study was 0.35 mGy/MBq (1.30 rad/mCi) for a patient in the THW group. Therapy with 7.4 GBq (200 mCi) ^{131}I , which generally is accepted to be safe, would have led to a blood dose of 2.6 Gy (260 rad). A further increase to an even higher activity, e.g. 11 GBq (300 mCi), bears the potential risk of serious hematologic complications. This clearly demonstrates the necessity of an individual diagnostic blood dose assessment before the application of higher activities.

The specific blood dose values in the rhTSH group were less than the mean value of the THW group in all but 1 patient, and the highest blood dose in the rhTSH group was only half of the maximum value in the THW group. A similar finding was published by Sisson et al. (8). Therapy with 11 GBq (300 mCi) ^{131}I would have been safe with blood doses of <2 Gy (200 rad) for every patient in the rhTSH group of our trial. This suggests that higher activities of radioiodine might be administered safely after stimulation by rhTSH.

Dosimetric studies with blood dose estimates for a larger number of patients are required to verify the observation that the uptake into the target tissue depends on the blood residence time. Assuming that the blood residence time directly influences the remnant uptake, it might be reasonable to generally adjust the administered activity in radioiodine therapies according to the residence time in the blood to provide comparable conditions for the uptake into

the target volume. The blood dose is primarily determined by the blood residence time $\tau_{\text{mL of blood}}$, and a high correlation ($r^2 = 0.96$) between blood dose and residence time is observed. Therefore, the proposed approach is equivalent to an adjustment of the therapeutic activity according to the blood dose. The method requires a pretherapeutic assessment of the specific blood dose with a tracer activity.

Normalized to the individual specific blood dose values, no difference was observed between the rhTSH group and the THW group for the remnant doses represented by the remnant residence times. The mean remnant residence time per mGy/MBq blood dose is 8.2 h/(mGy/MBq) (median, 4.2 h/(mGy/MBq)) in the rhTSH group and 6.8 h/(mGy/MBq) (median, 4.8 h/(mGy/MBq)) in the THW group (Wilcoxon rank test, $P = 0.98$).

The mean blood dose in the rhTSH group was 0.4 Gy (40 rad) for a fixed activity of 3.7 GBq (100 mCi). Given the equivalent 100% ablation rate in this clinical trial (10), escalation above this value does not seem warranted for remnant ablation. The high ablation rate reported by Barbaro et al. (7) achieved with fixed activities of 1.1 GBq (30 mCi) and rhTSH suggests that even a lower blood dose value might be sufficient. Admittedly, long-term outcome results of disease-free survival and disease-specific mortality rates comparing rhTSH ablation with THW ablation are not available.

The assumption that a blood dose of, for example, 0.4 Gy is adequate for remnant ablation might be used to illustrate the method of blood dose-dependent treatment for the patient with the highest specific blood dose (0.35 mGy/MBq) in this trial. The total radiation dose to the blood was 1.3 Gy (130 rad) for this patient. According to the proposed approach, he would have been treated with 1.1 GBq (30 mCi) to compensate for the long residence time of the radioiodine in the blood and would have received a blood dose of 0.4 Gy.

CONCLUSION

Differences in the iodine kinetics have been found in remnant ablation therapy in groups of patients with DTC after endogenous TSH stimulation by THW or after application of rhTSH. When rhTSH is used to prepare euthyroid patients, the mean residence times of the radioiodine in the whole body and blood are significantly lower than those when patients undergo THW. This can be explained by the preservation of normal renal function in euthyroidism.

The mean remnant uptakes 48 h after the radioiodine application were lower in the rhTSH group by almost the same factor as the mean blood residence times. The difference vanished after normalization of the uptakes to the individual blood residence times. An approach using therapeutic activities adapted to the individual blood residence times or, as a surrogate, the specific blood dose may be considered as a standard approach if the hypothesis can be proven that shortening of the residence time of radioiodine

in the blood affects the uptake by reducing the supply available for the thyroid tissue.

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