Increasing Efficacy and Safety of Treatments of Patients with Well-Differentiated Thyroid Carcinoma by Measuring Body Retentions of ^{131}I

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There is no consensus on the amount of ^{131}I for treatment of patients with well-differentiated thyroid carcinoma; usual amounts vary widely. Body retention of ^{131}I has been shown to be a valuable index of radiation toxicity. If a broad range of body retentions occurs among patients, then high and low retentions will be a basis for modifying the usual prescriptions for ^{131}I to ensure safety and increase efficacy. **Methods:** After withdrawal of thyroid hormone in 87 patients, the fractional retention of diagnostic ^{131}I in each body was measured at 2 d by a scintillation probe. In 43 patients, the retention was measured 2 d after therapeutic ^{131}I. **Results:** Diagnostic retention varied from 0.01 to 0.51, with a median of 0.15. These retentions did not correlate with any index of health, thyroid hormone, or carcinoma status. Seventeen patients, previously treated with ^{131}I, exhibited a significantly lower mean retention. In 43 patients, retention of diagnostic ^{131}I was highly correlated with retention of therapeutic ^{131}I: diagnostic predicted therapeutic retention with a mean error of 0.04. In 10 patients receiving thyroxine, the mean retention of diagnostic ^{131}I after recombinant human TSH (rhTSH) was strikingly lower, 0.06, with a range of 0.016–0.16. **Conclusion:** Body retentions of ^{131}I are easily measured and vary considerably among patients. Because increased therapeutic ^{131}I will impart greater irradiation of tumor, and body retention has been accepted as an index of toxicity from ^{131}I, the use of body retention could enable prescriptions of therapeutic ^{131}I that enable increased efficacy while ensuring safety. If tumor retention is not proportionally decreased with the body retention of ^{131}I after rhTSH, then rhTSH may enable increased therapeutic efficacy.

Key Words: well-differentiated thyroid carcinoma; radioiodine; dosimetry; body retention

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How many gigabecquerels (mCi) of ^{131}I should be given to a patient with well-differentiated thyroid carcinoma (WDTC)? Excluding the 1.11 GBq (30 mCi) given to ablate residual normal thyroid tissue, most prescriptions for radioiodine have varied from 3.7 to 7.4 GBq (100–200 mCi), giving a broad range for usual treatments (*1*), and larger amounts have been prescribed after dosimetric measurements on radioactivity in blood and body to ensure safety (*2–5*). ("Dose" is not used to avoid confusion with absorbed dose of radiation given in cGy or rad.) Maxon et al. found that treatment to render cervical node metastases scintigraphically invisible was 14,000 cGy (*6*), but such measurements are difficult and often impossible in patients with WDTC. The relative efficacy of any program of therapy is unknown, and, in specified circumstances, there has been no consensus on how many gigabecquerels (mCi) a given patient should receive (*7*).

Although tumor dosimetry is not feasible, the retention of radioiodine in the body of patients, which is a component of dosimetry applied to prevent untoward events, can be readily measured in nuclear medicine laboratories. Assays of blood activity can be estimated from values of body retention (*8*) but are uncommonly needed for calculating a treatment with ^{131}I if the circulating free thyroxine (T_4) level is low (*9*). This article describes the method of assay of body retention, defines the broad range of retentions found in patients, and suggests how, in currently prescribed or usual ^{131}I treatments, safety can be ensured and, in addition, efficacy can be increased.

MATERIALS AND METHODS

Experimental Subjects

Between July 1, 1999, and December 31, 2000, 97 patients were investigated for possible residual WDTC and for treatment thereof in the Nuclear Medicine Division at the University of Michigan Health System for this retrospective study. Excluded were 40 patients because of incomplete data collection and 2 others because of known large volumes of functioning tumor (*9*) that would make them atypical of the usual WDTC patients. For diagnosis, the remaining 55 patients were given either the adopted standard 37 MBq (1 mCi) or, as part of an investigation, 18.5 MBq (0.5 mCi) ^{131}I. Data were also available on 32 patients who were treated with ^{131}I between 1993 and 1996 and who received 74 MBq (2 mCi) diagnostic ^{131}I. Thus, the total study population included 87 patients (29 male, 58 female; age range, 8–85 y; mean ± SD, 44 ± 15 y).

Patients were instructed to follow a low-iodine diet (*10*) for 1 wk before diagnostic radioiodine was given and until 1 d after

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therapeutic ^{131}I if treatment was prescribed. ^{131}I was administered orally in liquid form. Twenty-four of the patients who received 37 or 18.5 MBq (1.0 or 0.5 mCi) and all of those who received 74 MBq (2.0 mCi) ^{131}I were subsequently treated with 1.07–12.95 GBq (29–350 mCi) ^{131}I. Treatments were usually administered 2 d after the diagnostic administration and after the diagnostic studies on that day; occasionally treatment was delayed for 7 d. Retention of the therapeutic radioiodine 2 d after administration was available in 43 of the 56 treated patients.

For reference, the 2-d body retentions of ^{131}I were measured in 10 patients who received intramuscular injections (0.9 mg) of recombinant human thyroid-stimulating hormone ([rhTSH] Thyrogen; Genzyme Corp.) on each of the 2 d preceding the administration of diagnostic ^{131}I. These patients were clinically euthyroid, although their basal TSH levels were suppressed below the normal range by thyroxine therapy.

Papillary carcinomas were staged by 2 systems: MACIS (metastasis, age, completeness of resection, invasion, and size), which provided numeric scores (*11*); and TNM, which determined stages 1–4 (*12*). Five patients did not have typical papillary carcinoma (1 tall-cell papillary, 1 follicular, 1 poorly differentiated, and 2 Hürthle cell carcinomas) and were not staged by the MACIS system. Data for staging were insufficient in 2 patients who underwent surgery at other institutions; in 1 patient, the presence or absence of cervical node metastases was unclear so that TNM could not assessed; in the other patient, too little information was available for staging by either system.

Techniques

A Captus 2000 uptake probe (Capintec) containing a 2 × 2 cm crystal was used to measure body retention. Using mock sources of ^{131}I in a flat field at 2.5 m from the probe, the isoresponse (coefficient of variation in the counts, 1.2%) region was a 63.5-cm square; there was a decrease in response of 5%–8% of counts in the centimeters above and below the isoresponse square. Patients sat on a stool with the probe aimed at their xiphoid so that a span of 65.5 cm would encompass all but the top of the head and the legs below the knees in virtually all patients. Counts were obtained in the anterior and the posterior positions, each for 2 min; background activity was subtracted, and a geometric mean was determined. The efficiency of the probe was evaluated each day. In each patient, 100% of the activity was determined 2 h after ingestion of ^{131}I (and before voiding of urine), and the fraction of residual activity was determined from counts made on day 2 (45–54 h) and after voiding. Day 2 was selected because retention at this time point is part of the assessment for safety by dosimetry (*2*).

Body retentions of therapeutic ^{131}I were also assayed from the counts made at 2 d using the probe. The cpm/MBq (cpm/mCi) calculated from the diagnostic data enabled the therapeutic counts to be converted to GBq (mCi); the fractional retention of the therapy was then determined from the administered GBq (mCi). No dead time (loss in efficiency) was found for the probe in counting ^{131}I sources up to 1.81 GBq (49 mCi). The largest retention of therapeutic ^{131}I at 2 d was 1.78 GBq (48 mCi).

On day 1, uptake of diagnostic ^{131}I in the necks of patients was measured by the same probe at 50 cm from the neck; counting with a lead shield in place provided the background radioactivity. A sample of ^{131}I of known radioactivity provided the reference standard.

Whole-body images were made for 10, 20, and 40 min after diagnostic ^{131}I of 74, 37, and 18.5 MBq (2.0, 1.0, and 0.5 mCi), respectively, using a Siemens Bodyscan camera (Siemens Medical). The images made at 2 d after administration of ^{131}I were inspected separately by 2 of the investigators for retention of radioactivity in the neck and chest and in the abdomen. Retentions in each area were scored 0–4 and a mean score was calculated.

Measurements of serum for TSH, free T_4, total T_4, and creatinine and of blood for urea nitrogen (BUN) were performed in the clinical laboratory by standard methods. For purposes of comparison, total T_4 values were multiplied by 0.15 to approximate the free T_4 level in the patient when there was no reason to believe that the total T_4 concentration was altered by unusual protein binding. Serum thyroglobulin and thyroglobulin antibodies were assayed by kits (Immulite) obtained from Diagnostic Products Corp.; when thyroglobulin antibodies were present, the thyroglobulin level was not used in the correlation. The lower limit of detection of TSH was 0.01 μU/mL and of thyroglobulin was 0.5 ng/mL; in analyses of data, concentrations below these detection limits were assigned values of 0.

This investigation was approved by the Institutional Review Board for Medical Research at the University of Michigan.

Statistical Analysis

Analysis was by *t* test, ANOVA, and least-squares regression.

RESULTS

The mean retention (±SD) of ^{131}I at 2 d in the 87 patients was 0.165 ± 0.087 with a range of 0.010–0.505 (Table 1). Slight and insignificant differences were observed in the retentions of patients receiving diagnostic ^{131}I of 74, 37, and 18.5 MBq (2.0, 1.0, and 0.5 mCi). The mean retention in females, 0.166, was almost identical to that in males, 0.164. A range of 0.090–0.248 included 68% of patients with 34% above and below the median of 0.152. The retention in the 56 patients who were subsequently treated with ^{131}I, and therefore were deemed to have persistent carcinoma, was 0.180 ± 0.088 and significantly higher ($P < 0.05$) than the retention for the 31 patients who were not treated and had no evidence of persisting disease (Table 1). In 17 patients, ^{131}I treatment had been given ≥1 y previously, and the mean retention (0.121) in these patients was significantly less ($P < 0.01$) than the mean retention (0.176) in the 70 patients previously untreated (Table 1).

After ^{131}I therapy, the retentions at 2 d in the 43 patients for whom data were available gave differences (respective diagnostic value – therapeutic value for each patient) with a range of −0.078 to +0.127 with a mean difference of 0.041 (Table 2). The correlation between retentions of diagnostic and therapeutic ^{131}I was high ($r = 0.797$) and $P < 0.001$ (Fig. 1). However, there was no statistically significant correlation between the administered therapeutic ^{131}I and the retention of therapeutic ^{131}I in 43 patients ($r = 0.281$).

No significant correlation was found between the retentions of diagnostic ^{131}I and the respective indices of age, body weight, BUN, TSH, free T_4, neck uptake at 1 d, apparent radioactivity in neck and chest and in abdomen on images at 2 d, serum thyroglobulin, and the staging level determined by MACIS and TNM (Table 3). The neck uptakes at 1 d were significantly higher ($P < 0.001$) in the 43

TABLE 1
Diagnostic Body Retention at 2 Days

Group	No.	Retention			
		Mean ± SD	Median	Range	68% range
All	87	0.165 ± 0.087	0.152	0.010–0.504	0.090–0.248
Diagnostic MBq (mCi)					
74 (2.0)	32	0.157 ± 0.061			
37 (1.0)	43	0.161 ± 0.1			
18.5 (0.5)	12	0.193 ± 0.095			
Sex					
Female	58	0.166 ± 0.095			
Male	29	0.164 ± 0.07			
During this study					
Patients treated	56	0.18* ± 0.088	0.166	0.01–0.504	
Patients not treated	31	0.139* ± 0.08	0.121	0.03–0.35	
≥1 y before this study					
Patients treated	17	0.121† ± 0.07	0.108		
Patients not treated	70	0.176† ± 0.088	0.157		

*$P < 0.05$.
†$P < 0.001$.

patients who received subsequent treatment than in those who were subsequently not treated. The higher uptakes reflected persisting disease, but in these 43 patients there was still no significant correlation with the respective retention values (Table 3). Retention of diagnostic radioiodine and serum creatinine approached statistical significance ($r = 0.37$; $P = 0.06$ in a 2-tailed analysis).

The mean body retention of ^{131}I at 2 d in patients who had received injections of rhTSH before diagnostic ^{131}I was 0.056 and highly significantly ($P < 0.0005$) less than those obtained in the hypothyroid patients (Table 4). Although the range of retentions seemed large, 0.016–0.160, only 2 of the 10 patients had values above 0.060.

DISCUSSION

Assessment of body retention is no more difficult or time consuming than assays of thyroid uptake. Such evaluations can readily be made in any clinical nuclear medicine laboratory. Our data also delineate kinetics of radioiodine not previously reported.

In our study, retentions of diagnostic ^{131}I varied widely, from 0.01 to 0.504. The variations were not related to different diagnostic amounts of ^{131}I. However, there was reasonable agreement between the respective retentions of diagnostic and therapeutic ^{131}I. In 43 patients, the largest errors were underestimating the therapeutic retention by 7.4% and overestimating it by 12.7%. Differences were not related to the amount of ^{131}I given in treatment. Retentions were significantly higher in patients with residual carcinoma that required treatment than in patients apparently free of disease and receiving no therapy; this pattern was also seen in the neck uptakes at 1 d. Such observations are not unexpected. However, the neck uptakes in the patients with residual disease still did not correlate with the respective retentions and, therefore, neck uptakes cannot substitute as an index for toxicity.

TABLE 2
Relationship of Retentions: Diagnostic and Therapeutic

Group	No.	Therapeutic GBq (mCi)		Retention	Retention difference*	
		Mean ± SD	Range	Mean ± SD	Mean† ± SD†	Range
All therapies	56	6.40 ± 2.96 (173 ± 80)	1.07–12.95 (29–350)			
Comparison						
Diagnostic	43		18.5–74‡ (0.5–2.0)	0.164 ± 0.079		
Therapeutic	43	5.88 ± 3.00 (159 ± 81)	1.07–12.95 (29–350)	0.144 ± 0.074	0.04 ± 0.036	−0.078 to +0.127

*Diagnostic − therapeutic.
†Of differences whether + or −.
‡MBq.

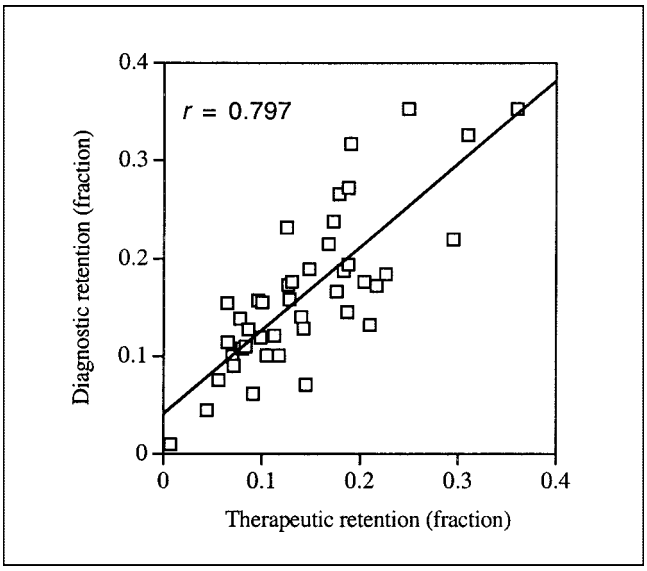

FIGURE 1. Scatter plot of diagnostic and therapeutic retentions of ^{131}I at 2 d in bodies of 43 patients.

Because hematologic toxicity is the most common untoward consequence of ^{131}I therapy, dosimetry of red marrow would be an ideal assessment. However, measurements of ^{131}I in the important bones have been at best very difficult. Moreover, guidelines to prevent toxicity from therapies with ^{131}I have been derived empirically from correlations of body retention and clinically observed events (*2*). The guidelines provide the best index of body dosimetry currently available (*3–6*). In a recent review of dosimetry in thyroid carcinoma, Van Nostrand et al. concluded that "dosimetrically determined doses of radioiodine are logically an improvement over empiric fixed doses" (*13*). In keeping with this logic, increased retention should dictate a smaller amount of therapeutic ^{131}I, and decreased retention should permit more gigabecquerels (mCi). However, this concept has not been adopted into the everyday practice of most physicians who treat patients with thyroid carcinoma. Although there is no consensus on how much radioiodine to administer to patients, our data show how the usual gigabecquerels (mCi) selected for a given patient could be modified by measuring retention of diagnostic ^{131}I in the body at 2 d to ensure safety and possibly increase efficacy. Arbitrarily, 1 SD around the median (68% of the values) was 0.09−0.248, and values within this range could be considered average so that the originally selected amount of ^{131}I would not be modified. The prescribed gigabecquerels (mCi) of ^{131}I could be increased if the value was $<$0.09 and decreased if the value was $>$0.248. The degree of change in the amount of treatment administered would be left to the therapist, but for retentions of $\leq$0.05 consideration could be given to increases of 50%–100%. Similarly, substantial reductions in treatment gigabecquerels (mCi) should be considered when retentions are $\geq$0.40.

With the exception of prior treatment with ^{131}I, no index in the clinical and laboratory profiles of the patients correlated with the body retention. Thus, there is currently no way of determining body retention of ^{131}I except by measuring it in a given patient.

The retentions in patients who had received prior ^{131}I treatment were significantly lower than those in patients who had not been treated. The reason for this difference is unknown. A lesser amount of functioning thyroid tissue was present in patients previously treated (mean neck uptake at 1 d, 1.1% of dose), but the mean neck uptake of ^{131}I at 1 d in patients treated for the first time was only slightly higher

TABLE 3
Correlations of Body Retention of Diagnostic ^{131}I with Other Indices

Index	No.	Mean ± SD	Range	*r*
Age (y)	87	44 ± 15	8–85	0.178
Weight (kg)	87	84.1 ± 24.6	91–387	0.092
BUN (mg/dL)	79	13.7 ± 4.1	6–24	0
Creatinine (mg/dL)	28	1.4 ± 0.5	0.5–2.9	0.37
TSH (mU/L)	86	117 ± 76	0.14–382	0.007
Free T_4 (ng/dL)	80	0.17 ± 0.09	0–1.67	0.016
Neck uptake (%)				
All patients subsequently treated or not	70	2.5 ± 2.6	<0.1–14.4	0.215
Patients subsequently treated	43	3.4 ± 2.9	0.01–14.4	0.13
Activity on image in neck or chest (score)	74	1.9 ± 1.2	0–4	0.215
Activity on image in abdomen (score)	74	1.7 ± 0.8	0–3.5	0.213
Thyroglobulin (ng/mL)	81	184 ± 936	0–7,940	0.091
MACIS (score)	80	5.63 ± 1.97	3.2–11.0	0.147
TNM (stage)	85	1.8 ± 1	1–4	0.156
Retention				
Therapeutic ^{131}I (fraction)	43	0.144 ± 0.074		0.797
Diagnostic ^{131}I (fraction)*	43	0.164 ± 0.079		

*Same group of patients used for correlation with retention of therapeutic ^{131}I.

TABLE 4
Body Retention of ^{131}I in Patients Receiving rhTSH

No.	Female	Male	Age range (y)	Range		Retention at 2 d	
				MBq	mCi	Mean ± SD	Range
10	8	2	26–62	77.7–148	2.1–4	0.056 ± 0.050*	0.016–0.16

*Differs from 87 patients in Table 1: $P < 0.0005$.

(2.7%), so it is not clear that thyroid tissue accounted for the difference in body retention. Because iodide is reabsorbed by the kidney tubules (*14*,*15*), it is possible that irradiation of the tubules by ^{131}I in some way impaired the reabsorption mechanism. Compared with mean retention (0.176) in patients not previously treated, the mean retention (0.121) in those who had previous treatment with ^{131}I was reduced by 5.5%. Whether this reduced retention affected the uptake of ^{131}I by the carcinomas is not known, but attention to body retentions will give information that will enable increases in the gigabecquerels (mCi) to be prescribed with safety in repeated therapies.

Although not part of the goal of this study, the difference in body retention of ^{131}I in the clinically euthyroid patients who received injections of rhTSH was striking. Rapid washout of the radioiodine has been recognized on images but retentions have not been quantitatively related to those in patients who are hypothyroid (*16*). Impairment of glomerular filtration rate, the main mode of iodide excretion, by hypothyroidism has been clearly established (*17*,*18*), but the reduction in iodine excretion is disproportionately greater than the decline in glomerular filtration (*14*), thereby at least partially explaining the lack of correlation between BUN and body retention. During euthyroidism, the more rapid excretion of ^{131}I may reduce that available for the carcinomas. When evaluating images for detection of thyroid carcinoma, the scans made after rhTSH appear to have sensitivity similar to that in images attained during hypothyroidism in some studies (*16*,*19*), but the latter appeared to be a more sensitive approach in another report (*20*). If the quantitative uptake and retention of ^{131}I by carcinomas after rhTSH is not reduced proportionally to the reduction in body retention, then, by using the rhTSH protocol, efficacy of treatments could be increased and safety maintained through administration of larger than the usual gigabecquerels (mCi) to patients who remain euthyroid.

Concern has been raised about a stunning effect by diagnostic ^{131}I on thyroid tissue including carcinoma—that is, reduction in the fractional uptake of subsequent therapeutic ^{131}I. Evidence for this effect has been changes in appearance of the thyroid tissues on diagnostic and therapeutic scintigraphic images (*21*,*22*), decreases in measured fractional uptakes of radioiodine in the tissues after diagnostic ^{131}I (*22–24*), and decreased responses to therapies when diagnostic ^{131}I has been used (*25*,*26*). However, the observed phenomenon may be due to, or largely due to, the effects of therapeutic ^{131}I; much of the consequence may arise from the early (first 2 d) effects from irradiation by the therapeutic ^{131}I. To avert possible stunning, ^{123}I has been proposed for diagnostic imaging (*26*). However, ^{123}I does not appear to be suitable for dosimetry. Compared with ^{131}I, ^{123}I imparts less energy per gigabecquerel (mCi) to tissues and, therefore, should have a lesser radiation effect, but this agent is not easily quantified at 2 d. Moreover, in one study there appeared to be little or no stunning effect when diagnostic ^{131}I was reduced to 74 MBq (2 mCi) (*27*). The value of the information obtained from body retention would seem to outweigh any effect of 74 MBq (2 mCi), and especially 37 MBq (1 mCi), of ^{131}I on the carcinoma to be treated.

CONCLUSION

The concept for this project was previously described (*28*). In summary, body retention of ^{131}I can be readily measured in a nuclear medicine laboratory. The diagnostic retention provides a reasonable estimate of retention of therapeutic ^{131}I. No clinical or laboratory index will predict the body retention. Because most patients with thyroid carcinoma receive modest treatment amounts of ^{131}I and appear to do well, it may be that the usual amounts are sufficient and do no major harm. Yet, for treatment of patients with more advanced disease, and for other patients in whom the therapist wishes to consider body burdens of radioiodine, body retention should be an important factor. Thus, measurement of diagnostic retention can serve to modify the usual prescription for therapy to ensure safety and increase efficacy in as many as 32% of the patients treated with ^{131}I for WDTC.

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