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Iodine-131 Therapy in Sporadic Nontoxic Goiter

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The effect of radioiodine in the treatment of nontoxic goiter is seldom evaluated quantitatively. The aim of this study was threefold: (a) to assess the effect of ^{131}I on goiter volume, (b) to establish a relationship between CT volume reduction and the amount of radioactivity taken up by the thyroid and (b) to assess the precision of scintigraphic thyroid volume measurements. **Methods:** In 27 patients with sporadic nontoxic goiter, the thyroid volume was estimated from a [^{99m}Tc]pertechnetate scintigram. Two different models (cylinder model and surface model) were applied. The ^{131}I dosage varied between 507 and 3700 MBq. In all patients, noncontrast CT scanning of the neck was performed before therapy and 1 yr after therapy. **Results:** The mean CT thyroid volume before therapy was 194 ± 138 ml. A reduction was obtained in all patients and averaged 34% ± 17%. The volume reduction measured by CT correlated well with the amount of ^{131}I in the thyroid ($r = 0.70$). In thyroids larger than 200 ml, both scintigraphic volume estimation methods were imprecise. For smaller volumes, the surface model was superior. Hypothyroidism developed in 14% of the patients. No other side effects occurred. **Conclusion:** Iodine-131 therapy for volume reduction in nontoxic goiter is a safe and effective treatment. For scintigraphic estimation of thyroid gland volumes smaller than 200 ml, the surface model is preferred.

Key Words: nontoxic goiter; radioiodine therapy; volume reduction

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TABLE 1
Patient Characteristics

Patient no.	Sex	Age (yr)	24-hr uptake* (%)	Dosage (MBq)
1	F	49	29	630
2	M	50	48	1245
3	M	71	32	740
4	F	78	37	1480
5	M	58	39	1850
6	F	48	40	555
7	F	50	38	555
8	F	60	41	925
9	F	66	31	1480
10	F	69	83	600
11	F	36	40	900
12	F	68	35	740
13	F	48	42	518
14	F	51	32	1900
15	F	62	21	925
16	F	64	66	507
17	F	43	60	1850
18	F	55	39	1295
19	F	62	37	2750
20	F	55	40	1295
21	F	66	45	800
22	F	57	34	1480
23	F	59	27	1850
24	F	42	64	1480
25	M	51	41	3700
26	F	65	44	1600
27	M	81	37	1160

*Normal value for 24-hr uptake: <30%.

The term nontoxic goiter refers to thyroid gland enlargement unassociated with hyperthyroidism. It is the most common thyroid problem encountered in clinical practice. Thyroid nodules are detected in fewer than 1% of the male population but occur in 5% of all females. There is an increase in frequency after the age of 45 to 9% in women aged 75 or older (*1*). Nontoxic goiter increases 20% in volume every 9 mo (*2*). Obstructive symptoms and cosmetic problems are usually predominant in the clinical picture, and volume reduction is frequently necessary.

Thyroid hormones have been used to shrink goiters and to arrest further growth (*2*). In a double-blind controlled study, it has been shown that levothyroxine (LT4) suppressive therapy is not effective in shrinking goiters (*3*). Furthermore, life-long suppressive LT4 therapy is associated with side effects such as decreased bone mineral density and cardiac arrhythmias. Surgical treatment is effective but carries the risk of recurrent laryngeal nerve damage and permanent hypoparathyroidism (*4*). Transient voice disabilities and hypothyroidism are relatively frequent complications (20% and 10%, respectively) (*5*). Moreover, after subtotal thyroidectomy, a recurrence of the goiter has been found in almost 20% of the patients (*5*). For these patients, as well as for those with high surgical risk, a nonoperative reduction of the thyroid volume would be desirable.

Over decades, radioiodine (^{131}I) has proved to be effective in the treatment of hyperthyroidism with diffuse or nodular goiters. Iodine-131 also has been used to shrink the goiter in nontoxic patients (*6–10*). In most studies, volume reduction was measured by ultrasound. The use of ultrasound for thyroid volume estimations has been studied chiefly in normal thyroids and diffuse goiters. For large multinodular goiters, however, ultrasound becomes less reliable because of frequent intrathoracic extension. Furthermore, ultrasound is observer-dependent, especially in large goiters in which it is not possible to visualize the whole gland in one view. Thyroid gland volume reduction by ^{131}I has rarely been evaluated by more reliable methods such as CT or MRI. The aims of this study were to determine thyroid gland volume reduction by therapeutic dosages of ^{131}I in patients with nontoxic goiter using CT as a gold standard; to relate this volume reduction to ^{131}I uptake by the thyroid gland; and to determine the reliability of scintigraphic volume measurements in patients with nontoxic goiter.

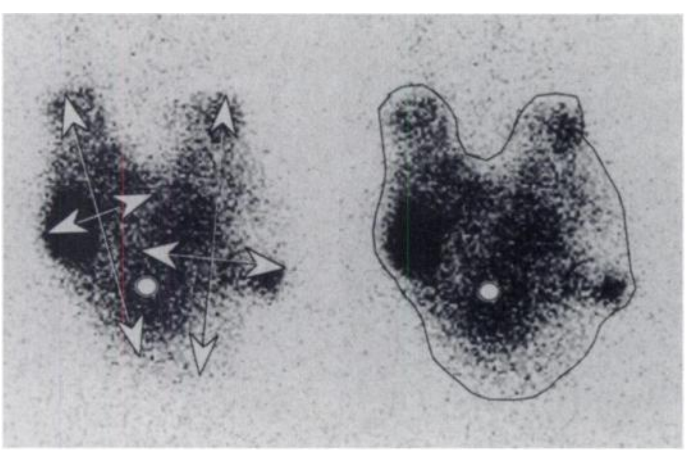

FIGURE 1. Examples of scintigraphic volume estimation with the cylinder (left) and volume models (right) in Patient 9.

METHODS

Patients

Twenty-seven patients with sporadic nontoxic goiter were included in the study. The group consisted of 22 women (mean age 57 yr, range 36–78 yr) and 5 men (mean age 62 yr, range 50–81 yr). Patient characteristics are summarized in Table 1. Inclusion criteria for ^{131}I treatment were growth of the goiter, obstructive or cosmetic symptoms, clinical euthyroidism and a preference of the patient for ^{131}I therapy over surgery. Those having had previous partial thyroidectomy or use of LT4 suppressive therapy were not excluded. None of the patients had previously undergone ^{131}I therapy. Before treatment, the plasma TSH level was within the normal range (0.35–6.0 mU/liter) in 11 patients and subnormal in 15 patients (<0.35 mU/liter). In one patient, the plasma TSH level was not available. In all patients, plasma total T4 (TT4) and free T4 (FT4) levels were in the normal range (60–140 nmole/liter and 6–23 nmol/liter, respectively). Two patients could not be evaluated for thyroid volume reduction, as they had undergone partial thyroidectomy or a second ^{131}I treatment within the 1-yr follow-up period.

Imaging Protocol

CT and thyroid scintigraphy were performed and ^{131}I uptake was measured within 4 wk before radioiodine treatment. Thyroid scintigraphy was performed after intravenous administration of 80 MBq [^{99m}Tc]pertechnetate on a round field of view or rectangular gamma camera equipped with a low-energy, high resolution, parallel-hole collimator. Two different scintigraphy-based methods were used to estimate thyroid volume.

In the first, the cylinder formula (Vcyl) is applied to both thyroid lobes:

$$\mathrm{Vcyl} = \mathrm{L} \times (0.5\mathrm{W})^2 \times \pi, \qquad \text{Eq. a}$$

TABLE 2
CT and Scintigraphic* Measurements

Patient no.	Volume (cyl) pretherapy	Volume (surf) pretherapy	CT volume pretherapy	CT volume post-therapy	Volume reduction (%)
1	52	51	52	33	37
2	161	153	175	108	38
3	49	58	48	19	61
4	500	254	491	403	18
5	400	305	454	273	40
6	60	50	42	18	57
7	100	80	64	51	20
8	160	120	134	119	11
9	350	222	259	215	17
10	134	142	140	135	3
11	100	97	123	82	33
12	63	91	95	71	19
13	58	63	56	36	35
14	165	307	434	317	27
15	50	44	43	15	65
16	90	84	76	31	59
17	300	287	269	118	56
18	254	233	339	306	10
19	378	293	424	305	28
20	140	143	205		
21	75	94	90	53	41
22	135	82	94	50	47
23	213	161	162	113	30
24	250	173	188	118	37
25	326	282	313	168	46
26	240	190	208	166	20
27	117	176	271		

*All numbers in milliliters, except volume reduction measured by CT (%).

where V represents the volume of each lobe, L is maximum length in centimeters, and W is maximum width in centimeters (Fig. 1).

In the second method, the surface formula (Vsurf) by Himanka and Larsson (*11*) is applied:

$$\text{Vsurf} = 0.33 \times A^{1.5}, \qquad \text{Eq. b}$$

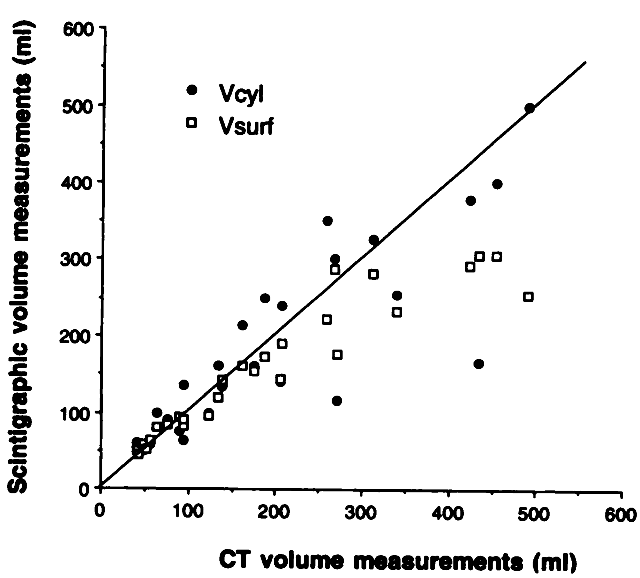

FIGURE 2. Relationship between scintigraphic and CT volume measurements of the thyroid before ^{131}I therapy. The line through the origin is the line of identity.

TABLE 3
Performance Evaluation of Predictors Vcyl and Vsurf Using Mean Error (me) and Mean Squared Error (mse) (*16*) for Thyroid Gland Volumes <200 ml and >200 ml

Precision	Vcyl (<200 ml)	Vsurf (<200 ml)	Vcyl (>200 ml)	Vsurf (>200 ml)
mse (ml^2)	798.6	142.3	11185.3	12577.2
rmse (=mse$^{1/2}$) (ml)	28.3	12	106	112
Bias me (ml)	10.6	−2.3	−45.0	−88.4

where A equals the thyroid projection area. This formula was derived experimentally through determination of volumes of surgical thyroid specimens by fluid replacement. Several of these specimens were of irregularly shaped thyroids. For scintigraphic estimation of thyroid surface, regions were drawn automatically using a 30% threshold of the maximum counts per pixel. In cases of very poor thyroid uptake, regions were drawn manually (Fig. 1).

The 5-hr and 24-hr ^{131}I uptakes were measured after ingestion of 0.37 MBq Na^{131}I tracer (Canberra 7350-PE collimator with a 2 × 2-inch NaI crystal). The collimator crystal was centered at the trachea or at the ^{131}I standard placed in a neck phantom at a distance of 25 cm. Thyroid uptake was measured using the formula: ^{131}I uptake = (neck counts − thigh background counts)/(standard counts − room background counts) (*12*). Calculation of the therapeutic ^{131}I dosage included corrections for thyroid weight and 24-hr radioiodine uptake, according to the formula:

$$D = (100/U) \times \text{Vcyl} \times C, \qquad \text{Eq. c}$$

where D is the administered dose of ^{131}I (in MBq), U equals the 24-hr uptake (%), Vcyl (which was used routinely for dosage calculations) represents the thyroid volume (in ml) and C was set at 3.7 MBq/ml. Nine patients received a lower dosage. Corrections were made: (a) for scintigraphically active thyroid volume, (b) in case D exceeded 3700 MBq or (c) if the estimated period of mandatory hospitalization in an isolated room was considered unacceptable. The dosage in these nine patients was 2.1 ± 0.6 MBq/ml. Prior to ^{131}I therapy, patients on LT4 had discontinued this medication for at least 4 wk.

CT was used as the gold standard for measurement of thyroid volume before treatment (CTpre). The use of CT for measuring thyroid volume is both accurate and reproducible (*13*). Noncontrast CT of the thyroid gland was performed using 5-mm contiguous sections. Volume measurements were performed using the summation-of-areas technique. At 12 ± 1 mo after treatment, CT (CTpost) was repeated. CTpre-CTpost provides the absolute volume reduction, while [(CTpre-CTpost)/CTpre] × 100% represents the relative volume reduction. In addition to CT volume reduction, we investigated the relationship between the two scintigraphic methods of volume estimation used in this study.

Dose Effect Relationship

The amount of ^{131}I per ml CT volume corrected for 24-hr uptake (C_{CT}) is related to the percentage of volume reduction (ΔCT). To describe this relationship, we used the sigmoid E_{max} model, which is the simplest model for the adequate description of drug effects over the whole range of concentrations (*14*). It is also a mathematical description of the well-known S-shaped curve, known from radiobiological models describing cell killing (*15*). The model is defined as:

$$E = \frac{E_{max} * C^N}{C^N + EC_{50}^N}, \qquad \text{Eq. 1}$$

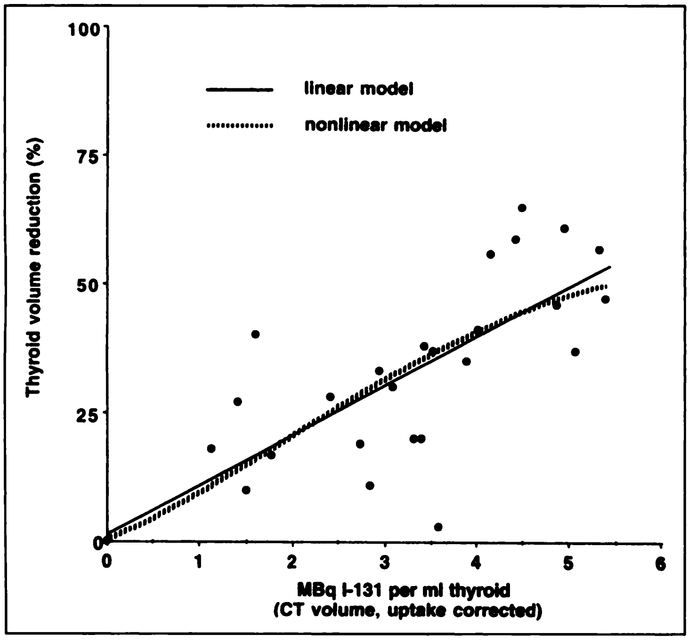

FIGURE 3. Relationship between the percentage of volume reduction as measured by CT and the amount of ^{131}I uptake per milliliter CT volume, corrected for 24-hr uptake, using linear and nonlinear models.

where E is effect, C is concentration, N is a number influencing the slope of the curve, E_{max} is the maximum effect attributable to the drug and EC_{50} is the concentration producing 50% of E_{max}.

For this study, the formula (*1*) can be rearranged into:

$$\Delta CT = \frac{100 * C_{CT}^{N}}{C_{CT}^{N} + EC_{CT50}^{N}}, \quad \text{Eq. 2}$$

where ΔCT is the percentage of volume reduction as measured by CT, 100 is the maximum effect and EC_{CT50} is the concentration per MBq/ml CT volume, uptake corrected producing 50% volume reduction.

For comparison, the relationship between C_{CT} and ΔCT was also tested by linear regression.

Statistical Analysis

Data were analyzed with the SYSTAT 5.2.1 program (SYSTAT, Inc., Evanston, IL). To describe the predictive performance of the scintigraphic volumes, the mean squared prediction error (precision) and mean prediction error (bias) were evaluated (*16*). To assess the dose effect relationship, statistical tests were used as mentioned previously.

RESULTS

Pretreatment Thyroid Volume Measurements by CT and Scintigraphy

The results of CT and scintigraphic measurements are summarized in Table 2. As illustrated in Figure 2, both scintigraphic volume estimations show a better relationship with CT measurements for smaller goiters (<200 ml). Table 3 shows the performance evaluation of Vcyl and Vsurf.

The mean squared error (mse) of the Vsurf method is considerably smaller than the mse of the Vcyl method for thyroid gland volumes smaller than 200 ml, indicating a greater precision of the Vsurf method. In thyroid gland volumes exceeding 200 ml, both methods are inadequate as demonstrated by the magnitude of the mean error.

Iodine-131 Dosage Versus Thyroid Volume Reduction

The administered dose of ^{131}I ranged from 507-3700 MBq (1289 ± 733 MBq, mean± s.d.). For the whole group, the mean administered dose corrected for Vcyl and 24-hr uptake was 3.3 ± 1.0 MBq/ml Vcyl (range: 1.1–4.8 MBq/ml Vcyl). As mentioned previously, nine patients received a lower dosage. In these patients, the administered dose ranged from 1.1 MBq/ml Vcyl to 2.9 MBq/ml Vcyl (mean: 2.1 ± 0.6 MBq/ml). For the remaining group (18 patients), the dosage was 3.9 ± 0.4 MBq/ml Vcyl (range: 3.5–4.8 MBq/ml Vcyl). Complete CT data were available for 25 patients. All statements about absolute and relative volume reduction are based on CT measurements unless indicated otherwise. Volume reduction was obtained in all patients. The mean volume reduction was 58 ± 48 ml (range: 5–180 ml), and the relative volume reduction was 34% ± 17% (range: 3%–65%).

Dose Effect Relationship

The relationship between the percentage of volume reduction as measured by CT (ΔCT), and the amount of ^{131}I per ml CT volume corrected for 24-hr uptake (C_{CT}) is described by the following formula:

$$\Delta CT = \frac{100 * C_{CT}^{1.4}}{C_{CT}^{1.4} + 5.3^{1.4}}. \quad \text{Eq. 3}$$

Statistical parameters are correlation coefficient (r) = 0.70; F-value = 92; confidence interval of EC_{CT50} = 3.8–6.9 MBq/ml. Linear regression analysis results in a correlation coefficient of the same order of magnitude (r = 0.72, F-value = 26), but from a dosimetric point of view, the sigmoid E_{max} model is preferred. Figure 3 depicts the relationship between ΔCT and C_{CT}.

Side Effects

In 21 patients, TSH values were available 1 yr after treatment. Hypothyroidism (TSH level > 6.0 mU/l) occurred in 3 of 21 patients (14%) (Patients 1, 6 and 17). No other side effects occurred, and in particular, no clinically detectable increase of goiter or exacerbation of obstructive symptoms were noted.

Clinical Response

Four (15%) of the 27 patients (Patients 1, 12, 20 and 27) were dissatisfied with the volume reduction results, although the objective volume reduction was satisfactory (37% and 19%, respectively) in Patients 1 and 12. Within the 1-yr follow-up period, Patient 20 had a partial thyroidectomy and Patient 27 received a second ^{131}I treatment. All other patients reported substantial improvement or complete relief of their complaints.

DISCUSSION

This study shows ^{131}I to be an effective therapeutic option for the reduction of thyroid volume in patients with sporadic nontoxic goiter, with a relatively small risk for hypothyroidism. Volume reduction was obtained in all patients. With a dosage of 3.3 ± 1.0 MBq/ml, the mean volume reduction was 34% ± 17%, which is of the same order as that reported by other investigators (*8–9*).

By using the sigmoid E_{max} mode, and CT-based measurements, we have found a good relationship between thyroid volume reduction and the amount of ^{131}I taken up per milliliter thyroid volume.

In our patient series, we found a wide range of thyroid volume reduction (3%–65%). No doubt, individual differences in ^{131}I uptake and biological half-life of ^{131}I in the thyroid are responsible for some of the varying responses. However, we propose that inappropriate estimation of thyroid volume, used for dosage calculations, is generally an underestimated factor. Accurate volume estimations are the basis of reliable dosimetric calculations.

It is obvious that if individual dosages can be optimized, benefits can be expected in terms of increased therapeutic effect, minimal risk of hypothyroidism and reduced radiation burden to the patient and the environment.

Thyroid gland volume can be estimated by several methods, of which the CT has a documented high rate of accuracy. Up to 40 yr ago, it was difficult—and sometimes impossible—to determine thyroid volume by palpation (*11*). At that time, scintigraphy was the only reliable method. In more recent published reports, there are numerous articles confirming the accuracy of CT volume measurements (*17-20*). In general, CT volume measurements of thyroid specimens are within 5%–10% of direct volume measurements. In an earlier study, our group reported a 5% intra- and interobserver variability for CT (*13*). Some investigators have used MRI (*8,9,21–23*). However, no references are available for either CT or MRI measurements for ^{131}I therapy dosage calculation. Ultrasonography also is recognized as a reliable modality for volume measurements, but only two groups have described the use of this modality for dosage calculation (*6,10*). In those series, no thyroid volumes over 300 ml were reported. It is possible that one specific problem with ultrasound, i.e., imaging of retrosternally located tissue, is the reason for this finding. CT and MRI apparently do not have this drawback.

Scintigraphic estimates of thyroid volume using the elliptoid method are reliable in the case of normal or slightly enlarged thyroid glands with homogeneous iodine uptake. For nontoxic goiter, this is not self-evident. In particular, estimation of actual functioning volume is hampered by physical difficulties, especially the classic problems of contour detection in the presence of high background activity and the effects of finite spatial resolution. Possibly SPECT or PET (using ^{124}I NaI) measurements are more accurate for dosage calculation purposes than planar scintigraphy (*24–26*). This needs to be confirmed by larger studies.

In a scintigraphic study of largely varying thyroid sizes and conditions, Himanka and Larsson found that the area of the frontal projection was the sole variable determining thyroid volume (*11*). This study confirms that their surface method (Vsurf) is more accurate than the cylinder method (Vcyl) but only in thyroid gland volumes smaller than 200 ml. For volumes greater than 200 ml, the mse was relatively large both for Vsurf and Vcyl, indicating that scintigraphic volume measurements are unreliable in larger thyroids. In this subgroup, CT is recommended for therapeutic ^{131}I dosage calculations.

CONCLUSION

Iodine-131 is a safe and effective treatment for volume reduction of nontoxic goiters, leading to a mean volume reduction of 34% ± 17% as measured by CT. For scintigraphic thyroid volume estimation, the surface method (Vsurf) is to be preferred in glands smaller than 200 ml.

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