Dosimetry and Risk Estimates of Radioiodine Therapy for Large, Multinodular Goiters

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In patients with a large, multinodular goiter (>100 g), radiation absorbed doses in the thyroid, surrounding tissues and remainder of the body were estimated after therapeutic administration of ^{131}I(3.7 MBq or 100 μCi/g of thyroid tissue retained at 24 hr). **Methods:** Thermoluminescent dosimeter (TLD) measurements were performed on 23 patients (12 euthyroid and 11 hyperthyroid; thyroid weight 222 ± 72 g; 2.1 ± 0.9 GBq ^{131}I) on the skin over the thyroid, over the submandibular gland and over the parotid gland. Thyroid radioactivity measurements were done daily in 6 euthyroid and 6 hyperthyroid patients (thyroid weight 204 ± 69 g; 1.9 ± 0.9 GBq ^{131}I). An iodine biokinetic model and the MIRD methodology were used to estimate absorbed doses in organs. Cancer risks were calculated using ICRP Publication 60. **Results:** Cumulated absorbed doses on the skin (TLD measurements) were 4.2 ± 1.4 Gy (thyroid), 1.2 ± 0.6 Gy (submandibular) and 0.4 ± 0.2 Gy (parotid). All these values were significantly correlated with the amount of radioiodine retained in the thyroid at 24 hr (euthyroid versus hyperthyroid not significant). Absorbed doses in the thyroid of 94 ± 25 Gy for euthyroid and 93 ± 17 Gy for hyperthyroid patients were calculated (thyroid radioactivity measurements). Extrathyroidal absorbed doses (means of 12 patients) were 0.88 Gy in the urinary bladder, 0.57 Gy in the small intestine, 0.38 Gy in the stomach, and ranged from 0.05 to 0.30 Gy in other organs (euthyroid versus hyperthyroid not significant). A 1.6% life-time risk of development of cancer outside the thyroid gland was calculated. When applied to people of 65 yr and older the estimated risk is approximately 0.5%. **Conclusion:** These data may help in choosing the treatment regimen for individual patients with a large, multinodular goiter, who have to be treated for hyperthyroidism or compressive problems. In younger patients, surgery may be preferred. However, for elderly patients and patients with cardiopulmonary disease, the advantages of noninvasive radioiodine treatment will outweight the life-time risk of this mode of therapy.

Key Words: radioiodine therapy; compressive goiter; dosimetry; carcinogenesis; multinodular goiter

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Surgery is standard therapy for a patient with a large, toxic or nontoxic, compressive goiter. However, it is not without risk, especially in elderly patients with cardiopulmonary disease (1–3). Radioiodine, a widely accepted treatment for patients with toxic, noncompressive goiters, is an alternative for these patients. In a recent study, we have shown that radioiodine therapy can induce an average reduction in thyroid volume of 40% after 1 yr and a significant widening of the tracheal lumen in patients with a large, compressive mutinodular goiter (4). However, reluctance to treat these patients with radioiodine may be due to a concern for excessive radiation absorbed doses. Many commonly used dosage schedules for radioiodine therapy

are aimed at delivering a certain amount of radioiodine per gram of thyroid tissue retained in the thyroid gland at 24 hr. The use of such a dosage schedule implies that large amounts of radioiodine are administered to patients with a large, nodular goiter.

The present study is focused on the dosimetric aspects of radioiodine therapy in patients with large goiters. We have estimated absorbed doses in the thyroid, in tissues directly near the thyroid and in tissues and organs in the remainder of the body after therapeutic administration of radioiodine in hyperthyroid and in euthyroid patients with large, multinodular goiters. Thermoluminescent dosimetry was used to estimate the radiation burden of tissues directly near the thyroid gland. Estimations of absorbed doses in the thyroid and in the remainder of the body were made using thyroid radioactivity measurements and a model of iodine kinetics in the body as described by Robertson and Gorman (5). Risks of radiation-induced cancer were assessed based on the 1990 Recommendations of the International Commission on Radiological Protection (6).

MATERIALS AND METHODS

Patients and Radioiodine Treatment

Twenty-three consecutive patients with a multinodular goiter of more than 100 g, as estimated from palpation and planar thyroid scintigraphy (7), were treated with radioiodine. The diagnosis of multinodular goiter was based on the presence of one or more thyroid nodules at palpation and an irregular distribtuion of [^{123}I] or [^{131}I]sodium iodide on a thyroid scan. Patients with a solitary hot nodule were excluded. In the 11 patients with toxic multinodular goiter the primary aim of radioiodine therapy was to treat hyperthyroidism. Eight of them had compressive symtpoms. All euthyroid patients (n = 12) sought treatment for compressive symptoms. In these patients, radioiodine therapy was chosen because of contraindications for surgery (n = 8; mainly because of cardiopulmonary disease) or refusal of the patient to undergo surgery (n = 4). Patients were classified as euthyroid when they had serum-free thyroxine (fT$_4$) and tri-iodothyronine (T$_3$) levels within the normal range of our laboratory (fT$_4$, 9.0–17.0 pmole/liter; T$_3$, 1.5–3.5 nmole/liter) and were not taking antithyroid or thyromimetic drugs. The serum level of thyroid stimulating hormone (TSH) was subnormal (<0.4 mU/liter) in seven patients. In two euthyroid patients, prior TSH suppressive treatment with L-thyroxine had failed to diminish goiter size. L-thyroxine had been withdrawn 2 mo before radioiodine treatment in these patients. All hyperthyroid patients used methimazole and L-thyroxine. They did not receive methimazole for 3 days before and 3 days after radioiodine therapy. Radioiodine was given as a single intravenous dose on an in-patient basis. The administered activity was aimed at delivering 3.7 MBq (100 μCi) of ^{131}I per gram of thyroid tissue retained at 24 hr, according to the following formula (8):

Administered activity (GBq)

$$= \frac{\text{thyroid weight (g)} \times 0.37}{\text{24-hr thyroid radioactive iodide uptake (\%)}}$$

Thyroid radioactive iodide uptake (RAIU) was measured 24 hr after oral ingestion of 7.4 MBq (200 μCi) [131]I (normal range 10–59%). Since gastrointestinal absorption of radioiodine is rapid and complete it is unlikely that the oral route of administration of the diagnostic activity may result in different values for 24-hr RAIU compared with the intravenous route. The thyroid weight was estimated from the planimetric surface on a rectilinear thyroid scintigram using the formula of Doering and Kramer: thyroid weight (g) = 0.326 $\times$ (surface in cm^2)$^{3/2}$ (7).

## Thermoluminescent Dosimeter Measurements and Dosimetric Calculations

Thermoluminescent dosimeter (TLD) measurements were performed following the therapeutic administration of radioiodine in 12 euthyroid and 11 hyperthyroid patients. Two freshly annealed TLDs sealed in a thin polyethylene bag were positioned with sticking plaster on the skin on each of the following three locations: directly over the thyroid gland, over the submandibular gland and over the parotid gland. The TLD on the thyroid gland was placed over the center of the most prominent nodule, which was checked not to be cold on thyroid scintigraphy. Distances between the TLDs on the salivary glands and the palpated ipsilateral top of the thyroid were measured. The TLDs were left in position for 24 hr and replaced daily for 5 to 15 days after the therapeutic administration of radioiodine. After preannealing, TLDs were read for light output (in nanocoulombs) on a TLD reader under dry N$_2$. The calibration factor of TLDs for the gamma irradiation of ^{131}I, as checked in vitro, was 100 microgray per nanocoulomb (μGy/nC). Data from a previous study (4) in patients with a large multinodular goiter (nine of whom also participated in the present study) suggest that the distance between the surface of the thyroid and the surface of the skin, as determined from axial magnetic resonance imaging slices, was more than 5 mm. Therefore, the contribution of beta irradiation was assumed to be negligible on the surface of the skin.

TLD measured values from Day 2 onward were fitted monoexponentially and extrapolated to infinity. The measured values and the integral of the extrapolated function were summed for each location in order to determine cumulated absorbed doses on the skin (Gy).

Thyroid Radioactivity Measurements, Dosimetric Calculations and Risk Estimates

In six euthyroid and six hyperthyroid patients, thyroid radioactivity measurements were performed every 24 hr after the therapeutic administration of radioiodine for 7 to 14 days. A 2 in $\times$ 2 in NaI (TI) detector with a diverged-lead collimator connected with an analyzer (type ST 6, Nuclear Enterprises, Reading, UK) was used. The collimator was provided with a lead collimator diaphragm complying with recommendations of the International Atomic Energy Agency (neck-to-detector distance 26 cm). An 18-mm thick lead shield was placed in front of the detector in order to reduce the count rate and avoid dead-time effects. Measurements were corrected for a 10-ml test tube standard with a known activity of ^{131}I and all values were corrected for background radioactivity in the room and for physical decay. The mean of three measurements of 1-min duration was used.

Thyroid radioactivity measurements were implemented in a simplified model for iodine biokinetics as described by Robertson and Gorman, diagrammatically represented in Figure 1 (5). In this model, intravenously administered radioiodide is removed from the extrathyroidal iodide compartment by excretion into the urinary
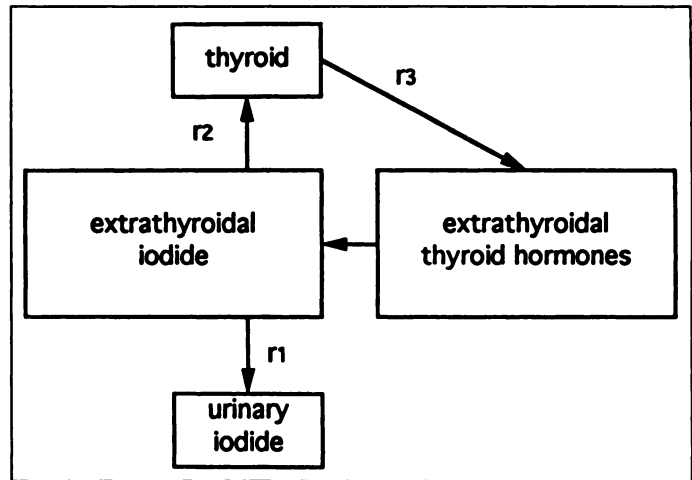
FIGURE 1. Simplified model for iodine biokinetics (5). r_1 = 0.072 hr^{-1} based on a normal renal function. r_2 and r_3 were calculated from thyroid radioactivity measurements. A total of 15% of the extrathyroidal iodide compartment is located in the stomach; 17% in the small intestine; and 40% of the extrathyroidal thyroid hormone compartment is located in the liver. The remaining parts are evenly distributed throughout the body.

iodide compartment, with fractional removal rate r_1 (in hr^{-1}), and by uptake into the thyroid, with fractional uptake rate r_2 (in hr^{-1}). In the thyroid radioiodide is incorporated in thyroglobulin. A 24-hr delay in the secretion of radioiodinated thyroid hormones is assumed (5). After that time, the loss of radioactivity from the thyroid into the compartment of extrathyroidal radioiodinated thyroid hormone is indicated by the fractional secretion rate r_3 (in hr^{-1}). Degradation of the radioiodinated thyroid hormone is assumed to be instantaneous (5). The rate of (renal) excretion of radioiodide resulting from thyroid hormone degradation is supposed to equal that of the administered iodide. The model does not take into account re-uptake into the thyroid of radioiodide resulting from thyroid hormone degradation outside the thyroid. A system of differential equations, using the three rate constants, r_1, r_2 and r_3, and the physical decay constant λ (0.00359 hr^{-1}) describes the rates of changes of radioactivity in the four compartments. The solutions of the differential equations describe the fractional activities, i.e., the fractions of the administered activity at time t in each of the compartments. These fractional activities are integrated in order to obtain the cumulated (time-integrated) fractional activities (cumulated activity per MBq of administered activity in MBq · h/MBq, i.e., in h; this parameter is also referred to as residence time) in each of the four compartments. Time-integrated activities resulting from the total administered activities of radio-iodine are referred to as cumulated activities (in MBq · hr).

Serum creatinine levels were within the normal range in all patients. Therefore, an r_1 of 0.072 hr^{-1} based on a normal renal function was assumed for all patients in our study (9). The r_2 was calculated from the radioactivity measurement at 24 hr and from r_1 (24-hr RAIU = RAIU$_{max}$ [1 − e$^{-24(r_1+r_2)}$] in which RAIU$_{max}$ is the theoretical maximal thyroid radioactive iodide uptake). Thyroid radioactivity measurements from Day 2 onward (corrected for physical decay) were fitted as a monoexponential function. The rate constant of this function was used as r_3.

In the biokinetic model of Robertson and Gorman (5), the extrathyroidal iodide and extrathyroidal thyroid hormone compartments are combined and assumed to be evenly distributed throughout the body, outside the thyroid and urinary bladder. We made the following amendments to the biokinetic model based on data in MIRD Pamphlet No. 12 and MIRD Report No. 5 (10,11). Of the extrathyroidal iodide compartment 15% was assumed to be located in the stomach and 17% in the small intestine. Of the extrathyroidal

thyroid hormone compartment, 40% was assumed to be located in the liver (and, proportional to the weight of the liver, 2.4% of the iodide compartment). Corresponding percentages of the residence times in the extrathyroidal iodide and thyroid hormone compartments were asigned to the stomach, small intestine and liver. The remaining parts of these residence times were assigned to the total body (i.e., evenly distributed throughout the body outside the thyroid, urinary bladder, stomach, small intestine and liver). To obtain the residence time in the urinary bladder, the cumulated fractional activity in the urine was corrected for voiding with a voiding interval of 4 hr (5). Only the urine that enters the bladder during a voiding interval is used in calculating the fractional activity in the bladder during that interval. A constant bladder volume was assumed.

Radiation absorbed doses (1 Gy = 100 rad) in organs were calculated using the MIRD method with tabulated S-values for adults (i.e., the mean radiation absorbed dose in a target organ per unit cumulated activity in a source organ) (12). The calculated residence times in the source organs thyroid, urinary bladder, stomach, small intestine and total body were entered in the MIRDOSE2 computer program (Oak Ridge, TN). In all patients, absorbed doses in the thyroid, as calculated in the MIRDOSE2 program, were corrected for differences in thyroid mass between Standard Man (12) and patients using the Standard Man thyroid mass (20 g)-to-patient thyroid mass ratio and for the increasing absorbed fraction of beta particles and photons with increasing thyroid volume, based on S-values for ^{131}I uniformly distributed in spheres of increasing volumes of 1 g/cm^3 density (13).

ICRP Publication 60 (6) was used to estimate the risk of radiation-induced cancer in our patients. In ICRP 60, absorbed doses weighted by a radiation factor (which is 1 for radiopharmaceuticals) are called equivalent doses (H; in Sievert, Sv; 1 Sv = 100 rem) (6). The sum of the fatal cancer risk (estimated at 5%/Sv whole-body irradiation), nonfatal cancer risk (estimated at 1%/Sv whole-body irradiation) and the risk of severe hereditary effects (estimated at 1.3%/Sv whole-body irradiation) is 7.3% per sievert total body irradiation and is called the total health detriment. The total health detriment is a measure of the adverse health effects that would eventually be experienced by an exposed group and its descendants as a result of the group's exposure to a radiation source (6). These probability coefficients (in %/Sv) are applicable to equivalent doses resulting from absorbed doses below 0.2 Gy and from higher absorbed doses when the dose rate is less than 0.1 Gy per hour. The relative importance of each of the various organs in contributing to this detriment (14) is expressed by its weighting factor (W_T) (6). The detriment for each organ is expressed as $W_T \times 7.3\%/Sv$ organ dose. The fatal and nonfatal cancer risk is extracted from the total health detriment by excluding 90% of the weighting factor for the gonads because this weighting factor applies for 90% to the risk of severe hereditary effects and for only 10% to the gonadal (especially ovarian) cancer risk. For other organs the weighting factor only applies to the cancer risk. Furthermore, the values for tissue weighting factors were used to determine the effective dose which is the sum of the weighted equivalent doses in all the tissues and organs of the body (effective dose = $\Sigma W_T \times H_T$) (6). Only the contributions of the organs and tissues outside the thyroid were summed, because equivalent and effective doses are not applicable to high doses as received by the thyroid during radioiodine therapy.

Statistical Analyses

The mean values ± s.d. are given. Statistical analyses were done using the Mann-Whitney U test for unpaired observations (p-values denoted as p), the Wilcoxon sign-rank test for paired observations (p-values denoted as p*) and the Spearman rank correlation test (p-values denoted as p**). The level of significance was 0.05.

RESULTS

No increases of compressive symptoms were observed after radioiodine treatment. One hyperthyroid patient complained about some further swelling of his goiter from the third until the sixth day after radioiodine therapy. For detailed information on the effectiveness of radioiodine treatment for large, multinodular goiters, the reader is referred to a recently published study from our group (4), in which a 20% to 70% reduction of thyroid volume (mean 40%) and significant decompression of the trachea was demonstrated using MRI 1 yr after radioiodine treatment. In the present group of patients no MRI measurements of thyroid volume reduction and decompression of vital structures were done.

Thermoluminescent Dosimeter Measrements

Table 1 shows patient characteristics and data of TLD measurements on the skin over the thyroid, the submandibular and the parotid gland in 12 euthyroid and 11 hyperthyroid patients. The thyroid weight was similar in both groups of patients. The 24-hr thyroid radioactive iodide uptake was significantly lower in euthyroid patients (p < 0.02). The total administered activity was higher in euthyroid than in hyperthyroid patients, although the difference was not significant. No significant differences in cumulated absorbed doses between euthyroid and hyperthyroid patients were observed at any of the three lcoations on the skin.

Cumulated absorbed doses at all three locations were significantly correlated with the total activity retained in the thyroid at 24 hr (administered activity × 24-hr RAIU) (r = 0.642, p** < 0.001 for the thyroid location; r = 0.696, p** < 0.001 for the submandibular location; r = 0.579, p** < 0.005 for the parotid location) (Fig. 2). The correlation of the cumulated absorbed dose on the skin with the total administered activity was only significant for the location over the thyroid gland (r = 0.557, p** < 0.01) and no correlation of cumulated absorbed doses on the skin with 24-hr RAIU was found (p** > 0.1). The effective half-time of ^{131}I in the thyroid gland, as measured by TLDs, was significantly higher for euthyroid patients (6.1 ± 0.8 days) than for hyperthyroid patients (5.5 ± 0.7 days) (p < 0.03).

Thyroid Radioactivity Measurements, Dosimetric Calculations and Risk Estimates

Table 2 shows patient characteristics and data of thyroid radioactivity measurements in six euthyroid and six hyperthyroid patients. The thyroid weight was similar for euthyroid and hyperthyroid patients. There were no significant differences in administered activity, 24-hr RAIU or effective half-time of ^{131}I in the thyroid (thyroid radioactivity measurements) between both groups. Residence times in source organs, as calculated from thyroid radioactivity measurements and the aforementioned biokinetic model (5) with modifications (10,11), did not differ significantly between euthyroid and hyperthyroid patients, except for the residence time in the liver, which was significantly higher for hyperthyroid patients (p < 0.03) (Table 2). Effective half-times of ^{131}I in the thyroid resulting from thyroid radioactivity measurements were not significantly different from those measured with TLDs in the same 12 patients (Wilcoxon sign-rank test, p* = 0.7). Moreover, a highly significant correlation was found between the cumulated activity (in MBq · hr) in the thyroid and the cumulated absorbed dose on the skin overlying the thyroid as measured with TLDs in the same 12 patients (r = 0.748, p** < 0.01).

TABLE 1
Patient Characteristics and Dta of TLD Measurements after Radioiodine Treatment of Euthyroid and Hyperthyroid Patients with Large Multinodular Goiters (>100 g)

	Euthyroid	Hyperthyroid
Number of patients	12	11
Age (yr)	62 ± 12 (44–81)	71 ± 8 (57–82)
Female:Male ratio	11:1	8:3
Serum level of thyroid-stimulating hormone*	0.33 ± 0.39 (<0.01–1.20)	(on thyroid medication)
Serum level of free thyroxine*	11.9 ± 1.9 (6.9–14.2)	(on thyroid medication)
Serum level of total triiodothyronine*	2.2 ± 0.5 (1.6–3.3)	(on thyroid medication)
Thyroid weight (g)	221 ± 81 (122–351)	224 ± 65 (130–312)
24-hr RAIU (%)	36 ± 11 (21–56)	51 ± 14 (32–88)[†]
Administered activity of ^{131}I (GBq)	2.3 ± 0.8 (1.2–4.0)	1.8 ± 0.8 (0.8–3.3)
Cumulated dose on skin thyroid (Gy)	4.4 ± 1.5 (2.4–7.2)	4.1 ± 1.4 (2.0–6.3)
Cumulated dose on skin submandibular gland (Gy)	1.2 ± 0.6 (0.5–2.4)	1.3 ± 0.6 (0.5–2.0)
Cumulated dose on skin parotid gland (Gy)	0.3 ± 0.1 (0.2–0.8)	0.4 ± 0.1 (0.2–0.7)
Distance thyroid-submandibular gland (cm)	4.7 ± 2.0 (2.5–7.5)	4.3 ± 1.7 (2.5–7.5)
Distance thyroid-parotid gland (cm)	10.7 ± 1.8 (8.5–13.5)	10.5 ± 2.0 (8.0–13.5)
TLD measured effective half-time thyroid (days)	6.1 ± 0.8 (4.4–7.3)	5.5 ± 0.7 (4.2–6.5)[‡]

The mean values ± s.d. are given; ranges are given in parentheses.

*Normal ranges: thyroid-stimulating hormone, 0.4–4.0 mU/l; free thyroxine 9.0–17.0 pmole/l; total triiodothyronine, 1.5–3.5 nmole/liter.

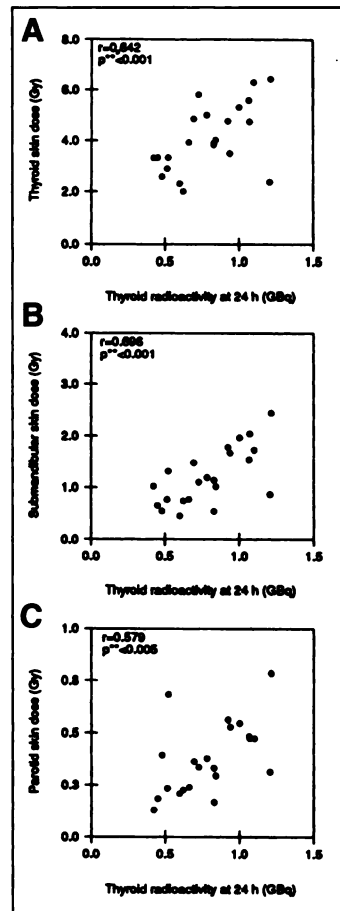[†]p < 0.02 euthyroid versus hyperthyroid patients.

[‡]p < 0.03 euthyroid versus hyperthyroid patients.

Table 3 shows the calculated absorbed doses in the tissues and organs for which a tissue weighting factor has been determined (6), expressed as dose per unit of administered radioiodine (in mGy/MBq) and as dose resulting from the total administered activities of radioiodine (in Gy). Outside the thyroid gland the highest absorbed doses per MBq of administered ^{131}I were calculated for the urinary bladder, followed by

FIGURE 2. Cumulated absorbed doses on the skin over the thyroid (A), over the submandibular gland (B) and over the parotid gland (C) plotted against the total radioactivities retained in the thyroid at 24 hr (administered activity × 24-hr RAIU(%)/100).

the stomach and small intestine. Inverse correlations were found between the 24-hr RAIU and the absorbed doses per MBq in the stomach (r = −0.97, p < 0.001), small intestine (r = −0.98, p < 0.001) and urinary bladder (r = −0.85, p < 0.01). The absorbed dose in the liver was positively correlated with the 24-hr RAIU (r = 0.83, p < 0.001). The absorbed dose in the liver (mGy/MBq) was significantly higher in hyperthyroid than in euthyroid patients (p < 0.03). There were no other significant differences for organ doses between euthyroid and hyperthyroid patients.

Extrathyroidal doses resulting from the total administered activities ranged between 0.06 Gy (testes) and 1.06 Gy (urinary bladder) in euthyroid patients and between 0.04 Gy (testes) and 0.71 Gy (urinary bladder) in hyperthyroid patients (average values of six patients in both groups). No significant correlations of absorbed doses (Gy) with 24-hr RAIU were found. The mean absorbed doses in most tissues were about similar for euthyroid and hyperthyroid patients (p > 0.3). The mean absorbed doses in stomach, small intestine and urinary bladder were higher for euthyroid than for hyperthyroid patients. However, these differences were not significant.

The effective dose for the combined organs and tissues outside the thyroid gland was not significantly different for euthyroid (0.27 ± 0.14 Sv) and hyperthyroid patients (0.19 ± 0.07 Sv). Using the total health detriment of 7.3%/Sv given in ICRP Publication 60 (6) and excluding the risk of severe hereditary effects, the life-time risk of cancer for the combined organs and tissues outside the thyroid can be estimated as 1.8% ± 1.0% for euthyroid patients and 1.3% ± 0.5% for hyperthyroid patients in the present study (difference euthyroid versus hyperthyroid not significant). A total health detriment of 7.3%/Sv is, however, an average for a population of all ages. For people aged 45 yr or older, the probability of radiation-induced cancer is less than half of the average for a population of all ages and for people of 65 yr and older it is only about one-third of the average (6,14,15). Because 8 of 12 patients in the present study were older than 65 yr and only one patient was younger than 60 yr an estimate of approximately 0.5% life-time risk of cancer (outside the thyroid gland) seems more appropriate.

TABLE 2
Patient Characteristics and Data of Thyroid Radioactivity Measurements After Radioiodine Treatment of Euthyroid and Hyperthyroid Patients with Large Multinodular Goiters (>100 g)

	Euthyroid	Hyperthyroid
Number of patients	6	6
Age (yr)	65 ± 10 (52–81)	70 ± 6 (63–80)
Female:Male ratio	5:1	3:3
Thyroid weight (g)	203 ± 84 (126–351)	206 ± 59 (130–274)
24-hr RAIU tracer activity (%)	37 ± 11 (21–48)	51 ± 11 (35–63)*
24-hr RAIU therapeutic activity (%)	37 ± 16 (17–58)	52 ± 5 (47–59)*
Therapeutic activity of ^{131}I (GBq)	2.2 ± 1.1 (1.2–4.0)	1.6 ± 0.6 (0.8–2.2)
Effective half-time of ^{131}I in thyroid (days)	5.7 ± 0.4 (5.1–6.1)	5.3 ± 0.5 (4.7–6.1)
Biological half-time of ^{131}I in thyroid (days)	21 ± 6 (14–31)	18 ± 5 (11–25)
Cumulated activity thyroid (MBq hr)	160 ± 110 (67–377)	155 ± 57 (82–215)
Residence time thyroid (hr)†	77 ± 34 (37–120)	99 ± 11 (82–116)
Residence time stomach (hr)‡	1.23 ± 0.31 (0.84–1.62)	0.9 ±0.08 (0.82–1.04)
Residence time small intestine (hr)‡	1.40 ± 0.35 (0.95–1.83)	1.09 ± 0.10 (0.93–1.18)
Residence time liver (hr)‡	0.70 ± 0.17 (0.47–0.90)	1.00 ± 0.16 (0.71–1.16)§
Residence time rest body (hr)‡	6.3 ± 1.1 (4.9–7.6)	5.5 ± 0.4 (5.0–6.0)
Residence time urinary bladder (hr)‡	1.5 ± .2 (1.2–1.7)	1.3 ± 0.1 (1.2–1.4)

*p < 0.02 euthyroid versus hyperthyroid patients.
†Calculated from thyroid radioactivity measurements.
‡Calculated using thyroid radioactivity measurements and the biokinetic model of Robertson and Gorman (5) with amendments based on MIRD Pamphlet no. 12 (10) and MIRD Report No. 5 (11).
§p < 0.03 euthyroid versus hyperthyroid patients.
The mean values ± s.d. are given; ranges are given in parentheses.

DISCUSSION

In the present study, TLD measurements showed cumulated (i.e., time-integrated) radiation absorbed doses of 4.2 ± 1.4 Gy on the skin directly overlying the thyroid, of 1.2 ± 0.6 Gy on the skin over the submandibular gland and of 0.4 ± 0.2 Gy on the skin over the parotid gland, after therapeutic administration of radioiodine in patients with a large, multinodular goiter

(mean thyroid weight 222 ± 72 g). There were no significant differences between euthyroid and hyperthyroid patients. Absorbed doses at all three locations were significantly correlated with the amount of radioiodine retained in the thyroid at 24 hr. Absorbed doses in the spinal cord must have been lower than the doses measured on the skin over the thyroid because the distance between the posterior edge of the thyroid and the spinal

TABLE 3
Radiation Absorbed Doses in Target Organs after Radioiodine Treatment of Euthyroid and Hyperthyroid Patients with a Large Multinodular Goiter (>100 g) Calculated with the MIRD Method

	Absorbed dose per unit administered activity (mGy/MBq)		Absorbed dose (Gy)	
Target organ	Euthyroid (n = 6)	Hyperthyroid (n = 6)	Euthyroid (n = 6)	Hyperthyroid (n = 6)
Thyroid*	51 ± 23	64 ± 19	94 ± 25	93 ± 17
Red bone marrow	0.092 ± 0.024	0.108 ± 0.008	0.19 ± 0.11	0.16 ± 0.08
Ovaries	0.044 ± 0.008	0.039 ± 0.002	0.10 ± 0.06	0.06 ± 0.02
Testes	0.025 ± 0.004	0.023 ± 0.001	0.06 ± 0.03	0.04 ± 0.01
Colon†	0.044 ± 0.008	0.038 ± 0.002	0.10 ± 0.06	0.06 ± 0.02
Lung	0.089 ± 0.028	0.107 ± 0.009	0.19 ± 0.11	0.17 ± 0.06
Stomach	0.33 ± 0.08	0.26 ± 0.02	0.74 ± 0.49	0.41 ± 0.16
Urinary bladder	0.48 ± 0.08	0.43 ± 0.03	1.06 ± 0.63	0.71 ± 0.30
Breast	0.045 ± 0.010	0.051 ± 0.003	0.10 ± 0.05	0.08 ± 0.03
Liver	0.078 ± .012	0.099 ± 0.011‡	0.17 ± 0.08	0.16 ± 0.06
Skin	0.056 ± 0.015	0.066 ± 0.005	0.12 ± 0.07	0.11 ± 0.03
Bone surface	0.116 ± 0.037	0.140 ± 0.013	0.24 ± 0.14	0.22 ± 0.09
Remainder§	0.085 ± 0.006	0.088 ± 0.003	0.18 ± 0.09	0.14 ± 0.05
Effective dose outside Thyroid (Sv)			0.27 ± 0.14	0.19 ± 0.07

The mean values ± s.d. are given.
*Thyroid absorbed doses as calculated with MIRDOSE2 are corrected for differences in thyroid mass between Standard Man (12) and patients using the Standard Man thyroid mass (20 g)-to-patient thyroid mass ratio and for the increasing absorbed fraction of beta particles and photons with increasing thyroid volume.
†0.57 × dose upper large intestine + 0.43 × dose lower large intestine (6).
‡p < 0.03 euthyroid versus hyperthyroid patients.
§Absorbed dose in the "remainder of the body" is the average dose in the following organs and tissues: adrenals, brain, upper large intestine, small intestine, kidney, muscle, pancreas, spleen, thymus and uterus (6).

cord is considerably larger than the distance between the anterior edge of the thyroid and the surface of the skin. This implies that the cervical spinal cord has absorbed less than one tenth of the dose which in external radiation therapy is considered the threshold dose above which necrosis of the spinal cord may be induced (approximately 55 Gy delivered in 30 fractions over 5 to 6 wk) (15). On the other hand, it is likely that in a number of our patients the esophageal and tracheal mucosa at the level of the thyroid gland have absorbed higher doses of gamma radiation than those measured with TLDs on the skin, because in many patients with a large goiter, thyroid tissue is immediately adjacent to the trachea and esophagus on the anterior as well as on the right and left side. However, it is not to be expected that significant doses of beta radiation have been absorbed in the esophageal and tracheal mucosa, because the maximal range of beta particles of ^{131}I in tissues is 3 mm and the average range only 0.3 mm.

The significant correlation between absorbed doses on the skin overlying the salivary glands and the amount of radioiodine in the thyroid at 24 hr suggests that these doses were for a large part caused by gamma radiation from radioiodine in the thyroid gland. Absorbed doses within the salivary glands will have been higher than those measured on the skin, because of beta irradiation from radioiodide concentrated in these glands. The methods we used do not permit further quantification of the absorbed doses within the salivary glands.

In accordance with earlier studies (16,17) TLD measurements proved an effective method of monitoring effective half-times of ^{131}I in the thyroid. For this purpose TLDs may be applied by the patients themselves at home, thus eliminating the need for frequent thyroid radioactivity measurements in the clinic (17). Our TLD measurements in 23 patients showed a small but significant difference in effective half-times of ^{131}I in the thyroid between euthyroid and hyperthyroid patients (6.1 ± 0.8 days and 5.5 ± 0.7 days, respectively). Thyroid radioactivity measurements with a NaI detector in 12 patients showed similar effective half-times of ^{131}I in the thyroid. Using this method, the difference between euthyroid and hyperthyroid patients was not significant (5.7 ± 0.4 days and 5.3 ± 0.5 days, respectively). The effective half-time of about 5.5 days for hyperthyroid patients found in our study is comparable to other reports on hyperthyroid patients (18–21). However, the observed effective half-times in hyperthyroid as well as in euthyroid patients are considerably lower than those reported in the dose estimate reports for radioiodine in ICRP Publication 53 (7.3 days) (22) and MIRD Report No. 5 (6.9 days) (11) which apply to tracer doses of ^{131}I in euthyroid adults. The fast release of radioiodine from the thyroid found in our study may have been caused by radiation-induced damage to thyroid cells from therapeutic activities of radioiodine (5,21,23) or may be related to the state of iodine sufficiency. In view of the small difference between euthyroid and hyperthyroid patients, the elimination rate of a therapeutic activity of ^{131}I from the thyroid appears to be less dependent on the functional state of the thyroid at the time of therapy.

A highly significant correlation between the cumulated dose on the skin overlying the thyroid and the cumulated activity within the thyroid as measured with a NaI detector was found. However, TLD measurements depend too much on thyroid mass, depth and geometry to warrant their use in estimating absorbed doses within the thyroid (24). Therefore, we used radioactivity measurements with a NaI detector to estimate absorbed doses in the thyroid. The absorbed dose in the thyroid of approximately 95 Gy for both euthyroid and hyperthyroid patients, found in our study, is in the lower range of doses

commonly used for the treatment of toxic multinodular goiter (80–200 Gy) (25–28). This is explained by the combination of a relatively low administered activity per gram of thyroid tissue and a short effective half-time in the thyroid. Uncertainty in our calculations of thyroid absorbed doses is caused by the inaccuracy of thyroid weight estimations by planar scintigraphy (29,30). Furthermore, the calculated absorbed dose in the thyroid is an average value for the whole thyroid gland. In a nodular goiter, considerable regional differences in absorbed doses are caused by inhomogeneous radioiodine uptake within the goiter.

Using radioactivity measurements and the biokinetic model of Robertson and Gorman (5), the mean values for absorbed doses in extrathyroidal tissues and organs ranged from 0.024 to 0.46 mGy/MBq of administered radioiodine. Absorbed doses per MBq in the urinary bladder, stomach and small intestine were inversely correlated with 24-hr RAIU, because a larger uptake of iodide into the thyroid gland reduces the residence time of [^{131}I]iodide in the urinary bladder and other extrathyroidal organs. The liver, unlike stomach, small intestine and urinary bladder, is the organ where ^{131}I incorporated in thyroid hormones is collected and metabolized. This was accounted for by assigning 40% of the extrathyroidal thyroid hormone compartment to the liver (10,11). This explains why the absorbed dose per MBq in the liver was positively correlated with the 24-hr RAIU, which is an indicator of the synthesis of thyroid hormones. Furthermore, the residence time and the absorbed dose per MBq in the liver were significantly higher in hyperthyroid than in euthyroid patients, reflecting the higher metabolism of radioiodinated thyroid hormones in hyperthyroidism. However, for the absorbed doses resulting from the total administered activities of radioiodine, neither significant correlations with the 24-hr RAIU nor a significant difference between hyperthyroid and euthyroid patients were found, because in our dose calculations the total administered activity is inversely related with 24-hr RAIU.

The absorbed doses per MBq of administered ^{131}I found in our study are in accordance with data in the literature, obtained by other techniques of measurement and other biokinetic models (11,22,31–33). However, our patients with large, multinodular goiters and a low thyroid radioiodide uptake received considerably larger total activities of radioiodine than the amounts that are commonly used in patients with Graves' disease. Therefore, extrathyroidal radiation absorbed doses (in Gy) were about four times as high as those reported for patients with Graves' disease in the literature (5,34–37).

The risk of induction of thyroid cancer by external radiation is dose dependent (38). Absorbed doses in the thyroid during radioiodine therapy are more than 10 times as high as doses reported for external radiation exposure (38). However, in studies with a long-term follow-up of large numbers of patients treated with radioiodine for hyperthyroidism no significantly increased risk of thyroid cancer was found (36,37,39,40). It has been suggested that high doses, as absorbed in the thyroid during radioiodine therapy for hyperthyroidism, lead to substantial cell killing and cell sterilization instead of the production of carcinogenic mutations in the cell's DNA (36,38,41). Although our patients with large goiters received higher total amounts of radioiodine than the patients in the aforementioned follow-up studies (36,37,39,40) absorbed doses in the thyroid were similar. Therefore, an elevated risk of thyroid cancer is not to be expected in these patients with a large goiter.

From studies with follow-up till 35 yr, there is no evidence that the overall cancer incidence and cancer mortality in patients with Graves' disease treated with radioiodine are

elevated (36,37,42,43). Literature on cancer incidences after radioiodine therapy relating specifically to patients with nodular goiter is sparse. In one study, a slightly elevated overall cancer incidence was reported in patients with toxic nodular goiter treated with radioiodine (average administered activity 700 MBq or 19 mCi), possibly related to higher administered activities than in patients with Graves' disease (average administered activity 360 MBq or 10 mCi) (36). This is still to be confirmed in other studies. With respect to the incidence of cancers of individual extrathyroidal organs and tissues in patients treated with radioiodine for hyperthyroidism (Graves' disease or nodular goiter), the risk of leukemia appears not to be elevated (44–46). The risk of cancer of the stomach may be slightly increased (36,37). In some studies, the incidences of bladder cancer and of breast cancer have been reported to be increased (45,47,48). However, these findings have not been confirmed by other studies (36,37,45).

In our study, patients with a large, multinodular goiter were treated with considerably larger amounts of radioiodine (1900 MBq or 51 mCi on average) than the average doses administered in the aforementioned studies. Using a total health detriment of 7.3%/Sv for a population of all ages (6) and excluding the risk of severe hereditary effects, we calculated a 1.6% life-time risk of fatal and nonfatal cancer for the combined organs outside the thyroid. By comparison, the life-time risk of fatal cancer for an unexposed population of all ages is approximately 20% (49) and this percentage is of course higher when nonfatal cancers are included. In older people, the full incidence of radiation-induced cancer is not expressed because their life expectancy is shorter than the average latent period (14,49). Accordingly, we calculated a lower risk (0.5%) for people over 65 yr of age. This figure is in the same order of magnitude as that reported for the surgical mortality of subtotal thyroidectomy (1,3). The risks of surgery are of course higher in elderly patients, in patients with a large goiter and in those with cardiopulmonary disease (2). Furthermore, the morbidity of thyroid surgery, including nonfatal complications, is considerably larger (1–3).

Until now, no follow-up data on cancer incidence in patients with a large goiter treated with high doses of radioiodine are available. It has to be stressed that the risk of radioiodine therapy calculated in our study is only a rough estimate of risk. Because radiation risk estimates are predominantly based on epidemiological data of populations after instantaneous external irradiation (mostly survivors of the atomic bombs) they comprise a number of uncertainties, e.g., uncertainties inherent in dose estimations, in the selection of an appropriate risk model, and in the applicability of risk estimates measured in one population to other exposed groups (6,49,50). In the case of radioiodine therapy the cancer risk may be overestimated because the carcinogenic effectiveness per gray of gamma and beta radiation is reduced at the low dose rates which are delivered by the internally deposited ^{131}I with its physical half-time of 8 days (49).

CONCLUSION

The estimated risks of both surgery and radioiodine should be carefully weighed in all patients with a large, multinodular goiter who have to be treated for hyperthyroidism or compressive problems. In younger patients surgery may be preferred, especially when the amount of radioiodine to be administered, as calculated from a radioiodine tracer study, is high or whenever there is any suspicion of thyroid malignancy. However, for elderly patients and patients with cardiopulmonary

disease, the profits of noninvasive radioiodine treatment will outweigh the life-time risk of this mode of therapy.

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Radiation Dose from Breastfeeding Following Administration of Thallium-201

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Radiation exposure to a breast feeding infant was estimated when the mother underwent a nuclear medicine procedure using ^{201}Tl. **Methods:** A lactating mother was administered 111 MBq of ^{201}Tl for a brain scan. Breast milk samples were collected over a period of three days, and the rate of ^{201}Tl secretion was determined. The infant was not breast fed during that time. Based on our data, we determined the time-activity function for radioactivity in the breast milk. From these data, and assuming an intake of 1000 ml/day, we calculated the fraction of administered activity that might be taken in by the infant. We also calculated the intake assuming breastfeeding delays of 2, 24, 48, 72, 96 and 500 hr. **Results:** We calculated the radiation dose to various organs and the effective dose to an infant and a 1-yr-old for breastfeeding delays of 2 to 500 hr. The effective dose to a 1-yr-old from an administration of 111 MBq of ^{201}Tl to the mother ranged from 0.90 mSv to 0.00072 mSv, and the effective dose to a newborn ranged from 1.6 mSv to 0.0013 mSv depending on delay time. **Conclusion:** Our estimates of radiation exposure to an infant from breastfeeding indicate that in this case, a 1-yr-old would have received less than the NCRP's proposed limit on annual effective dose to members of the general public of 1 mSv with a 48-hr delay and no restrictions on holding the child. A newborn would have received less than the proposed infrequent exposure limit of 5 mSv without any delay or restrictions in breastfeeding.

Key Words: breast milk; radiation dose; radioactivity

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It is generally not desirable to administer radionuclides to patients who are breastfeeding. In those cases, however, where it is deemed necessary for the health of the mother to proceed with a nuclear medicine study, the recommendation often is to stop nursing for some period of time. The ICRP recommendations (*1*) for cessation of breastfeeding, if any, depend on which of the defined groups the radionuclide falls into. Thallium-201

falls into group 1, for which the recommendation is to stop nursing for a period of 3 wk. This is the most conservative approach, short of complete cessation of breastfeeding, from the viewpoint of radiation safety. It may, however, be highly undesirable for many other reasons. The literature provides limited data on the secretion of radiopharmaceuticals in breast milk (*2–4*). We measured ^{201}Tl excretion in breast milk of a patient after administration of thallous chloride for a brain scan.

MATERIALS AND METHODS

The patient was a 32-yr-old female with a history of a brain tumor which had been treated with multiple surgical resections and radiation therapy. The patient was scheduled in the nuclear medicine clinic for a ^{201}Tl brain scan which was performed with 111 MBq (3 mCi) to evaluate for abnormal uptake which would indicate residual tumor and serve as a baseline for further imaging. At the time of the study, the patient was breastfeeding. The child was a normal, healthy 5-mo-old. The decision to undergo the study rather than to delay it to a later date was based on the strong desire of the patient and her family to proceed.

The mother was instructed that she should temporarily cease breastfeeding and use a breast pump from the time of administration of the radioactivity until we could make a further evaluation. No restrictions were imposed on holding her infant. Breast milk samples were collected by the patient at the times she would normally have breast fed over a period of three days beginning with the time of administration. Samples from each breast pumping were collected in 20 ml test tubes, labeled with the date and time of expression, and refrigerated. The samples were returned to the nuclear medicine clinic 3 days later. The milk samples and a ^{201}Tl standard were counted in a scintillation well counter. The milk sample results were recorded in terms of the radioactive concentration (Bq/ml) and decay corrected to the time of administration. A total of 10 samples were collected over a period of 72 hr from the time of administration. The corrected radioactivity concentration is shown in Table 1.