Radioiodine Therapy of the Autonomous Thyroid Nodule in Patients with or without Visible Extranodular Activity

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Patients with an autonomously functioning thyroid nodule (ATN) may be present with various clinical, biochemical and scintigraphic features. To optimize ^{131}I dose planning and treatment timing in these patients, relationships between dosimetric data and clinical follow-up events must be established. **Methods:** We retrospectively reviewed the records of 88 patients who received ^{131}I (intended dose of 80 Gy) for an ATN, of whom 39 had evidence of extranodular activity (ENA) and 76 presented with overt thyrotoxicosis. In all of the patients, dosage calculation was monitored to estimate precisely both beta and gamma absorbed doses received by the ATN and the nodule-free lobe. The mean duration of follow-up was 75 mo (max 180) and always included biochemical thyroid tests. Finally, we compared the dosimetric profiles of four dosage schemes which had been normalized by simulation to ensure that the same absorbed dose threshold value was always delivered to the ATN. **Results:** About 75% of the patients were cured at 6 mo for a mean 305 MBq administered. The absorbed doses delivered to the nodule-free lobe ranged from 12% (no ENA) to 86% (ENA) of the values delivered to the ATN, mainly in the form of beta irradiation. Life-table estimates for hypothyroidism and death were 9.6% and 22% at 75 mo, respectively. Hypothyroidism mainly developed in patients with nonsuppressed TSH levels but regardless of ENA, which often accounted for multifocal disease. **Conclusion:** We suggest that fixed doses bordering on 370 MBq are advizable in younger individuals and in patients with mild thyrotoxocosis, while 555 MBq–740 MBq can be administered in other patients and that ENA indicates multifocal autonomy in patients with toxic ATN and is a further indication for radioiodine treatment which should be begun as soon as possible to avoid the development of cardiac complications.

Key Words: iodine-131 therapy; autonomous thyroid nodule; dosimetry

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Radioiodine therapy is a widely accepted method for the treatment of hyperthyroidism (*1*) due to autonomous thyroid nodules (ATN). Fixed therapeutic ^{131}I doses, ranging from 555 MBq to 740 MBq, have been reported to cure a large majority of patients within a few months after therapy (*2*). Moreover, the incidence of hypothyroidism following ^{131}I therapy is usually low in these patients (*3*). The two main factors associated with the occurrence of this side effect in ATN patients are significant ^{131}I uptake in the presumably healthy extranodular tissue and elevated serum antithyroid antibody titers (*1,3,4*).

However, new insights into ATN pathophysiology and recent technological advances, such as the assessment of thyroid function by ultrasensitive TSH determination or routine ultrasound imaging of the whole gland, should modify the ATN treatment strategy. The evolution of ATN into a toxic state is usually a very slow, gradual process when it occurs (*5,6*). For several years, early diagnosis of what is sometimes called low toxic forms of ATN (*3*), biochemically defined on the basis of isolated suppressed ultrasensitive TSH values, has routinely been performed. Many clinicians consider that ^{131}I therapy should be postponed in patients with extranodular activity (ENA). However, this recommendation should be reappraised, because associated autonomous millimetric nodules are often imaged with adequate nuclear imaging doses of ^{123}I and sonography (*7*). In addition, the widespread nature of this disease has been previously demonstrated at tissue level using microautoradiographic techniques. Whether similar therapeutic strategies should always be applied in these various situations remains to be investigated.

We treated 88 patients with ATN, 39 of whom had evidence of extranodular tissue function. Since we carefully monitored the calculation of dosages, we were able to estimate beta and gamma absorbed doses in both the ATN and the extranodular parenchyma. Based on a follow-up review and our dosimetric findings, a modulated therapeutic strategy is suggested.

METHODS

Patients

The records of 88 patients who received ^{131}I for an ATN between 1979 and 1989 were selected. All patients had a physical

examination with special attention paid to signs and symptoms of hyperthyroidism and were found to have a clinically solitary thyroid nodule. A recent history of cardiac disorders such as supraventricular arrhythmia or cardiac failure and any past history of intrinsic cardiopathy were systematically recorded. The patients with cardiac disturbances were always referred for ^{131}I treatment by the cardiologists, once the clinical cardiac symptoms were practically normalized with appropriate therapy, which may have included antithyroid drugs. Patients who had received antithyroid drugs less than 4 wk before therapy were excluded. Patients with a previous history of thyroid surgery or ^{131}I therapy, with iodine overload or who lacked the data required for a reliable estimation of the absorbed doses (see below) were also excluded. The population selected was fully comparable to the overall population (n = 117) with regard to age, sex and nodule weights.

Radioimmunological assays (Henning, Berlin, Germany) were always used to assess the thryoidal biochemical status. Thyroid hormone levels were considered to be elevated when they exceeded the following values: free T3 over 11.7 pmole/liter or free T4 over 30 pmole/liter (available after 1984), and a total T3 over 3348 pmole/liter or free T4 index level over 137 arbitrary units (1979–1984). TSH values were considered to be suppressed when the thyrotropin-releasing hormone test showed a maximal TSH variation of <2 mU/liter, or when ultrasensitive determinations, available as of 1984, showed values of ≤0.1 mU/liter (reference range: 0.3–3.5 mU/liter, threshold detection level: 0.03 mU/liter) (*8*). Antithyroid antibody levels were determined by passive hemagglutination. A follow-up review was undertaken. Patients were usually clinically and biochemically re-evaluated at 3 and 6 to 9 and 12 to 15 mo after ^{131}I therapy and every 2 to 5 yr after the first year. The mean duration of follow-up was 77 mo (3–180) for biochemical data and 91 mo for lifespan.

A ^{131}I thyroid rectilinear scan was systematically performed 24 or 48 hr after oral administration of a test dose, and always revealed a single hot nodule. In older records of patients who had normal hormone levels, we requested that ^{131}I uptake, measured before and after exogenous administration of T3 (75 μg/d, for 7 days), not be suppressed, to establish that the hot nodule was indeed an ATN (*1*). In addition, especially in patients with no ENA, postbovine-TSH images (n = 25) were obtained and showed the restoration of tracer uptake in extranodular tissue.

When dynamic isotopic tests were performed, a new scan was obtained for dose calculations, after a period of at least 6 wk. Extranodular activity was visualized in the nodule-free lobe in 44% of the patients. Using the same test dose, ^{131}I uptake measurements were performed at 3, 6, 24, 48 or 72 hr and at least twice after the 96th hr (maximum 912 hr) in accordance with IAEA recommendations (*9*).

Absorbed Dose Determinations

The weight of the ATN (indexed 1) and of the nodule-free lobe (indexed 2) was assessed by planimetry (*10*). The scan was digitized into a 64 × 64 matrix (Tridac BA 163/3, Intertechnique, France) and the surface areas of the lobes were derived using the ROI method with the CINE 200 computer system. The weight of the nodule-free lobe was usually derived from a follow-up scan, under endogenous TSH stimulation of tracer uptake, or from a pretherapy scan performed after exogenous administration of TSH. The distance (X) between the centre of the ATN and that of the other lobe was determined from the same scan. We also used the scans corresponding to the therapy period to distinguish between a diffuse or a partial pattern of ENA distribution within the nodule-free lobe. Regional ^{131}I uptake by the ATN and by the nodule-free lobe was calculated by multiplying the 24 hr uptake value by the relative counts obtained in two symmetric rectangular ROIs which included both the nodule f1 = C1/(C1 + C2) and the nodule-free lobe f2 = C2/(C1 + C2). The effective cumulated ^{131}I activity was directly calculated up to the 48th and 72nd hr by integration and thereafter by postulating monoexponential decay of the isotope in the thyroid. Average absorbed doses for ^{131}I beta and gamma radiations were calculated using:

$$\overline{AD_\beta} = \tilde{A} \times W^{-1} \times n_\beta \bar{E}_\beta \text{ and}$$

$$\overline{AD_\gamma} = \tilde{A} \times W^{-1} \times \sum_j \Delta_j \phi_j,$$

where $\tilde{A}$ is the cumulated activity, W the mass of the target, $\overline{E_\beta}$ and n_β the average energy of beta spectrum (184 keV) and the average number of particles emitted per disintegration (1.003) respectively, Δ_j the equilibrium dose constant (gr-Gy/Bq-s) and ϕ_j the absorbed fraction. Thus, if the target and source are the same, the average absorbed dose corresponding to beta-emitting radiations can be calculated with the specified units:

$$\overline{AD_{\beta,i}}(Gy) = 0.12 \times f_i \times \tilde{A}(MBq\text{-}hr) \times W_i^{-1}(g^{-1})$$

with i = 1 (ATN) or i = 2 (nodule-free lobe).

For self gamma dose calculations, we determined the absorbed fraction values corresponding to small volumes (*11*) taking into account the five main photon emissions of ^{131}I (*12*). The average photon energy emitted per disintegration ranged between 15.25 (W = 10 g) and 31.77 (W = 80 g) keV. Finally, the gamma radiation exposure rate constant delivered by the ATN to the nodule-free lobe (and vice versa) was calculated for a separate point source and target at a distance X, expressed in meters. With Γ being the air Kerma rate constant ($14.8\ 10^{-18}$ Gy m^2 Bq s^{-1}), τ the factor enabling conversion to the dose absorbed in water (1.111) and μ the linear attenuation coefficient in water (0.032 cm^{-1} for a 364 keV energy emission), then:

$$\overline{AD_{\gamma,i}} = \Gamma \times f_i \times \tau \times \tilde{A}(Bq\text{-}s) \times X^{-2} \times e^{-\mu X},$$

where i = 1 (ATN) or 2 (nodule-free lobe).

In these calculations, the absorbed doses delivered to the invisible healthy parenchyma surrounding the ATN, were not taken into account.

Therapeutic Dose

The patients were given a therapeutic dose (TD) which was supposed to deliver a mean absorbed dose of 80 Gy to the nodule. To calculate the corresponding therapeutic activity, we used the Marinelli method (*13*) which postulates a maximal uptake at time 0 (Up0) followed by monoexponential decay of the isotope in the thyroid. The value of the biological decay constant is derived from the late ^{131}I biological uptake values (>24 hr) while the physical decay constant is set at ln2/8.05 (dy^{-1}). Having integrated from t = 0 to infinity, the cumulated activity is TD Up0 $(ln2/HL)^{-1}$, where TD is the therapeutic dose and HL the effective half-life of the isotope. Using this specific value in Equation 1 and given that the mean absorbed dose was 90% dependent upon beta emission, then with the specified units:

$$TD(MBq) = 80(Gy) \times W(g) \times [0.042 \times HL(dy) \times Up0(\%)]^{-1}.$$

Effects of Dose Selection Methodology

To investigate the putative benefit of using more or less sophisticated dosage schemes, we calculated by simulation the absorbed doses delivered to the nodule and to the nodule-free lobe using three methods of dose selection and compared results to that of a fixed dose of 740 MBq known to be effective in treating toxic ATN (*2*). Total absorbed doses in the ATN were calculated for 740 MBq in our series and were classified in ascending order. The 10th percentile value (104 Gy) was retained as plausible to guarantee cure in the majority of patients. To perform a many-one comparison, simulation was used to normalize the remaining three methods. The choice of the appropriate values, calculated by simulation, guaranteed that 104 Gy was always the 10th percentile value of absorbed dose dispersion, regardless of the dosage scheme.

Characterization of Extranodular Tissue: Autonomy and Nuclear Imaging

To characterize whether the visualization of ENA reflected autonomy or TSH-stimulated uptake, we compared the regional ^{131}I counts measured in the nodule-free lobe to the corresponding ultrasensitive TSH values in our group of patients, and studied all the scans performed before and after ^{131}I therapy.

Statistics

Patient characteristics and actual dosimetric data were compared using the unpaired Student's t-test. In the simulation, values obtained with the fixed dose method were compared to the data obtained with the three other methods of dose selection using Dunnett's many-one multiple comparison t-test. Survival curves and the occurrence of hypothyroidism were computed according to the Kaplan-Meier method and statistical comparisons performed with the logrank test.

RESULTS

As presented in Table 1, patients clinical events were comparable regardless of ENA. Seventy-two patients with suppressed TSH levels were considered hyperthyroid while 7 were found to be clinically euthyroid. A greater weight gain after iodine therapy was observed in patients with biochemical evidence of thyrotoxicosis at the time of therapy. Table 2 showed a correlation between thyroid hormone secretion and both the weight of the ATN and the values of the cumulated uptakes.

About 60% of the patients became euthyroid 3 mo after therapy, 74% at 6–9 mo, 81% at one yr and only 77% at the end of the follow-up because of the late onset of hypothyroidism. At the end of the follow-up, hypothyroidism was mild in 4 patients (TSH <10 μU/ml) and 8 others required replacement therapy. The development of this side effect was not related to ENA, to the presence of antithyroid antibodies ($p = 0.82$), to exogenous TSH administration ($p = 0.76$) nor to absorbed doses at the thyroid level ($p = 0.4$ to 0.9). Two related factors were involved here, clinical euthyroidism at the time of therapy ($p < 0.0001$) and nonsuppressed TSH levels ($p < 0.001$). Finally, hypothyroidism developed only in patients without cardiac complications ($p = 0.043$) probably because these patients had a longer lifespan.

Twenty patients died. This corresponds to a life-table estimate of 23% at 90 mo. Two independent factors were involved: first an older age at the time of therapy (74 ± 4 yr versus 62 ± 10 yr., $p < 0.0004$ logrank test) and particularly

TABLE 1
Characteristics of the Patients with an Autonomous Thyroid Nodule (ATN) According to Scintigraphic and Biochemical Status

	Scintigraphic status		Biochemical status			
	Visible extranodular activity		Hormone levels		TSH levels	
Patient characteristics	No	Yes	Elevated	Normal	Suppressed	Nonsuppressed
Number	49	39	56	32	79	9
Age (yr)	64 ± 10	65 ± 12	65 ± 11	64 ± 12	64 ± 11	69 ± 11
Sex (% female)	83.7	92.3	85.7	90.6	88.6	77.7
Associated cardiac disease (%)*	38.7	35.9	44.6	25	39.2	22.2
Clinical toxicity (%)	87.7	84.6	96.4	68.7§	91.1	44.4§
Therapy failure (%)	10.2	17.9	16	9.4	15.2	0
Hypothyroidism (%)†	6.9	12.2	5.7	16.2	7.9	23.8§
Death (%)†	23.3	16.4	21.2	17.0	19.3	25.0
Weight gain after therapy (kg)	4.9 ± 4.0	4.2 ± 3.7	5.6 ± 4.1	2.9 ± 2.9††	4.9 ± 3.9	1.9 ± 1.2‡

Elevated levels for thyroid hormone values refer to normal ranges in our laboratory given in the methods. Thyroid stimulating hormone levels are considered as suppressed for patients having ultrasensitive TSH levels <0.1 mU/l (>1984) or a flat TSH response (ΔTSH <2 mU/l) to exogenous TRH (1979–1984).

*Patients with a history of tachyarrhythmia, cardiac failure or intrinsic cardiopathy. Therapy failure refers to a persistence of hyperthyroidism at 12 mo or the need for retreatment or surgery. The weight gain after therapy was the maximal variation observed within the first two yr of follow-up. Age and weight gain (mean ± s.d.) are compared with the Student's t-test and observed percentages using the chi-square test.

†Estimated rates for hypothyroidism and death, computed according to the Kaplan-Meier method, are presented at 75 mo post-treatment; comparisons are made with the logrank test.

‡$p < 0.05$.

§$p < 0.001$.

TABLE 2
Characteristics of Autonomous Thyroid Nodule (ATN) in Patients According to Scintigraphic and Biochemical Status

Patient characteristics	Scintigraphic status: Visible extranodular activity No	Scintigraphic status: Visible extranodular activity Yes	Biochemical status: Hormone levels Elevated	Biochemical status: Hormone levels Normal	Biochemical status: TSH levels Suppressed	Biochemical status: TSH levels Nonsuppressed
Number	49	39	56	32	79	9
Nodule weight (g)	38.9 ± 19.9	37.5 ± 13.4	43.6 ± 18.2†	28.9 ± 10.2	39.2 ± 17.3	30.9 ± 15.7
Weight of the ATN-free lobe (g)	11.5 ± 5.8	12.1 ± 6.2	12.6 ± 6.5*	10.8 ± 5.1	11.8 ± 6.2	11.6 ± 4.2
X (mm)†	33.4 ± 6	32.6 ± 5	34.7 ± 5	30.7 ± 5.9	32.6 ± 5.6	35.4 ± 6.7
24-hr ^{131}I uptake (%)	46 ± 13	48 ± 14	51.6 ± 11.9†	38.8 ± 12	48.8 ± 12.6†	29.9 ± 7.4
Effective half-life (dy)	5.69 ± 1.1	5.84 ± 1.1	5.7 ± 1.2	5.8 ± 1.0	5.73 ± 1.1	5.97 ± 1.0
Relative counts§	0.031 ± 0.034†	0.211 ± 0.12	0.110 ± 0.1	0.113 ± 0.1	0.109 ± 0.12	0.127 ± 0.135
ATN-free lobe ^{131}I uptake (%)	1.32 ± 0.85†	10.6 ± 7.5	5.92 ± 7.3	4.56 ± 5.7	5.66 ± 7.0	3.38 ± 3.4
Effective cumulated uptake (% hr)	7542 ± 2919	7978 ± 2311	8377 ± 2506*	6613 ± 2587	7975 ± 2608*	5628 ± 2269

Values are mean ± s.d. Comparisons were performed using the Student's t-test (*$p < 0.01$, †$p < 0.001$). Elevated levels for thyroid hormone values refer to the normal ranges in our laboratory given in the methods. Thyroid stimulating hormone levels are considered as suppressed for patients with ultrasensitive TSH levels <0.1 mU/l or a flat TSH response (ΔTSH <2) to exogenous TRH (period 1979–1984).

†The distance X, between the nodule and the nodule-free lobe was that measured between their respective centres.

§The relative counts, f2 = C2/(C1 + C2), referred to the ratio of ^{131}I activity taken up by the nodule-free lobe (see Methods).

a cardiac involvement ($p < 0.0001$, log-rank test) such as the aggravation of intrinsic cardiopathy or the discovery of a complication, mainly in the form of supraventricular arrhythmia. It is noteworthy that 92% of the patients who died had become euthyroid after ^{131}I and that none of the patients who had been treated in the euthyroid state died subsequently.

Absorbed dose estimates are reported in Table 3. In patients with no ENA, the mean absorbed dose value delivered to the ATN was 10% lower compared to the intended value of 80 Gy, using the Marinelli method. This simply indicates that time-activity integrals are overestimated by 11% with this modelisation. The nodule-free lobe received only 12% of the dose delivered to the ATN. In contrast, in ENA patients the nodule-free lobe received a mean absorbed dose as high as 86% of the dose delivered to the ATN. In addition, absorbed dose levels in the ATN were found to be lower in ENA patients, due to the use of a global uptake instead of a regional uptake, to calculate the therapeutic dose. Gamma irradiation accounted for about 12% of the whole dose to the ATN, regardless of ENA. However, in patients with no ENA, the gamma-dose represented 21% of the whole dose delivered to the nodule-free lobe.

According to simulation data reported in Table 4, no significant decrease was found in the levels of the planned therapeutic doses, whatever the dosage scheme applied. Radiation doses to the nodule-free lobe were found to be considerably different according to ENA, but not according to dosage schemes tested.

TABLE 3
Mean Beta and Gamma Absorbed Doses (Gy) Delivered to the Autonomous Thyroid Nodule (ATN) and the Nodule-Free Lobe

	ATN patients		
Visible extranodular activity (ENA)	No ENA	ENA present	P
Therapeutic dose (MBq)	325 ± 142	279 ± 116	0.107
Beta-absorbed dose 1	64.1 ± 11.2	50.7 ± 17.5	0.0001
Beta-absorbed dose 2	6.7 ± 4.6	44.1 ± 31.2	0.0001
Self gamma-absorbed dose 1	7.8 ± 1.9	5.9 ± 1.9	0.0001
Self gamma-absorbed dose 2	0.59 ± 0.39	3.86 ± 2.7	0.0001
Cross gamma-absorbed dose 1-2	0.04 ± 0.03	0.22 ± 0.15	0.0001
Cross gamma-absorbed dose 2-1	1.2 ± 0.9	0.87 ± 0.39	0.046
Total absorbed dose 1	72 ± 12.5	56.9 ± 19.0	0.0001
Total absorbed dose 2	8.5 ± 5.3	48.9 ± 33.8	0.0001

Values are mean ± s.d. and compared using the Student's t-test. Index 1 corresponds to the ATN while Index 2 indicates the nodule-free lobe. 2-1 (1-2) indicates the absorbed dose delivered by the ATN to the nodule-free lobe (the nodule-free lobe to the ATN), respectively. Absorbed doses were calculated assuming that the isotope is homogeneously distributed in its target. Cross gamma radiation doses (i-j) were calculated treating the ATN and the nodule-free lobe as point sources (see methods).

TABLE 4
Influence of Dose Selection Methods on Therapeutic Dose (TD) Levels and Absorbed Dose Profiles Determined Separately for the Autonomous Thyroid Nodule (1) and the Nodule-Free Lobe (2)

Dosage scheme	TD equation	*Specific values	TD (MBq)	Absorbed dose 1		Absorbed dose 2	
				ENA	no ENA	ENA	no ENA
Fixed dose	TD = constant activity	740 MBq	740	167 ± 74	188 ± 72	143 ± 99	20 ± 12
Weight modified method	TD = C W	C = 22.3 MBq/g	856 ± 385	173 ± 61	199 ± 82	164 ± 130	25 ± 21†
24-hr uptake based method	TD = 100 C W (24 Up)$^{-1}$	C = 8.82 MBq/g	729 ± 262	146 ± 41†	170 ± 44†	132 ± 96	21 ± 17
Marinelli method	TD = AD W (0.042 HL Up0)$^{-1}$	AD = 184 Gy	662 ± 302	124 ± 27‡	149 ± 20‡	115 ± 89†	18 ± 11

Values of the therapeutic doses (MBq) and of the corresponding absorbed doses (Gy) are mean ± s.d. W refers to ATN weight (g) in the different TD equations.

*The specific values used in the TD equations are calculated by simulation to guarantee that the same threshold value of 104 Gy is always the 10th percentile value of the corresponding absorbed dose distribution in the autonomous nodule (see section: influence of the method of dose selection). The absorbed doses delivered to the nodule-free lobe (absorbed dose 2) are given according to visible extranodular activity (ENA). The different methods are compared to the fixed dose using the Dunnett's many-one t-test (†$p < 0.05$, ‡$p < 0.01$).

§The individual determination of the isotope's effective half-life and of the extrapolated uptake at time 0, Up0, are required for the Marinelli method. Uptake values are expressed as percentages.

The relationships between ultrasensitive TSH values and regional activity taken up by the nodule-free lobe are presented in Table 5. No linear correlation was found when the scans performed in the pretherapy period were studied, regardless of ENA. In contrast, in treated patients who had recovered a normal thyroid function after therapy, TSH and regional counts in the nodule-free lobe correlated closely ($p < 0.0001$).

DISCUSSION

In this study of patients with ATN, an evaluation of radioiodine therapy was attempted according to clinical, biochemical and scintigraphic presentations, which often were not superimposable. For instance, many patients with clinical evidence of supraphysiological secretion of thyroid hormones, though in the normal range, only presented with low ultrasensitive TSH values. However, these biologically low toxic forms may account for severe clinical manifestations, especially in patients with intrinsic cardiac diseases, and because tissue sensitivity to thyroid hormone levels gives rise to wide variations among individuals. A nonsuppressed TSH value may even be sampled in the morning since modifications in circadian TSH secretion are thought to be an early marker of thyrotoxicosis (*14*). Finally, clinical euthyroidism, despite suppressed TSH values, is a common feature, especially in patients receiving beta blockers. On the other hand, ENA may represent either persistent TSH-stimulated ^{131}I uptake by the healthy tissue or multifocal autonomy.

Given that the rapid elimination of hyperthyroidism is

TABLE 5
Relationships Between TSH Values and Regional ^{131}I Counts in the Nodule-Free Lobe Derived from 250 Scans on According to Visible Extranodular Activity (ENA) and Time of Therapy

	Regional counts*		TSH†		Correlation‡
	n	mean ± s.d.	n	mean ± s.d.	slope/r/p
		Pretherapy period (mean: −3.2 ± 11 mo)			
Whole scans	107	0.108 ± 0.114	49	0.05 ± 0.09	−0.06/0.05/ns
No ENA	57	0.028 ± 0.016	31	0.04 ± 0.05	
ENA	50	0.199 ± 0.109	18	0.06 ± 0.13	
p§		0.001		NS	
		Post-therapy period (mean: +8.4 ± 7.9 mo)			
Whole scans	143	0.204 ± 0.151	61	0.92 ± 1.12	4.1/0.6/0.0001
No ENA	39	0.025 ± 0.016	18	0.06 ± 0.08	
ENA	104	0.271 ± 0.121	43	1.3 ± 1.16	
P§		0.0001		0.0001	

Values are mean ± s.d.

*The regional counts: f2 = C2/(C1 + C2) refer to the ratio of ^{131}I counts measured in the nodule-free lobe.

†Ultrasensitive determinations of TSH levels (normal range: 0.3–3.5 μU/ml) were only available after 1984.

‡Linear correlation between the TSH values and the relative counts for the nodule-free lobe; ns: $p > 0.05$, r: correlation coefficient.

§Comparisons between TSH values and regional counts were performed using the Student's t-test according to ENA.

desirable and that hypothyroidism is a lesser evil compared to the failure of treatment, absorbed doses of 150–400 Gy are usually advocated (*15–17*). The intended 80 Gy used in this study yielded a 14% failure rate at one yr, a value comparable to that reported by authors who are accustomed to treating with therapeutic doses bordering on 370 MBq (*4,18*). A further drawback was that the achievement of cure was delayed. However, in patients with mild thyrotoxic states, these two drawbacks may be considered limited, because there is a substantial decrease in whole-body irradiation obviously resulting from the use of such levels of activity (mean 305 MBq).

Hypothyroidism mainly developed during the long term follow-up, suggesting that TSH levels should be reverified every 3 to 5 yr after obtainment of the cure. This side effect was frequent in clinically euthyroid patients or those with unsuppressed TSH levels. In the latter cases, undesirable diffuse irradiation occurred in the TSH-dependent healthy tissue. Since progression to clinical toxicity may take years to occur (*3,19*), the need for prophylactic ^{131}I administration should be further investigated. The exogenous administration of T4 or T3 before that of radioiodine has been shown to be effective in preventing hypothyroidism in compensated ATN and should be considered in such cases (*19*).

The rectilinear scanners, used in this work, usually permitted the visualization of ENA, provided the regional count ratios between the ATN and the nodule-free lobe were less than 15:1. In general, regional quantification of radioiodine uptake is not performed because it is of limited interest for diagnostic purposes. However, such measurements provide an interesting tool to demonstrate that ENA is a manifestation of multifocal autonomy in many patients. In these patients, visible ENA corresponded to regional counts ranging from 3% to 7%, although ultrasensitive TSH values were found to be blunted. In patients with higher TSH values (0.15 μU/ml to 0.30 μU/ml) and even more so in euthyroid or treated patients, the regional uptake by the nodule-free lobe results from various combinations of TSH-dependent uptake and multifocal autonomy. In this context, ^{131}I appears to be the best suitable treatment for targeted destruction of disseminated autonomous tissue. The visualization of ENA in patients with a toxic ATN could be a further indication for this therapy.

A rather high level of irradiation was delivered to the nodule-free lobe in ENA patients, though only 20% of the whole activity taken up by the thyroid could be found in this lobe. The 3:1 weight ratio measured between the ATN and the nodule-free lobe in our group accounts for this discrepancy. Average absorbed doses in the nodule-free lobe were calculated assuming an homogeneous distribution of the dose. In patients who had a diffuse pattern of ENA distribution (n = 11), a reliable estimate of the functional weight, which was derived from a TSH stimulated scan, was grossly provided. In cases of multifocal autonomy, precise estimates of the absorbed dose in the nodule-free lobe are unrealistic because both planimetry and ultrasound overestimate these accessory targeted volumes (*20,21*). In fact, higher beta radiation doses are delivered to much smaller volumes. Since ^{131}I-beta-emission is only effective on a short path length, most of the nontargeted tissue surrounding these autonomous areas mainly received gamma radiation doses whose levels are low. This probably explains why similar rates of hypothyroidism were observed in our hyperthyroid patients, regardless of ENA ($p = 0.36$, log rank test).

According to simulation data, we found that the dosage schemes had a slight influence on therapeutic and absorbed dose profiles. We reported opposite findings in patients with toxic diffuse goiters (*22*), probably because in these cases thyrotoxicosis was mainly due to stimulation by TSH-receptor antibodies. On the contrary, in ATN the occurrence of hyperthyroidism is roughly dependent on a critical mass of autonomously functioning tissue (*20*) and variations in iodine kinetics and uptake are limited from one patient to another. Consequently, a fixed therapeutic dose appears advisable from the point of view of convenience to the patient and cost effectiveness. It may nevertheless be interesting to screen patients with the most favorable dosimetric data, such as a high iodine uptake or a low ATN weight, who will require lower therapeutic activities compared to that given by the fixed dose. To ensure that the diagnosis and treatment in such patients occurs on the same day, a single-uptake based scheme using early modified uptake values to predict the actual 24 hr measurement could be proposed (*23*). In this case, to avoid underdosing patients with ENA, regional uptake by the ATN should be preferred to global uptake.

This study confirms that toxic ATN is a severe disease with a life-table estimate of death in 23% of cases at 90 mo. However, death occurred long after iodine administration (range: 12–108 mo) and was not related to ENA or therapeutic dose levels. This suggests that hyperthyroidism and related complications are responsible for this fatal outcome rather than ^{131}I, as recently reported (*24*). Long-term exposure to inappropriate levels of thyroid hormones causes supraventricular arrhythmia and aggravates underlying cardiac disorders (*25*), which cannot always be reversed, even once cure has been achieved. In addition, evidence of left ventricular hypertrophy has been reported in patients free of intrinsic heart disease but with subclinical hyperthyroidism (*26*). To prevent such cardiac complications as well as the development of osteoporosis, we suggest that radioiodine should be given as soon as possible, e.g., in patients with ATN and suppressed TSH levels. Because modern TSH assays are very sensitive and widely available, such early diagnosis will be facilitated. In this category of patients, who are likely to be younger, the use of lower fixed therapeutic doses (296 MBq–370 MBq) appears more advisable in terms of radiation exposure and has been shown to be effective in this and previously published works (*4,18,27*). In older patients, and if the goal is to eradicate thyrotoxicosis as rapidly as possible, fixed doses ranging between 555 MBq and 740 MBq are advisable.

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