

# Optimized Dose Planning of Radioiodine Therapy of Benign Thyroidal Diseases

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Thyroid uptake measurements were performed on 246 patients, who underwent radioiodine therapy for benign disease up to 192 hr after oral application of either the test activity (7 MBq) or the therapeutic activity (150–1100 MBq). Using the complete set of uptake values, the cumulated activity in the thyroid was calculated and the dose-to-activity ratio (D/A) deduced. An empiric factor was derived, which allows prediction of the D/A with high precision, using only the late uptake measurement at 96 hr or 192 hr. The correlation between the value calculated from the complete set of uptake values and that of only one at 96 hr or 192 hr was  $R = 0.99$  and  $0.97$ , respectively. The activity required for intended dose can thus reliably be determined by a single, late uptake measurement. In a second analysis, the correlation between the D/A of the test and the therapeutic activity was established. There were two essential findings: For those patients who were without or under stable thyroid-specific medication there was a strong correlation between the two D/A values. The therapeutic value was on the average approximately 15% lower than the test ratio, which is assumed to be due to an enhanced iodine turnover under therapeutic conditions. In patients whose medication changed close to the test study or therapy, the measured test and therapeutic D/A were strongly noncorrelated.

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**R**adioiodine therapy in benign thyroid diseases has been performed as a routine nuclear medicine procedure for about 50 yr (1,2). Nevertheless, disagreement exists about the optimal dose for treatment of the different diseases and the concept of dose planning (3,4). Some centers neglect the need for dose planning at all and apply standard activities (5–13). Others rely on the 24-hr uptake value or combine it with an individually derived or assumed average-efficient half-time values of thyroid-gland activity (14–16). Finally, some centers determine the kinetics of test activity over a couple of days (17,18). The precision of dose prediction is correlated with the number of uptake measurements and the duration of the study. The diversity of procedures and the different intended doses prove that

the therapeutic safety margin is large. However, it seems reasonable that the number of post-therapeutic hypothyroid patients and the number of recurrences are influenced by the actual dose to the target tissue. Moreover, there are additional aspects that suggest the use of minimal activity to cure the disease. Overtreatment means unnecessary radiation exposure for the patient, which is obviously undesirable, especially for younger patients, and for the environment. In European countries, which require the patients to remain in a ward until their whole-body activity has declined beneath a low limit (e.g., approximately 75 MBq  $^{131}\text{I}$  in Germany), the duration of stay and costs of treatment correlate with the administered level of activity. The optimal concept is application of a disease-determined dose. Depending on the kind of disease—Plummer's, Graves', toxic adenoma, or euthyroid goiter—different doses are intended (19–21). The optimal value of those doses is, however, still under discussion (22–24). Nevertheless, dose planning is required and is performed by measurement of the kinetics of a tracer iodine activity. In this study, all relevant aspects of dose planning correlated with iodine kinetics were investigated. Finally, the therapeutic outcome and actual applied dose are correlated.

## MATERIALS AND METHODS

Because in the literature relevant terms are occasionally confused or not correctly and consistently used, terms used in this paper are defined in Table 1.

A total of 246 patients who had undergone radioiodine therapy because of benign thyroid disease fulfilled the conditions below and were analyzed in detail. Indented doses were mostly 150 Gy for patients with toxic adenoma or multifocal autonomy and 100 Gy for other diseases.

Iodine kinetics were measured both for the test (7 MBq) and the therapeutic (190–1100 MBq) course. All patients—except those who were treated mainly for reduction of an euthyroid goiter—had a completely suppressed basal TSH (and insufficient response in the TRH challenge) and in case of toxic adenoma showed either nonperinodular uptake or only slight uptake in the  $^{99\text{m}}\text{Tc}$ -pertechnetate scan.

Patients were subdivided into the following five groups:

1. Toxic adenoma ( $n = 103$  patients):  $\leq$  three well defined hot lesions in the  $^{99\text{m}}\text{Tc}$  scan;
2. Multifocal autonomy ( $n = 42$ ):  $>3$ , mostly vaguely circumscribed hot lesions;

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**TABLE 1**  
Definition of Important Technical Terminology

Activity	MBq	Measure of number of radioactive nuclei
Dose	Gy	Energy/mass (deposited in tissue)
$t_{1/2}$		Time of decline to half of the initial value. Makes sense only for an analytically defined mathematical function (e.g., monoexponential).
Cumulated activity (= time-activity integral)	MBq/hr	$\int_0^\infty \text{activity}(t) \cdot dt$ (t: time) It is strictly correlated with the deposited dose.
Dose-to-activity ratio	Gy/MBq	The dose deposited in the target tissue by unit activity.

3. Disseminated autonomously functioning thyroid (n = 29): essentially homogeneous activity accumulation, no evidence of Graves' disease;
4. Graves' disease (n = 24): diagnosis relying on typical combinations of clinical signs (endocrine orbitopathy), laboratory parameters (Thyrotropin Receptor Autoantibodies (TRAB)) and ultrasonography (echopenic pattern); and
5. Euthyroid goiter (n = 48), treated mainly for size reduction, some insignificant autonomy might be present.

The separation of Groups 1, 2 and 3 is somewhat arbitrary because a more or less continuous spectrum of autonomy is present in these patients. The discrimination between Groups 1 and 2 or 2 and 3 was performed taking the precision of the volumetry into consideration. On the other hand, neither the results of this study nor its conclusions are influenced by the definition of these groups.

All groups were subdivided into patients who were either without medication or under unchanged thyroid-specific medication and those who had a reduction in thyrostatic medication within 4 wk prior to the test examination. Some patients were treated with levothyroxine to suppress perinodular tissue. This medication was required to be constant for at least 6 wk. Data were analyzed for all patients and for the groups separately as a function of thyroid mass.

The administered iodine activity was measured before and thyroid uptake was measured 8, 24, 32, 48, 72, 96 and 192 hr after oral application with a 3" × 3" NaI(Tl) detector. For the high therapeutic levels of radioiodine, a lead shield was used in front of the detector to reduce the count rate and avoid dead-time effects. Scatter from the patient's body was shielded with a 5-cm thick lead shield. In a thorough investigation using tissue-equivalent (water) scatter phantoms, the response of the two set-ups was compared for a variety of activity distributions. Results agreed within 1% for reasonable conditions (activity in the thyroid ≥ activity in the rest of the body). These conditions were always fulfilled at 24 hr or later.

The detector sensitivity was checked daily using a mock iodine standard ( $^{133}\text{Ba}$ ) for which count rates were determined daily prior to patient investigations. The uptake values were not corrected for radioactive decay because the amount of  $^{131}\text{I}$  actually present in the thyroid is relevant for dose calculation.

Figure 1 displays a sketch of a typical time-activity curve. Uptake values were used to calculate the cumulated activity represented by the area under the graph in the figure. For this calculation, a computer code was used to calculate the integral from 0 to 192 hr directly from the data by interpolation. The contribution for 192 hr to infinity was calculated using an exponential function fitted to the uptake values measured between 72–192 hr. The

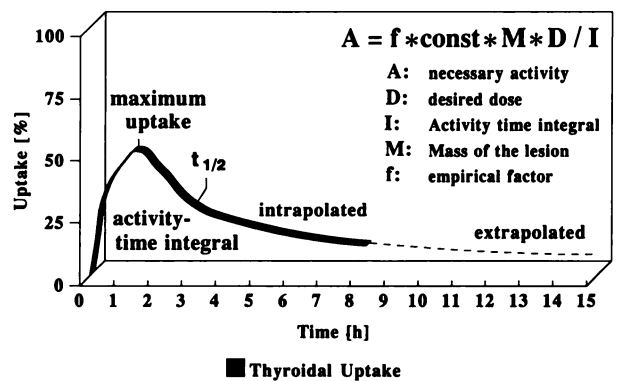
doses per unit activity (D) achieved under test and therapy conditions were compared for the test ( $D_{te}$ ) and the therapeutic ( $D_{th}$ ) activity and were expressed as relative differences  $d = (D_{te} - D_{th})/D_{te}$ .

Volume estimations were based on results of the thyroid scan as well as on sonography. The area of the hot lesion(s) in the scintigram was used and combined with the ventral-dorsal diameter determined by ultrasonography. The volume was calculated employing the ellipsoid formula:

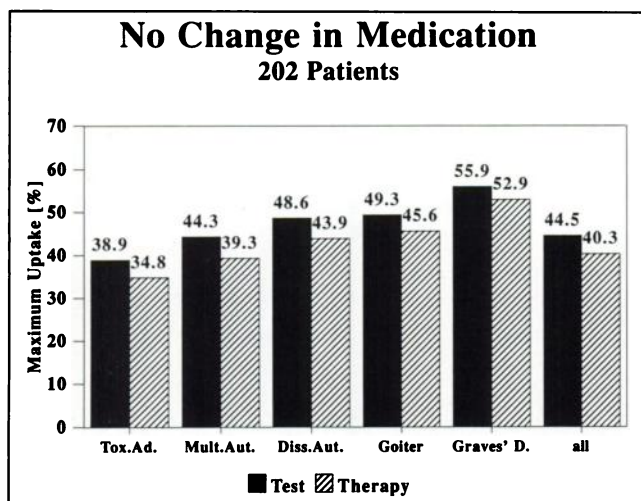
$$\text{Volume} = \pi/6 \times \text{height} \times \text{depth} \times \text{width}.$$

The mass of the lesion was calculated from ultrasonography in the case of unifocal autonomy. In the case of multiple unifocal lesions, individual masses were added. Multifocal lesions require a more complicated approach. For the other diseases, the target volume was identical to the thyroid, for which the volume was again calculated according to the ellipsoid equation with the height and width taken from the scintigram and the depth measured in the sonogram. Errors in volume measurement may be relatively high for large multinodular thyroids or in the case of multifocal autonomy. However, all comparisons in the present paper rely on intraindividual ratios and are therefore independent from uncertainties in the measured value of the thyroid mass.

### Radio Iodine Therapy of the Thyroid Oral $^{131}\text{I}$ Administration



**FIGURE 1.** Sketch of radioiodine kinetics in the thyroid gland or an autonomous lesion, represented by iodine uptake measured over the thyroid. The constant in the equation is a well defined physical constant depending only on the emitting nuclide and the absorbing material. "f" is an empirical factor that corrects for differences between the kinetics of a tracer and a therapeutic activity.



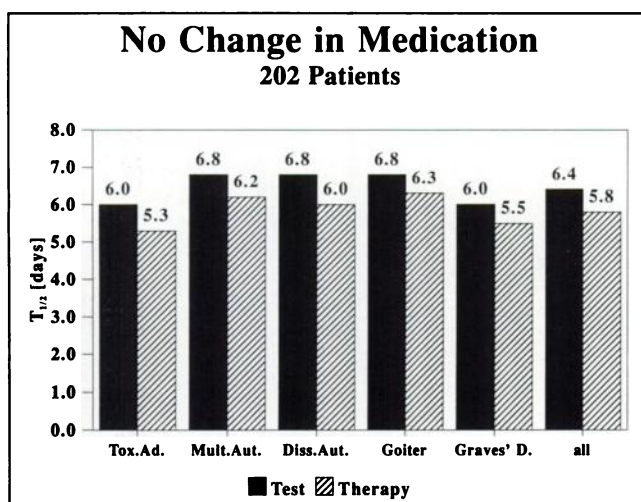
**FIGURE 2.** Comparison of average thyroid iodine uptake values after application of the test and the therapeutic activity. Only patients with no, or unchanged, thyroid-specific medication are included.

## RESULTS

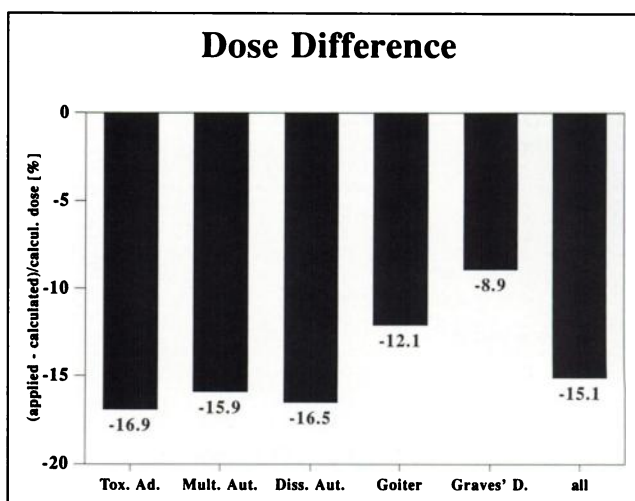
The study was designed to answer three questions: (1) What is the correlation between test and therapeutic activity kinetics, and in particular, how does the D/A change? (2) Is there an easy-to-achieve parameter that predicts D/A? And finally, (3) how does the clinical outcome depend on the applied dose?

### Correlation Between Test and Therapeutic Activity Kinetics

Figures 2 and 3 compare the average maximum uptake and effective half-life ( $T_{1/2}$ ) that were measured under test and therapeutic conditions. These parameters were found to be only slightly different. They were consistently changed in a manner that can be interpreted as an enhanced turnover which we assume is due to radiation effects of the therapeutic activity. A proof for this hypothesis



**FIGURE 3.** Comparison of average iodine half-life values (fitted to the data of and after 72 hr) after application of the test or the therapeutic activity. Only patients with no, or with unchanged, thyroid-specific medication are included.



**FIGURE 4.** Average of the ratios of intended dose (calculated on the basis of tracer activities) and actual applied dose. Numbers are identical to the average of the relative difference between the D/A for iodine of tracer or therapeutic activity.

could not be derived from our data, however. In contrast, analysis of patients with a change in thyroid-specific medication between test and therapy course demonstrated only a weak correlation between the test and therapy values. Changes in  $T_{1/2}$  and maximum uptake for those patients are in the order of 30% or more in each direction.

The most important value seen from the practical point of view is the D/A, which is strongly correlated between test and therapy course in those patients under stable thyroid-specific or without thyroid-specific medication.

Figure 4 compares this D/A. It is decreased on an average of 15% under therapeutic conditions independent of the kind of disease. The standard deviation is  $\pm 5\%$ . Therefore, the empirical factor  $f$  of Figure 1 is  $1/1.15 = 0.85$ .

### Correlation of Parameters

The correlation of all available parameters with D/A was investigated. According to the pragmatic concept of following parameters, a linear correlation with the activity predicted from the complete test course was assumed: half-life of thyroid activity decline ( $T_{1/2}$ ), maximum uptake ( $U_{max}$ ), mass of lesion or thyroid ( $M$ ) and  $M/(U_{max} \cdot T_{1/2})$ ,  $M/(U_{24h} \cdot T_{1/2})$ . Table 2 summarizes these results.

The most relevant parameter is obviously the mass of the lesion, whereas there is no correlation at all between the necessary activity and the maximal uptake. However, as pointed out earlier, the actual maximal uptake is difficult to determine. In the present study it is derived from a smooth fit to the measured data.

Overall, the correlation of the above tested parameters and the therapeutic activity derived from the complete set of uptake measurements was disappointing. On the other hand, measurement of all the uptake values for the test course is time-consuming for clinical staff and expensive because of travel expenses and travel time required by patients. The study therefore tried to establish an easily

**TABLE 2**  
Results of Correlation of Various Parameters and Thyroidal D/A for Radioiodine

Activity A = B * Variable + C					
Independent parameter	Function	B	C	Correlation coefficient	n
Mass	$A = B \cdot M + C$	12.7	252	0.71	246
$U_{\max}$	$A = B \cdot U_{\max} + C$	-0.60	515	-0.02	246
$T_{1/2}$	$A = B \cdot T_{1/2} + C$	-87.5	1014	-0.26	246
$M/(U_{24 \text{ hr}} \cdot T_{1/2})$	$A = B \cdot M/(U_{24 \text{ hr}} \cdot T_{1/2}) + C$	1735	8	0.71	193
$M/(U_{\max} \cdot T_{1/2})$	$A = B \cdot M/(U_{\max} \cdot T_{1/2}) + C$	1670	4	0.74	246
$M/U_{96 \text{ hr}}$	$A = B \cdot M/U_{96 \text{ hr}}$	2.46	—	0.97	175
$M/U_{192 \text{ hr}}$	$A = B \cdot M/U_{192 \text{ hr}}$	1.62	—	0.99	175

Correlation derived from complete test course over 9 days.

achievable parameter that predicts D/A with sufficient accuracy.

The measurement of maximum uptake well known in the literature seems to be problematic for two reasons. First, to determine maximum uptake, a large number of measurements are needed to hit the right moment. In addition, no information exists about  $T_{1/2}$ , which is of at least equal importance for the cumulated activity that determines D/A. We therefore evaluated whether a late uptake value is a suitable parameter. After a longer time period, e.g., on the order of 100 hr, an error in the time schedule of 1 or 2 hr is of decreasing effect because there is no rapid change in the declining activity curve. From the practical point of view, these uptake values are therefore stable for timing errors. In addition, assuming mathematically similar functions, late uptake is proportional to maximum uptake. Moreover, late uptake is influenced by  $T_{1/2}$  in the right direction: e.g., a small  $T_{1/2}$  is correlated with a low cumulated activity and reduces the late uptake value. We empirically evaluated the correlation of cumulated activity and the uptake value

at  $96 \pm 2$  hr and  $192 \pm 4$  hr. An excellent correlation was found in the 175 patients in whom the time conditions were fulfilled:

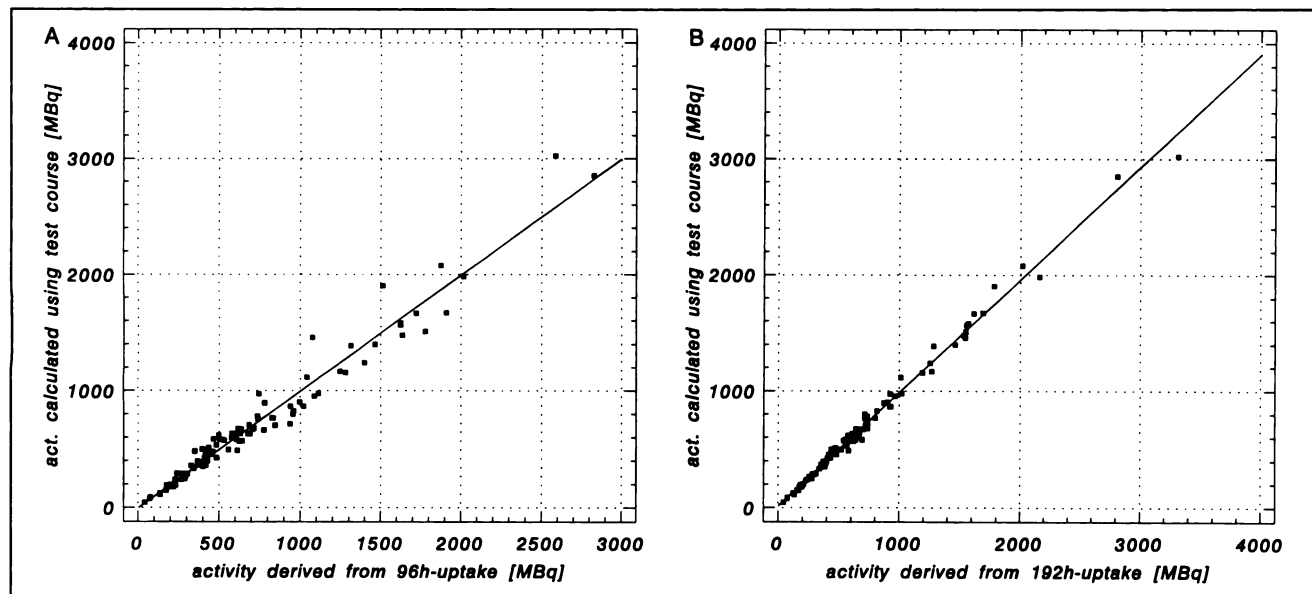
$$\text{activity [MBq]} = \text{const}(t) \times \text{mass [g]}$$

$$\times \text{dose [Sv]}/\text{uptake}(t) [\%]$$

$$\text{const (96 hr)} = 2.46 \pm 0.24 [(\text{MBq} \times \%)/(\text{g} \times \text{Sv})]$$

$$\text{const (196 hr)} = 1.62 \pm 0.13 [(\text{MBq} \times \%)/(\text{g} \times \text{Sv})].$$

The correlation was better than 0.97 for the 96-hr uptake value (Fig. 5A) and better than 0.99 for the 192-hr data point (Fig. 5B). The empirically determined proportionality constants given in the formula have a s.d. of <10%. The factors were found to be independent of goiter volume, maximum uptake,  $T_{1/2}$  of the iodine turnover, the sex and age of the patient, the total amount of activity and dose or the kind of disease. These empiric parameters derived from 175 patients have already been used for more than 2 yr and were found to give excellent agreement between the 96-hr



**FIGURE 5.** Scattered plot comparing the activity calculated from the tracer activity kinetics (complete data set) and (A) the uptake value after  $96 \pm 2$  hr or (B) the uptake value after  $192 \pm 4$  hr. In both groups 175 data pairs were included.

and 192-hr values. In addition, a check with a control group of 100 patients investigated with the test course as described in the section "Materials and Methods," resulted in the same constants. The major uncertainty in dose planning is now the determination of the mass of the target volume.

### Clinical Outcome

Outcome was evaluated 12 mo post-therapy in 153 patients (unifocal autonomy: 61, multifocal autonomy: 33, disseminated autonomy: 16, Graves' disease: 16, euthyroid goiter: 27). We were unable to evaluate the remaining 93 patients because their records were not available to use. Criteria for outcome evaluation were divided into four categories. *Success* was defined as euthyroidism, normalization of scintigram or a hot lesion turning to a cold lesion. *Partial success* was defined as residual warm lesion but proof of irrelevance of the autonomy by laboratory, suppression scintigraphy and clinical findings. *Hypothyroidism* included subclinical hypothyroidism defined by normal thyroxine and triiodothyronine serum levels but increased basal TSH or overstimulation after TRH. *Recurrence* included all patients that did not fit the other three categories.

We further categorized the patients by achieved therapeutic dose: correct dosage, overdosage, and underdosage. Correct dosage was defined as disease-specific standard dose  $\pm 20\%$ ; overdosage and underdosage are results above or below these limits. Table 3 correlates the outcome for patients with toxic adenoma with the therapeutic dose actually administered. Overtreatment and undertreatment were in part precipitated by empirical deviations from the proposal of the test course, which were chosen according to clinical experience in patients with recurrence, for example. "Success over all" includes all patients in whom autonomy was eliminated or reduced to a clinically unimportant extent and comprises the outcome criteria success, partial success and hypothyroidism. Note that rate of recurrence is higher for low doses. However, statistical significance could not be established because of the low number.

In diagnoses other than toxic adenoma, results were as follows. In the two patients with euthyroid goiter who developed hypothyroidism, both had been overtreated. In patients with multifocal autonomy, two developed hypothyroid within 1 yr following therapy and both had been overtreated. Four of seven patients with recurrence had been undertreated. None of the patients with disseminated

**TABLE 4**  
Outcome for All Patients Based on Dosage

Outcome criteria	Correct dosage	Over dosage	Under dosage
Success	20 (57%)	31 (54%)* <sup>1</sup>	22 (36%)* <sup>1</sup>
Partial success	6 (17%)	7 (12%)* <sup>1</sup>	17 (28%)* <sup>1</sup>
Hypothyroidism	2 (6%)* <sup>1</sup>	9 (16%)* <sup>1,2</sup>	2 (3%)* <sup>2</sup>
Success over all	28 (80%)	47 (82%)	41 (67%)
Recurrence	7 (20%)	10 (18%)* <sup>1</sup>	20 (33%)* <sup>1</sup>

\*<sup>1</sup> and \*<sup>2</sup> = statistically significant difference on the 1 or 2  $\sigma$  level, respectively.

autonomy developed hypothyroidism. Two of three cases with recurrence had been undertreated. Of the four patients with Graves' disease who developed hypothyroidism, three had been overtreated. Recurrences occurred independent from dose but was quite high in undertreated patients. Outcomes for all study patients based on dosage are illustrated in Table 4. "Success over all" includes all patients in whom autonomy was eliminated or reduced to a clinically unimportant extent and comprises the outcome criteria success, partial success and hypothyroidism. Although the numbers are low, it is clear that recurrence occurs in underdosed patients, and hypothyroidism occurs in overdosed patients.

The relatively high incidence of recurrence is due to intended application of low dosage known to be on the lower end of therapeutic concepts. Our goal was to avoid unnecessary hypothyroidism and use minimum amounts necessary. Following the study, intended doses were increased to 200 Gy for toxic adenoma and 150 Gy for Plummer's disease.

### DISCUSSION

Precise dose planning for radioiodine therapy requires significant effort. Such planning often was neglected in the past and only standard activities applied. Since the current trend is toward enhanced consciousness for radiation risk, precise planning is required just for ethical reasons (25). In this study we compared the effective half-life for iodine in the thyroid, the maximal iodine uptake and the D/A determined with the tracer and the therapeutic activity. For patients with stable thyroid-specific medication, these three parameters changed slightly but significantly, in a way that can be interpreted as enhanced iodine turnover. A strong intraindividual correlation between the test and the therapy course was found in these patients, which is in disagreement with Creutzig and Hundeshagen (26) who reported no significant change on the average but a poor correlation in 46 patients, a comparatively small number. Decreased  $T_{1/2}$  (27,28) and reduced maximal uptake values (28-30) are common findings. However, the methodology of the former studies usually excluded the reliable interpretation of minor changes. Either the number of patients was low and there was no intraindividual comparison per-

**TABLE 3**  
Outcome for Toxic Adenoma Depending on Applied Dose

Outcome criteria	Correct dosage	Over dosage	Under dosage
Success	7 (50%)	12 (55%)	8 (32%)
Partial success	3 (21%)	4 (18%)	7 (28%)
Hypothyroidism	1 (7%)	1 (5%)	2 (8%)
Success over all	11 (79%)	17 (77%)	17 (68%)
Recurrence	3 (21%)	5 (23%)	8 (32%)

formed or the thyroid relevant conditions were changed or not documented (6,16,17,26–28,30,31). Maurer et al. (17) measured the tracer kinetics over a long period of time, up to 12 days, and Seed and Jaffe (28) proposed measurements for more than seven days. In the present study, kinetics were investigated over nine days for both the test and the therapeutic activity. The change in radioiodine kinetics was therefore reliably introduced into the activity calculation which might explain the good correlation of data.

As pointed out by Berding and Schicha (16), stable (borderline euthyroid) conditions are the prerequisite that allows dose planning and optimal therapy. Study findings strongly confirm this statement. Changes in thyroid-specific medication in close correlation to test or therapy course resulted in an uncontrolled dose.

The rate of recurrence and the incidence of hypothyroidism in patients after radioiodine therapy are strongly study-dependent (19,30,32–36) for several reasons. There is a well known geographic dependency in thyroid disease because of the different amounts of alimentary iodine intake that occur in different geographic locations which might interfere with the therapeutic outcome. Methodological problems also exist. For example, definitions may differ among studies, and some are not clear at all. Success may be defined as “absence of hyperthyroid laboratory values,” as “positive TRH stimulation test,” as “a normal scan,” or, in the case of focal disease, as “a hot lesion turning to cold.” The incidence of hypothyroidism in patients strongly depends on the delay between therapy and follow-up. Evaluation of patients at late time points is difficult, however. In addition to multiple dropouts, a significant number of patients, at least in Germany, are found to be under levothyroxine medication, for unknown reasons.

We reexamined our patients 12 mo after therapy and detected only a few cases of early hypothyroidism. Compared to the literature (19,30,33,34,37), this rate is at the lower end of incidence of hypothyroidism. Patients with early hypothyroidism typically are found after high doses, which is in agreement with Alevizaki et al. (38) that early hypothyroidism is dose-dependent, whereas late hypothyroidism may be of more complex origin (39).

The study illustrates a strong correlation between kinetics of the test activity and the therapeutic activity, indicating that therapeutic dose induced by therapeutic activity can be reliably predicted from a test activity. In addition, the study established an appropriate and easy method to determine the activity required to deposit the intended dose. Only one late uptake measurement is necessary.

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## EDITORIAL

# Optimization of Radioiodine Therapy of Thyrotoxicosis: What Have We Learned After 50 Years?

In nuclear medicine, the treatment of thyrotoxicosis with radioactive iodine is considered the quintessential therapeutic intervention (1,2). None would doubt that this therapy can be effective; nevertheless, after half a century and treatment of hundreds of thousands of patients, the indications, patient selection, goals of therapy and dose selection remain highly controversial, varying greatly from country to country and institution to institution (1-12).

Bockisch et al. (13) bring a number of these points into striking relief. Their study population differs greatly from that usually encountered in the United States, in that there was a relative paucity of Graves' disease and a high frequency of unifocal, multifocal or diffuse autonomy as the cause of hyperthyroidism. In addition, a significant number of euthyroid patients who were not candidates for surgery were treated with radioiodine to shrink goiters.

Thyrotoxicosis due to a wide range of etiologies is potentially treatable by radioiodine, but it is necessary to exclude, by quantitative or qualitative tracer studies, patients for whom this would be inappropriate (e.g., those with factitious thyrotoxicosis, destructive thyroiditis and markedly expanded iodine pool leading to low uptake) (1,2,7).

Radioiodine therapy is remarkably

safe, as it must be for radiotherapeutic intervention in a benign condition for which alternative therapies exist (1,2,10,14-16). With the exception of hypothyroidism, side effects are uncommon, but may include radiation thyroiditis, temporary exacerbation of thyrotoxicosis, nausea, vomiting and anorexia (1,2,15,17,18). Radioiodine treatment of Graves' disease may result in an exacerbation of ophthalmopathy although the data are by no means consistent (19,20). There has been a disproportionate concern for radiation-induced carcinogenesis, leukemogenesis, mutagenesis and teratogenesis. The risk of thyroid cancer following radioiodine therapy is reduced (1,2,14). The risks of leukemia and other malignancy are either no greater than in appropriate control populations, or they are marginally increased. Little or no convincing data exist for radioiodine therapy causing increases in infertility or mutagenesis and teratogenesis in subsequent pregnancies above the relatively high background incidence of these phenomena (1,2,7,10,15,16), with the exception of risk of intrauterine thyroid ablation when radioiodine is administered during pregnancy (when the ability of fetal thyroidal iodine concentration has developed) (21). While risk cannot be said to be nonexistent, failure to convincingly demonstrate these effects contrasts with the small, but by no means trivial, morbidity and even mortality that may result from untreated thyrotoxicosis, untoward reactions to antithyroid drugs and aesthetic and surgical complications

and catastrophes (1,2). There is a growing recognition, particularly in the U.S., that younger patients, including women in the reproductive age group and even children, may be suitable candidates for radioiodine therapy (1-3,5,10,16).

The goal of therapy when treating thyrotoxicosis is prompt, predictable elimination of the hypersecretory endocrine state with a single dose of radioiodine (1,2,7). Controversy arises about whether hypothyroidism following radioiodine therapy is a complication or otherwise negative endpoint (1,2,8,12,15,17,18,22). Because modern thyroid stimulating hormone (TSH) assays are a highly sensitive and specific means to diagnose post- $^{131}\text{I}$  hypothyroidism at an early phase and physiologically adjust thyroid hormone replacement, hypothyroidism cannot be considered a serious negative outcome. The general availability of cheap, predictively bioavailable synthetic thyroid hormone also contributes acceptability of hypothyroidism as an endpoint. While supraphysiological hormone replacement may increase the risk of osteoporosis, synthetic thyroid hormone is among the cheapest and safest drugs available when administered in appropriate doses and with appropriate TSH monitoring. Once the dose has been titrated, it is usually stable and requires only infrequent biochemical monitoring.

Once selection criteria and therapeutic goals are defined, the appropriate choice of radioiodine dose is most controversial. Bockisch et al. define

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