The outcome of radioiodine treatment in Graves’ disease is determined by the 131I turnover rate and by the timing of 131I uptake measurements

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Submitted for publication
Summary

In a previous study of radioiodine therapy in patients with Graves’ hyperthyroidism, we established that the clinical outcome was not linearly related to the radioiodine uptake and to the thyroid volume. Later we demonstrated that the timing of the uptake measurements influenced the measurement results. Others had found that the 5/24-h $^{131}$I uptake ratio could serve as an alternative to multiple measurements of the effective half-life.

A re-evaluation of the radioiodine therapy results was made, using a protocol in which the uptake measurements immediately preceded the radioiodine treatment. With other parameters essentially unaltered, the radioiodine therapy results were compared with the results from the former protocol. The value of the 5/24-h $^{131}$I uptake ratio was also assessed.

The percentage of patients with euthyroid outcome had not changed but a significant shift had occurred from hypothyroidism to persistent hyperthyroidism. This effect was most pronounced for patients in the low radioiodine uptake tertile and in patients with small thyroids. The 5/24-h $^{131}$I uptake ratio (mean ± sd) was 0.74 ± 0.16 for patients with a hypothyroid outcome, 0.81 ± 0.17 for patients with a euthyroid outcome, and 0.88 ± 0.16 for patients with persistent hyperthyroidism.

Because of variations in radioiodine uptake over short periods of time, uptake measurements directly preceding the radioiodine treatment are recommended. This recommendation has a significant influence on the outcome of radioiodine therapy. The 5/24-h uptake ratio appears to be a strong predictor of the radioiodine therapy outcome.
131I turnover and timing of uptake measurements determine therapy outcome

6.1 Introduction

For radioiodine treatment of Graves' hyperthyroidism there are roughly two strategies with regard to dosage calculation, i.e. fixed and individualized schemas. Each have their own advantages and disadvantages. In several European countries, primarily for reasons of radiation safety, individualized dosage schemas are a legal requirement. The most widely used is the becquerel-per-gram method, necessitating measurements of the radioiodine uptake and of the thyroid volume. Despite this additional effort the short-term cure rate is no better than with fixed dosage schemas. In an earlier study of patients with Graves' disease, using the becquerel-per-gram method, we obtained a 70% cure rate (31% euthyroidism, 39% hypothyroidism) one year after treatment. In that study, long intervals had been allowed between uptake measurements and radioiodine treatment. Later we demonstrated that substantial intraindividual variations in radioiodine uptake and radioiodine turnover rate occur over relatively short periods. A recommendation to minimize the time between uptake measurements and radioiodine therapy was recently included in the guidelines of the American Society of Nuclear Medicine, and was also mentioned in a textbook of nuclear medicine. It seemed apposite to study the clinical effects of these recommendations.

A prospective investigation was conducted with a view to studying the effects of the timing of the radioiodine uptake measurement on the clinical outcome of radioiodine therapy in patients with Graves' disease. A protocol maintaining a 1-day interval between uptake measurements and therapy was compared with the protocol used in a historic control group in which arbitrary intervals had been allowed. The investigation was approved by the hospital's ethics committee.

6.2 Patients and methods

Patients

A follow-up study was conducted on 204 patients with Graves' hyperthyroidism who had been referred for radioiodine therapy by internists from 16 regional hospital sites. Patients who were referred for retreatment were not accepted for inclusion in this study. In 17 patients, a double radioiodine dosage was administered because an increased radioiodine turnover rate had been established at the first uptake test (see Radioiodine uptake measurements); these patients were excluded from the analysis. Also excluded were 22 patients who had been lost to follow-up. A total of 165 evaluable patients remained. The classic criteria for
Graves’ disease, used in the historic control group, were also applied here. All patients had used antithyroid drugs (ATD) in combination with levothyroxine (LT4) for 1-1.5 years before radioiodine therapy, and all had had a relapse after discontinuation of the medication. In all cases, ATD and LT4 were withheld for 3 days before the radioiodine uptake measurements; without exception the patients were clinically euthyroid at the time of radioiodine treatment. The medication was not resumed until the fourth day after radioiodine therapy.

Radioiodine uptake measurements
As part of a study of the stability of radioiodine uptake values, the 5-h and 24-h radioiodine uptake measurements had been performed twice: first at the time of referral for diagnosis (‘test 1’) and second immediately preceding the radioiodine treatment (‘test 2’). A scintillation probe (Canberra 7350-PE collimator with a 2×2” NaI crystal) was used for the radioiodine uptake measurements. Quality assurance and regular quality controls of the probe were procured. The 131I uptake was measured 5 h and 24 h after ingestion of a capsule containing a tracer dose of 0.37 MBq 131I-NaI (Mallinckrodt Medical bv, Petten, The Netherlands). On the first day patients were allowed a light breakfast only. The probe was positioned at the patient’s thyroid region for 4 min, at a fixed distance of 25 cm. To allow background (BKG) correction, the probe was then positioned at the patient’s thigh, also for 4 min and at the same distance. After correction for BKG, the activity in the thyroid was compared with the activity measured from a standard containing 0.37 MBq 131I, placed in an anthropomorphic perspex thyroid/neck phantom, after correction for room BKG that was measured for four minutes. In terms of percentage the 131I uptake by the thyroid is:

131I uptake = [(cpm\text{neck} - cpm\text{thigh})/(cpm\text{standard} - cpm\text{room BKG})] \times 100%.

Thyroid volume measurement
Immediately after the 24-h uptake measurement, an estimation of the thyroid volume was made from planar thyroid scintigraphy. The acquisition was done on an Elscint Apex 609 gamma camera with LEHR collimator, 20 min after intravenous administration of 80 MBq 99mTc-pertechnetate. The patient was in a supine position, with the neck slightly extended. Acquisition parameters: anterior view, 128×128×16 matrix, pixel size 4.42×4.42 mm (19.54 mm²), zoom factor 1, acquisition time 300 s. The volume calculation was exercised with the surface model instead of the cylinder model. These two methods correlate well for thyroid volumes up to 200 g. The surface model, a semi-automated com-
computer algorithm, was preferred as it eliminates observer variations. This model is based on the empirical formula:

\[ V = 0.33 \times A^{3/2}, \]

where \( V \) is the thyroid volume and \( A \) is the thyroid's surface which is derived from the frontal projection area. After applying a 30% threshold to the scintigraphic image, the thyroid's surface was measured automatically.

**Therapeutic dosage**

The therapeutic \(^{131}I\) dosage was based on the standard formula:

\[ D = V \times (100\% / U) \times C, \]

where \( D \) is the therapeutic \(^{131}I\)-NaI dosage (MBq), \( V \) is the thyroid volume (ml), \( U \) is the 24-h uptake (%), and the constant \( C \) equals 3.7 MBq/ml. \(^4\) The dosage was corrected for changes in the 5-h uptake value between tests 1 and 2. The actual amount of \(^{131}I\) administered per gram thyroid tissue varied from 2.7 to 5.3 MBq/ml (at 24 h). The therapeutic \(^{131}I\) dosage was administered on the day following the final measurements. All diagnostic and therapeutic dosages were administered as capsules (Mallinckrodt Medical bv, Petten, The Netherlands).

**Clinical evaluation**

In order to assess the influence of the timing of the radioiodine uptake procedure, all methods had been essentially unaltered in comparison with that of the historic control study. Subjects were divided in tertiles according to the 24-h uptake (< 60%, 60-79%, and 80-100%) or in two categories of thyroid volume (< 60 ml and ≥ 60 ml). The clinical outcome was evaluated after a follow-up period of 13.9 ± 8.3 months (mean ± sd). A diagnosis of euthyroidism, hypothyroidism or persistent hyperthyroidism was based on clinical presentation, TSH levels (normal 0.35-5.0 mIU/l) and use of medication. In addition, we investigated the relation between the clinical outcome and biological parameters such as radioiodine turnover, age and gender.

**Statistical analysis**

The results from the two studies were compared using the chi-square test, the one-way ANOVA test and linear regression analysis. \( P = 0.05 \) was maintained as the limit of statistical significance. Statistical calculations were executed with SPSS v6.1 for Macintosh (SPSS Inc., Chicago, IL).
6.3 Results

Overall outcome

In comparison with the former treatment protocol the overall incidence of early hypothyroidism was reduced from 39% to 27%, while persisting hyperthyroidism had increased from 30% to 40% (Pearson’s chi-square = 5.30, $P = 0.021$); these differences were just below the level of significance when euthyroid outcomes were also included in the analysis ($P = 0.069$). The number of euthyroid outcomes was unaltered (31% versus 33%, n.s.).

Age and gender

The female-to-male ratio in this study was 5:1 (see table 6.1). There were no age differences between the sexes ($P = 0.64$). The clinical outcome was affected neither by age ($P = 0.97$), nor by gender ($P = 0.36$), see table 6.2.

| Table 6.1 Patient data for female, male, and all patients with regard to thyroid volume, $^{131}$I uptake, $^{131}$I turnover rate, $^{131}$I dosage per gram, and age. |
|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|
| thyroid volume (ml)                                   | 137 female patients (mean ± sd)                      | 28 male patients (mean ± sd)                          | all patients (mean ± sd) |
|                                                     | 45.6 ± 28.9                                         | 48.9 ± 22.1                                         | 46.2 ± 27.8              |
| 5-h uptake (%)                                       | 55.5 ± 22.3                                         | 60.1 ± 22.2                                         | 56.3 ± 22.3              |
| 24-h uptake (%)                                      | 65.2 ± 18.6                                         | 70.9 ± 16.6                                         | 66.2 ± 18.4              |
| 5/24-h uptake ratio                                  | 0.82 ± 0.18                                         | 0.82 ± 0.17                                         | 0.82 ± 0.17              |
| dosage/ml at 24h (MBq)                               | 3.8 ± 0.5                                           | 4.0 ± 0.5                                           | 3.8 ± 0.5                |
| age (years)                                          | 45.8 ± 15.0                                         | 47.3 ± 14.3                                         | 46.0 ± 14.8              |

| Table 6.2 Clinical outcome in relation to thyroid volume, $^{131}$I uptake, $^{131}$I turnover rate, $^{131}$I dosage per gram, and age by gender. |
|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|
| thyroid volume (ml)                                   | hypothyroid (mean ± sd)                              | euthyroid (mean ± sd)                                | hyperthyroid (mean ± sd) |
|                                                     | 38.7 ± 22.3                                         | 43.9 ± 23.7                                         | 52.9 ± 32.4              |
| 5-h uptake ‘test 2’ (%)                              | 46.5 ± 23.2                                         | 54.9 ± 20.0                                         | 63.8 ± 20.8              |
| 24-h uptake ‘test 2’ (%)                             | 59.5 ± 19.9                                         | 65.8 ± 16.6                                         | 70.8 ± 17.5              |
| 5/24-h uptake ratio                                  | 0.74 ± 0.16                                         | 0.81 ± 0.17                                         | 0.88 ± 0.16              |
| dosage/ml at 24h (MBq)                               | 3.9 ± 0.6                                           | 3.8 ± 0.5                                           | 3.8 ± 0.5                |
| age (years)                                          | all patients                                        | 44.3 ± 14.9                                         | 47.9 ± 15.5              | 45.7 ± 14.3              |
|                                                     | female patients                                     | 44.1 ± 14.5                                         | 47.3 ± 15.8              | 45.6 ± 14.8              |
|                                                     | male patients                                       | 44.7 ± 17.0                                         | 50.9 ± 14.4              | 46.4 ± 11.3              |
Table 6.3  Clinical outcome in the former and the present study protocols (percentages between brackets).

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<td>56 (39)</td>
<td>44 (27)</td>
</tr>
<tr>
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<td>47 (31)</td>
<td>54 (33)</td>
</tr>
<tr>
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<td>67 (40)</td>
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<table>
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<td>39 (30.2)</td>
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<tr>
<td>euthyroidism</td>
<td>39 (33.6)</td>
<td>43 (33.3)</td>
</tr>
<tr>
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<tr>
<td>total</td>
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<td>129</td>
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<table>
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<th>60-80%</th>
<th>&gt;80%</th>
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<td>former</td>
<td>present</td>
<td></td>
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<td>21 (30.0)</td>
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<tr>
<td>total</td>
<td>56</td>
<td>56</td>
<td>70</td>
</tr>
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</table>
Thyroid volume and outcome

The mean thyroid volume for female and male patients is given in table 6.1. As in the historic control group, the thyroid volume had a pertinent influence on the outcome of radioiodine therapy ($P = 0.03$). In comparison with the historic controls there was a significant decrease of hypothyroidism accompanied by an increase of persistent hyperthyroidism in patients with a thyroid volume < 60 ml (chi-square = 4.7, $P = 0.02$); the percentage of euthyroidism remained unchanged. In patients with thyroids $\geq$ 60 ml the same tendency was observed, but the changes in this relatively small group were not significant (chi-square = 1.6, $P = 0.21$; see table 6.2). A comparison of the results from the two studies is represented in table 6.3.

131I-uptake and outcome

The mean 5-h and 24-h uptake percentages (of test 2) for female and male patients are given in table 6.1. The relation between the radioiodine uptake and the clinical outcome which had been observed in the historic control group was confirmed in the present study (see table 6.2). The relation with the clinical outcome was somewhat clearer for the 5-h uptake than for the 24-h uptake. In comparison with the former protocol there was a nonsignificant decrease of hypothyroidism and a concurrent increase of hyperthyroidism in the lower uptake tertiles (uptake < 60%: chi-square = 2.5, $P = 0.12$; uptake 60-80%: chi-square = 3.14, $P = 0.08$; see also tables 1, 2 and 3).

Radioiodine turnover rate and outcome

The turnover rate (mean $\pm$ sd, 95% confidence interval between brackets) was $0.74 \pm 0.16$ (0.69-0.79) for patients with a hypothyroid outcome, $0.81 \pm 0.17$ (0.76-0.84) for those who became euthyroid, and $0.88 \pm 0.16$ (0.84-0.92) for those with persistent hyperthyroidism (see figure 6.1). The mean turnover rate in the group of patients with persisting hyperthyroidism differed significantly from the others ($P < 0.05$). The correlation between the radioiodine turnover rate and the 5-h uptake ($R^2 = 0.69, P < 0.0001$) as well as the 24-h uptake ($R^2 = 0.32, P < 0.0001$) was not strong, but highly significant. As the radioiodine turnover rate had not been taken into account in the historic control group, a comparison of this parameter could not be made.

131I dosage per ml (corrected for uptake) and outcome

The amount of $^{131}$I administered per ml thyroid tissue corrected for 24-h uptake ranged from 2.7 to 5.3 MBq/ml (70-140 µCi/ml). The mean and standard devia-
131I turnover and timing of uptake measurements determine therapy outcome

...tion of the 131I dosages was significantly different in the three outcome groups. Most patients who had received dosages > 3.9 MBq/ml (105 μCi/ml) became hypothyroid (see table 6.1).

6.4 Discussion

The importance of standardized methodology can hardly be overemphasized. In the area that was presently investigated – standardization of the timing of the uptake measurements before radioiodine therapy – a significant shift was observed in the clinical outcome from hypothyroidism to persistent hyperthyroidism (or more likely from hypothyroidism to euthyroidism, and from euthyroidism to hyperthyroidism) in comparison with our earlier study. As the net percentage of euthyroid outcomes remained unaltered, the ‘cure rate’ (defined as the number of patients with euthyroid or hypothyroid outcome divided by the total number of patients treated) had dropped from 70% to 60%. We and others regard euthyroidism as the only true cures and hypothyroidism as a relatively undesirable outcome. The prevention of hypothyroidism after radioiodine therapy may have greater clinical implications than is usually acknowledged. In a recent study it was stated that the functioning and the well-being of hypothyroid patients is better with combined T₃/T₄ medication than with T₄ alone. We
argue that the same advantages may be expected from the preservation of normal thyroid function. In another study, a patient valuation study of radioiodine treatment of Graves’ disease, 33% of patients who were biochemically well adjusted to thyroxine still had problems with mood, weight, and fatigue.14

It is not certain whether the time-standardized uptake measurements truly reflect the functional state of the thyroid gland at the time of radioiodine treatment, but a shorter interval is not feasible. A comparison of pretherapeutic uptake measurements with posttherapeutic measurements such as was done by Bockisch et al. in a small number of patients with Graves’ disease,15 could possibly elucidate this matter but methodological problems should not be underestimated.

The relation between thyroid volume and clinical outcome, also demonstrated by others,2,16 was again confirmed. It has been proposed that the deviant response of large Graves’ thyroids to radioiodine therapy may result from the presence of autonomous tissue with functional differences in uptake and organification of iodine, or from increased stimulation of thyrocytes by TSH receptor antibodies;17-19 such changes are unpredictable and therefore difficult to account for. Interestingly, the clinical outcome after medical treatment of Graves’ disease shows a similar relation with goiter size: relapse is seen significantly more often in patients with larger goiters.20 In the present study (as well as in the historic control study) all patients who were referred for radioiodine treatment had persisting hyperthyroidism after medical treatment. It seems reasonable to presume that larger goiters were overrepresented in our study; it is inferred that such a selection bias would have a negative influence on the cure rate. Earlier we have argued that the correlation between thyroid volume and clinical outcome may be in part the result of inaccurate volume measurements.5 The accuracy of planar scintigraphy in measuring the functional thyroid volume as such is questionable.21-26 Planar scintigraphy and alternative modalities such as SPECT and ultrasonography need critical validation.

The 5-h uptake value appeared to be a better indicator of the clinical outcome than the 24-h uptake value; this was also reported by Hayes et al.27 This finding may be secondary to the fact that the correlation with the 5/24-h uptake ratio is substantially better for the 5-h than for the 24-h uptake value.

As in the previous study, there was no relation between the clinical outcome and the patients’ gender or age. The fact that other researchers did find such a relation might be explained by the clear association that they observed between age, gender, and higher thyroid volumes.28
The radiation absorbed dose delivered to the thyroid gland is the most important factor concerning the clinical outcome of radioiodine therapy in patients with Graves' hyperthyroidism. Accurate dosimetry, however, is very complex. Several factors contribute positively or negatively to the radiation absorbed dose. Thyroid volume, \(^{131}I\) uptake, \(^{131}I\) turnover rate and administered \(^{131}I\) dosage per volume thyroid tissue were the most pertinent in our study. Antithyroid medication has a strong influence on the outcome of radioiodine therapy. ATD had been invariant in all patients in this study and its influence could therefore not be studied.

One of the drawbacks of the classic dosage formula, \(D = V \times \left(\frac{100\%}{U}\right) \times C\), is that it does not account for the effective half-life \((T_{\text{eff}})\) of thyroidal radioiodine. \(T_{\text{eff}}\) varies with the biological half-life \((T_{\text{biol}})\), which may be 24-100 days in euthyroid individuals, about 6 days in most hyperthyroid patients, and as little as 3 days in hyperthyroid patients with rapid turnover ('small iodine pool'). Assessment of the \(T_{\text{eff}}\) is often regarded as cumbersome, because it entails multiple measurements over a 5-7 day period. \(T_{\text{eff}}\) is a function of \(T_{\text{biol}}\), and the radioiodine turnover rate has a nonlinear inverse relation to \(T_{\text{biol}}\). Aktay et al. had already established a relation between the radioiodine turnover rate (defined as the 5/24-h radioiodine uptake ratio) and the therapy outcome; by their definition the turnover rate was 'rapid' when it was greater than 1. In the present study we found relatively clear cut-off points at 0.75 and 0.85 for the radioiodine turnover rate with respect to posttreatment outcome (even after exclusion of patients with a turnover rate > 1 at 'test 1'). A combination of risk factors accentuated the differences in clinical outcome: hypothyroidism occurred in 44% of patients who had a thyroid volume < 60 ml combined with an \(^{131}I\) turnover rate < 0.75, whereas only 12% hypothyroidism occurred in patients with a combination of thyroid volume > 60 ml and \(^{131}I\) turnover rate > 0.85.

We support the opinion that the turnover rate is a useful alternative to multiple uptake measurements over several days. Identification of patients with increased risk of hypothyroidism or persistent hyperthyroidism could possibly lead to quantifiable adjustments to the standard dosage formula.

6.5 Acknowledgements

We express our gratitude to the internists from the following hospitals for referral of the patients and for supplying the follow-up data: Beatrix Ziekenhuis, Gorinchem; Bosch Medicentrum, 's-Hertogenbosch; Centraal Militair Hospitaal,
Utrecht; Eemland Ziekenhuis (locations St. Elisabeth Gasthuis, De Lichtenberg); Internistenpraktijk Berg & Bosch, Bilthoven; Lorentz Ziekenhuis, Zeist; Medisch Centrum Molendael (locations Baarn, Soest); Mesos Ziekenhuis (locations Oudenrijn Ziekenhuis and Ziekenhuis Overvecht), Utrecht; St. Jansdal Ziekenhuis, Harderwijk; Ziekenhuis Gelderse Vallei (locations Veenendaal, Bennekom, Ede, Wageningen); University Medical Center Utrecht.

We are grateful to Ms. Sally Collyer for critical reading of the English text and for her most valuable suggestions.

6.6 References

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