Improved dose concept for radioiodine therapy of multifocal and disseminated functional thyroid autonomy

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The present study analyzes the improvement of the outcome of radioiodine therapy in non-immunogenic hyperthyroidism by adapting the target dose to the 99mTc-pertechnetate thyroid uptake under suppression (TcTUₜᵢ) prior to radioiodine therapy. The TcTUₜᵢ is a substitute for the non-suppressible iodine turnover. The 89 patients presented with a basal thyrotropin level of <0.1 mU/L, normal values for free triiodothyronine and thyroxine and with multifocal or disseminated thyroid autonomy. These terms describe the scintigraphic distribution pattern of autonomous iodine turnover. Thirty-two patients had a TcTUₜᵢ between 1.6 and 3.2% (group A) and 57 had a TcTUₜᵢ > 3.2% (group B). Fifty-five patients (three of group A and 52 of group B) were treated previously for overt hyperthyroidism with antithyroid drugs. Target doses of 150 and 200 Gy were used in both groups and 300 Gy in group B only. Six months after radioiodine therapy, a basal TSH level of ≥0.5 mU/L as criterion of therapy success was observed in 94% of group A and in 54% of group B. Further differentiation of group B shows an increasing success rate with the target dose used: 45% after 150 Gy, 50% after 200 Gy and 90% after 300 Gy. In patients with a basal TSH level of <0.5 mU/L after radioiodine therapy, the TcTUₜᵢ was evaluated again. Persistence of functional thyroid autonomy, defined as TcTUₜᵢ > 1.6%, was found in 89% (one patient of group A, 24 patients of group B) and still observed a high extent of autonomous function in 25% of them, evidenced by a TcTUₜᵢ > 3.2% (seven patients of group B, target doses of 150 or 200 Gy). No case of overt hyperthyroidism was observed within the first 6 months after radioiodine therapy and no difference was found in therapy outcome between multifocal and disseminated thyroid autonomy. As a consequence, the target dose should be adapted to the TcTUₜᵢ prior to radioiodine therapy in the range of 150–300 Gy to the total thyroid gland.

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Dose determination for radioiodine therapy (RIT) of benign thyroid diseases in an area of iodine deficiency like Germany is based almost always on absorbed target dose calculations (1). An administered radiation dose of 131I is calculated to deliver a predetermined target dose to the thyroid using Marinelli’s formula (2). This formula takes into account the effective half-life and the maximum uptake of 131I as well as the target volume, i.e. the thyroid mass or the autonomously functioning volume. This is of relevance in an area of iodine deficiency, where non-immunogenic hyperthyroidism usually is associated with large goiters and the outcome of RIT is correlated closely to the thyroid volume (3). In contrast to immunogenic hyperthyroidism, the target volume for RIT in non-immunogenic hyperthyroidism is limited to the functional autonomous mass. This cannot be estimated with sufficient accuracy by sonography in the case of multifocal autonomy (MFA) and disseminated autonomy (DISA) (4, 5). Both MFA and DISA describe the scintigraphic distribution pattern of autonomous iodine turnover within the thyroid.

Therefore, the total thyroid mass is defined as the target volume and the target dose is reduced from 400 Gy, used for the sonographically detectable unifocal autonomy, to 150 Gy (4). This “dosimetric compromise” results in a normal TSH response to TRH within 1 year after RIT in 86% of patients with MFA (4) and 85% of patients with DISA (6). However, there are indications of inferior results of RIT using the above-mentioned concept in patients with a 99mTc-pertechnetate thyroid uptake under suppression (TcTUₜᵢ) >3.2% prior to RIT (5) and in patients who previously have been overtly hyperthyroid (7). The TcTUₜᵢ represents the amount of non-suppressible iodine turnover that correlates with the risk of developing hyperthyroidism, especially after iodine excess (8).

In order to improve the “dosimetric compromise”, the outcome of RIT in non-immunogenic hyperthyroidism is analyzed in dependence on the scintigraphic
distribution of thyroid autonomy, the predetermined target dose and the TcTUₜ.

Subjects and methods

Subjects

The study population consisted of 89 patients (17 men, 72 women) suffering from non-immunogenic hyperthyroidism, who underwent RIT in two departments of nuclear medicine in Germany (Freiburg and Göttingen). The mean age was 63 ± 9 years, range 40–82 years. The mean thyroid volume was 72 ± 23 ml, median 70 ml and range 25–120 ml. Fifty-five patients were treated formerly for overt hyperthyroidism with antithyroid drugs. During the last 3 months prior to RIT: all patients presented with basal TSH < 0.1 mU/l and free thyroxine and free triiodothyronine in the upper normal range without receiving any antithyroid drugs or thyroid hormones. Iodine excess during this period was excluded by history. The patients were differentiated further into those with MFA and DISA, according to the classification of thyroid diseases as recommended by the Thyroid Section of the German Society of Endocrinology (9). Multifocal autonomy is defined as more than two focal areas of insufficient suppression and DISA as insufficient suppression of the total thyroid uptake without any regional differences (8). Multifocal autonomy was found in 63 and DISA in 26 patients. Immunogenicity in patients with DISA is ruled out largely by normal values for autoantibodies against TSH receptor, thyroid peroxidase and thyroglobulin, by the lack of Graves’ ophthalmopathy and by history.

Protocol

Before RIT. Thyrotropin was determined using a commercially available immunoradiometric assay (RIA-gnost hTSH, Behring, Marburg, Germany). Its sensitivity limit (20% interassay coefficient of variation) is 0.06 mU/l. The reference range for euthyroidism is 0.1–4.0 mU/l.

Thyrotropin receptor autoantibodies were measured by a radioimmunoassay (TRAK, Henning, Berlin, Germany). The reference range was <8 U/l.

Determination of TcTUₜ was performed using an improved technique reported by Bähr et al. (10). A TcTUₜ > 1.6% indicates functional thyroid autonomy at a confidence level of 95% (11).

For sonographic estimation of the total thyroid volume, the formula of Brunn et al. (12) was applied, including a correction for bigger cysts and calcifications. This formula has an average inaccuracy of 15–20%, which can be accepted for dose determination.

Dose determination. Radiation dose administered was calculated to deliver a predetermined target dose to the total thyroid volume using the formula shown in Fig. 1. This is a Marinelli formula modified by applying the effective half-life and the maximum uptake of "131I, both determined 2 weeks before RIT in a radioiodine-uptake test lasting 4–7 days, instead of a fixed half-life and the 24-h uptake used originally. The approximation errors in physical treatment planning are not marginal and the inaccuracy in determining the three considered factors (thyroid volume, maximum uptake and effective half-life) may total 30% and more (1). However, under conditions of constant thyroid drug dosage and near-euthyroidism, the difference between the intended and the applied dose does not exceed 15% (1). Target doses of 150 Gy were used in Freiburg and 200 or 300 Gy in Göttingen. A dose of 300 Gy was determined only for patients with TcTUₜ > 3.2%. To deliver these target doses to the total thyroid volume, radiation doses of 300–1100 MBq "131I were applied.

Follow-up. All patients had a follow-up examination 6 months after RIT. Successful treatment was assumed if the basal TSH level was ≥0.5 mU/l. This threshold excludes autonomous thyroid function with a probability of 88% in an area of iodine deficiency like Germany (13). On the other hand, a basal TSH level of <0.5 mU/l is indicative of persistance of functional thyroid autonomy. For estimation of the extent of the remaining autonomy after RIT, the TcTUₜ was determined additionally in such cases.

Evaluation

The frequency of a basal TSH ≥0.5 mU/l after RIT was compared between patients with MFA and DISA in dependence on the target dose used. Additionally, these patients were evaluated in view of differences in the TcTUₜ and thyroid volume prior to RIT. The patients were divided into two groups: group A consisted of 32 patients (36%) with a TcTUₜ of 1.6–3.2% and group B of 57 patients (64%) with a TcTUₜ of >3.2%. Three patients of group A (9%) and 52 patients of group B (95%) were treated previously for overt hyperthyroidism. Both groups were evaluated in view of discrepancies in therapy outcome depending on thyroid volume or MFA/ DISA. Afterwards, the patients were divided into subgroups according to the target dose received. Group A1 consisted of 23 patients receiving 150 Gy and A2 of nine patients receiving 200 Gy. In group B, 31 patients received 150 Gy (B1), 16 patients 200 Gy (B2) and 10 patients 300 Gy (B3). The therapeutic effect is compared between group A and B and all subgroups.

\[
\text{radiation dose (MBq)} = \text{const} \times \text{target dose (Gy)} \times \text{thyroid volume (ml)} \times \frac{\text{maximum } ^{131}\text{I uptake} (\%)}{\text{effective half-life (d)}} 
\]

*physical constant depending on the emitting nuclide and the absorbing material.

Fig. 1. Modified Marinelli formula used for dose determination.
Furthermore, the average TcTU₃ values prior to RIT are compared to evaluate the characteristics of patients with and without therapy success.

Lastly, the frequency distribution of TcTU₃ levels in patients with a basal TSH of <0.5 mU/l after RIT is shown to estimate the risk of recurrent hyperthyroidism, especially after iodine excess.

Statistics
Data were expressed as mean values ± 1 SEM. The unpaired Student's t-test was used for normally distributed variables. The analysis of variances, as appropriate, was done by the F-test. The chi-squared test was used to compare the extent of abnormalities of frequencies between various groups. If the total extent of the compared groups was below 60, Fisher's exact test (14) was performed.

Results
Patients with MFA were treated successfully by ¹³¹I in 68% and those with DISA in 73%. There is no significant difference between the outcome of RIT in patients with MFA and DISA at any target doses used (Table 1). The TcTU₃ prior to RIT was not significantly different in patients with MFA and DISA (4.7 ± 2.2% versus 3.9 ± 1.5%). Additionally, no significant difference was found in the mean thyroid volume between MFA and DISA (69 ± 21 ml versus 78 ± 25 ml).

In Table 2 the results of RIT in group A (TcTU₃ = 1.6–3.2%) and B (TcTU₃ > 3.2%) are shown in total and at all target doses used. A target dose of 150 or 200 Gy was superior in patients of group A compared to group B. Less than 50% of patients in group B1 and B2 were treated sufficiently. Only in group B3 (300 Gy) was a success rate of 90% observed, similar to groups A1 and A2 (90–100%). The frequency of MFA and DISA is not significantly different between the two groups (group A: 69% MFA, 31% DISA; group B: 72% MFA, 28% DISA). Influence of the mean thyroid volume on therapy outcome in groups A and B was ruled out (70 ± 22 ml versus 75 ± 24 ml, NS).

The results of three different target doses were compared in group B (Fig. 2). The rate of success (basal TSH > 0.5 mU/l) was significantly higher in patients receiving a 300 Gy target dose than in those receiving lower doses. The results of 150 Gy (B1) and 200 Gy (B2) are not significantly different. Furthermore, no significant difference was found between groups A1 and A2 (not figured).

Table 3 shows the mean TcTU₃ values prior to RIT in relation to the effect of therapy and in dependence on the target dose used. Patients treated sufficiently are characterized by a significantly lower TcTU₃ value prior to RIT than those without therapy success (3.8 versus 6.0%, p < 0.001). Owing to the limited number of patients, this difference is not significant for 300 Gy, but significance was attained for target doses of 150 and 200 Gy.

The mean TcTU₃ values 6 months after RIT in the 28 patients with a basal TSH of <0.5 mU/l are shown in Fig. 3. A relevant extent of autonomous function according to TcTU₃ > 3.2% is found in seven patients (25%), all belonging to group B. Six of them received 150 Gy and one patient received a 200 Gy target dose. Only one patient of group B3 was not cured sufficiently. This patient's TcTU₃ after RIT was 2.2%, indicating functional autonomy. In three cases, the results of basal TSH measurement for detecting remaining thyroid autonomy could not be confirmed by TcTU₃ > 1.6%.

Discussion
Today, about 50% of all cases of non-immunogenic hyperthyroidism treated by radiiodine are classified as MFA or DISA (15). This differentiation is due to improvements in scintigraphic techniques (10, 11, 16) and has led to previously unknown problems concerning the determination of the radiation dose to be applied. As was known from pathophysiological series, autonomy of growth and function are independent traits of epithelial cells (17). Therefore, RIT is performed only in patients with evidence of autonomous iodine turnover but not of autonomous growth. Follicles with autonomous iodine turnover are found autoradiographically inside and outside thyroid nodules (18) and also regardless of the existence of nodules (19).

Table 2. Frequency of successful radiiodine therapy (RIT; basal TSH > 0.5 mU/l) in dependence on the ¹²³I-corticectomate thyroid uptake under suppression (TcTU₃) prior to RIT and different target doses.

<table>
<thead>
<tr>
<th>Radiiodine therapy</th>
<th>Group A (TcTU₃ ≤ 3.2%)</th>
<th>Group B (TcTU₃ &gt; 3.2%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 Gy</td>
<td>21/23 (91%)</td>
<td>14/31 (45%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>200 Gy</td>
<td>9/9 (100%)</td>
<td>8/16 (50%)</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>300 Gy</td>
<td>–</td>
<td>9/10 (90%)</td>
<td>ND*</td>
</tr>
<tr>
<td>Total</td>
<td>30/32 (94%)</td>
<td>31/57 (54%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*ND: not done.
Because of this heterogeneous distribution of autonomous follicles within the thyroid, the mass of autonomously functioning tissue cannot be assessed by quantitative sonography (20). Therefore, the attempt to determine sonographically the autonomous volume in MFA or DISA has been replaced by a "dosimetric compromise" (4–6). For this concept, the whole thyroid gland is taken as target volume and the target dose reduced from 400 Gy, which is still administered to unifocal autonomy, to 150 or 200 Gy. The functional autonomous volume can be determined with sufficient accuracy only in selected cases of unifocal autonomy, where most of the autonomous follicles are concentrated in a sonographically detectable area within the gland (20, 21). In such cases a correlation was found between the mass of autonomously functioning tissue and the TcTUs (20–22). These study groups developed three different formulae to calculate this correlation (20). Though the differences between these formulae are not marginal, which might be due to various concentrations of autonomous follicles in the thyroid nodules examined.

Table 1. The $^{99m}$Tc-pertechnetate thyroid uptake under suppression (TcTUs) prior to radioiodine therapy in patients with and without successful treatment in dependence on different target doses.

<table>
<thead>
<tr>
<th>Radioidine therapy</th>
<th>Basal TSH $&gt;0.5$ mIU/l</th>
<th>Basal TSH $&lt;0.5$ mIU/l</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(success)</td>
<td>(no success)</td>
<td></td>
</tr>
<tr>
<td>150 Gy</td>
<td>3.3 ± 1.2%</td>
<td>5.6 ± 2.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(N = 35)</td>
<td>(N = 19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 Gy</td>
<td>3.6 ± 1.4%</td>
<td>6.7 ± 1.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(N = 17)</td>
<td>(N = 8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 Gy</td>
<td>6.1 ± 1.9%</td>
<td>7.7%</td>
<td>NS</td>
</tr>
<tr>
<td>(N = 9)</td>
<td>(N = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3.8 ± 1.7%</td>
<td>6.0 ± 1.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(N = 61)</td>
<td>(N = 28)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Provided that a correlation between the mass of functional thyroid autonomy and the value of TcTUs can be transferred from unifocal autonomy to MFA and DISA, a proportionally higher target dose ought to be required for patients with TcTUs $>3\%$ for reliable elimination of thyroid autonomy. Consequently, the outcome of RIT using a fixed target dose must decrease with increasing TcTUs. This phenomenon was observed previously using a target dose of 200 Gy (5) and is confirmed by the present results: more than 50% of patients with TcTUs $>3.2\%$ are not treated sufficiently with a target dose of 150 or 200 Gy. Further, as was shown by a recent study, RIT using target doses between 150 and 200 Gy failed in 50% of patients with MFA and DISA who previously had been overt hyperthyroid (7).
Fig. 3. Frequency distribution of the post-therapeutic TcTUs in 28 patients with basal TSH < 0.5 mU/l after RIT: 89% of patients had relevant residual functional thyroid autonomy (TcTUs > 1.6%) and 25% were furthermore at a high risk for recurrence of hyperthyroidism, especially after iodine excess (TcTUs > 3.2%).

In an area of iodine deficiency, the value of TcTUs is accepted commonly for estimation of the functional relevance of thyroid autonomy in vivo (8, 11, 16, 22). Hyperthyroidism is observed almost always in patients with TcTUs > 3%, especially after iodine excess (8, 16, 20, 22). Thyroid autonomy of this extent is very frequent: in a large series of 236 consecutive patients with thyroid autonomy, about 75% of them presented with TcTUs > 3.2% (8). The frequency of thyroid autonomy increases further with the age and goiter size of patients: 65% of patients over 45 years of age and 77% of patients with goiters above 50 g in weight presented with functional thyroid autonomy (8). In the present study, 95% of patients in group B (TcTUs > 3.2%) but only 9% of patients in group A (TcTUs = 1.6–3.2%) were treated previously for overt hyperthyroidism by antithyroid drugs. However, the TcTUs enables individuals to be identified with a high risk for developing hyperthyroidism already in the euthyroid state (8, 16).

Radioiodine therapy should be offered especially to older patients with concomitant cardiac or other diseases and/or a higher probability of iodine excess. In those cases, the first RIT should ensure sufficient elimination of thyroid autonomy. Using the “dosimetric compromise” in its original form, about one-third of such patients were at risk for recurrence of hyperthyroidism after RIT. Consequently, an improvement of dose determination is necessary for patients with TcTUs > 3.2% or who present with overt hyperthyroidism in their history.

Influence of MFA and DISA
It is anticipated that the same dose concept can be applied to patients with MFA as to patients with DISA (6). In the present study no differences were observed between MFA and DISA even after different target doses. Consequently, there is no need to differentiate between MFA and DISA for dose determination.

Interdependencies between TcTUs and target dose
In an area of iodine deficiency, the TcTU is influenced by the individual iodine supply. Under TSH suppression (TcTU), the effect of iodine supply was negligible until
an iodine excretion of 89 µmol/mol creatinine was reached (11). Patients near euthyroidism with relevant thyroid autonomy always have an iodine excretion below this threshold (8). It can be assumed that the patients in the present study had no higher iodine excretion. However, the value of TcTUs may be influenced above this threshold by the individual iodine intake.

Superior results of RIT were observed in patients with TcTUs of 1.6–3.2% compared to those with TcTUs > 3.2% (94% versus 54%, p < 0.001). This finding is true for the 150 Gy as well as for 200 Gy target dose. Patients without sufficient outcome of RIT with 150 or 200 Gy had a higher TcTUs prior to RIT than those treated successfully (6.0 versus 3.8%, p < 0.001). Patients with an average TcTUs of 6.0% need a target dose of 300 Gy for sufficient therapy outcome.

In patients of group B (TcTUs > 3.2%) the rate of success depends on the target dose used: basal TSH > 0.5 mU/l occurs in 45% of patients after 150 Gy and in 90% after 300 Gy. This observation indicates a linear correlation between the amount of autonomous tissue and the target dose required for its reliable elimination.

Post-therapeutic hypothyroidism

In the present study, no case of overt but one case of subclinical hypothyroidism (basal TSH > 4 mU/l, free thyroxine and free triiodothyronine in the normal range) occurred within the first 6 months after RIT. Because of the relative shortness of this period, the frequency of hypothyroidism may increase in further follow-up. The well-known inaccuracy of the dose calculation procedure of about 15% (1) may lead to a few additional cases of hypothyroidism in a larger series of patients. Therefore, a definitive statement on the hypothyroidism rate following the TcTUs-adapted dose concept cannot be given at this moment. A larger series of patients and a longer follow-up period are required for this purpose.

Reliability of TSH measurement

The TcTUs is the most specific parameter indicating functional thyroid autonomy in an area of iodine deficiency (11). However, 6 months after RIT for non-immunogenic hyperthyroidism, a TRH test enables any remaining thyroid autonomy to be detected in most cases (5). These findings were confirmed by the present results: the positive predictive value of a basal TSH level of <0.5 mU/l indicating persisting thyroid autonomy after RIT was 89%. On the other hand, the value of basal TSH < 0.5 mU/l as a screening test for thyroid autonomy in iodine-deficient areas is limited because its positive predictive value is only 55.5% in untreated outpatients (13).

Conclusion

The present study demonstrates the usefulness of TcTUs measurement for individual dose determination in non-immunogenic hyperthyroidism. While targeted doses of 150 or 200 Gy are sufficient for reliable elimination of thyroid autonomy in patients with a TcTUs of 1.6–3.2%, higher doses are required above this threshold. Consequently, a dose adaptation between 150 and 300 Gy to the TcTUs prior to RIT is recommended. Short-term post-treatment hypothyroidism seems to be avoidable with this concept. The promising results of this retrospective analysis still have to be confirmed by a prospective study.

References

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