Dose selection for radioiodine therapy of borderline hyperthyroid patients with multifocal and disseminated autonomy on the basis of ^{99m}Tc-pertechnetate thyroid uptake

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Received 17 August and in revised form 11 November 2001 / Published online: 29 January 2002

Abstract. The aim of this study was to optimise radioiodine therapy of diffuse and nodular toxic goitre by calculation of the radiation dose delivered to the thyroid on the basis of the pretreatment technetium-99m pertechnetate thyroid uptake under thyrotropin suppression ($TcTU_s$). The $TcTU_s$ value serves as a substitute for the non-suppressible iodine turnover and the functional autonomous mass. Marinelli's formula was used to calculate tissue absorbed doses of 150 Gy, 200 Gy, 250 Gy and 300 Gy to the thyroids of 438 patients with multifocal and disseminated autonomy. The mean age of patients was 70±9 years, and the mean thyroid volume was 54±26 ml. Two hundred and sixty-one of the patients had at least one documented previous episode of overt hyperthyroidism. Tissue absorbed doses were adapted to the pretreatment $TcTU_s$: 150 Gy for a $TcTU_s$ of 1.5%–2.49%, 200 Gy for a $TcTU_s$ of 2.5%–3.49%, 250 Gy for a $TcTU_s$ of 3.5%–4.49% and 300 Gy for a $TcTU_s$ of ≥4.5%. Normalisation of $TcTU_s$ and thyrotropin (TSH), thyroid volume reduction and frequency of hypothyroidism and recurrent hyperthyroidism were evaluated 1 year after a single radioiodine therapy. The presented dose strategy resulted in normalisation of $TcTU_s$ in 96% and an increase in TSH to the normal range in 92%. Recurrent hyperthyroidism was observed in only five patients. Thyroid volume decreased from 54±26 before treatment to 34±20 ml, a mean reduction of 37%. The frequency of hypothyroidism, at 0.9%, was encouragingly low. Dose selection in accordance with pretreatment $TcTU_s$ can be recommended for elimination of functional autonomous tissue with a single radioiodine therapy in patients of advanced age with enlarged thyroid glands and relevant autonomous masses who are at risk of developing iodine-induced hyperthyroidism.

Keywords: Radioiodine therapy – Dose calculation – Diffuse toxic goitre – Nodular toxic goitre

Eur J Nucl Med (2002) 29:480–485
DOI 10.1007/s00259-001-0722-0

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Introduction

Despite almost 60 years of experience with radioiodine therapy (RIT) in hyperthyroidism, little consensus exists among experts on the optimal method of dose selection or even the best method of dose determination [1]. Marinelli's formula has been developed to provide a consistent framework for absorbed dose calculations that uses universally accepted units and measurements [2]. This formula requires determination of the effective half-life and the maximum uptake of radioiodine, usually derived from a radioiodine uptake test prior to RIT, and the target volume [3]. Determination of the target volume can be done easily by ultrasound in the case of a single hyperfunctioning thyroid nodule but is almost impossible when there is a multifocal and disseminated pattern of functional autonomous cells. To overcome this problem, a "dosimetric compromise" has been suggested in which the total thyroid volume, rather than hyperfunctioning thyroid nodules, is considered as the target volume and the tissue absorbed dose is subsequently reduced to 50% [4]. However, studies using such an approach have shown that the results of RIT with ≤200 Gy tissue absorbed dose are significantly worse in patients who have been overtly hyperthyroid or have presented with a technetium-99m pertechnetate thyroid uptake under thyrotropin suppression

($TcTU_s$) of >3.2% [5, 6]. RIT failed to eliminate functional thyroid autonomy in about 50% of such patients. The $TcTU_s$ value has gained significance as a measure of the non-suppressible iodine turnover or the functional autonomous mass, which can be used to identify patients who are at risk of developing overt hyperthyroidism [7, 8]. As a consequence, dose selection on the basis of the pretreatment $TcTU_s$ has been recommended [9]. This modified dosimetric approach has been prospectively evaluated over a 5-year period. The results of the first 75 patients treated were reported 3 years ago [10]. This study summarizes the results of RIT using $TcTU_s$-adapted dose selection in more than 400 patients with goitres and multifocal and disseminated thyroid autonomy.

Materials and methods

Patients. Consecutive patients (*n*=438; 298 women and 140 men) who were referred to two centres for RIT of diffuse or nodular toxic goitre and who had a complete follow-up for between 6 and 24 months after RIT were included in this prospective analysis. The mean age of the patients was 70.0±8.9 years (range 35–96 years). RIT was regarded as indicated in the presence of overt hyperthyroidism or symptomatic borderline hyperthyroidism and scintigraphically confirmed multifocal and disseminated thyroid autonomy with a $TcTU_s$ of ≥1.5% [11]. A total of 261 patients (59.6%) had at least one documented previous episode of overt hyperthyroidism, while the remaining 177 patients (40.4%) were borderline hyperthyroid. All patients had a goitre with a volume of more than 18 ml. Thyroid nodules were palpable in 344 cases (78.5%). None of the patients had undergone a previous surgical intervention to the thyroid or previously received radioiodine treatment. All patients presented with endogenously suppressed thyrotropin (TSH ≤0.1 mU/l) and peripheral euthyroidism (normal values for free triiodothyronine and free thyroxine) at the time of radioiodine test and therapy. Patients who were overtly hyperthyroid at the time of RIT were not included in the present evaluation. Occasional antithyroid drug medication was discontinued at least 3 weeks prior to RIT. Urinary iodine excretion was below 10 µg/dl in 258 patients (58.9%) and between 10 and 30 µg/dl in the remaining 180 patients (41.1%), indicating mild iodine deficiency in the patient sample studied [12].

Methods. The TSH level was determined using an immunoradiometric assay (RIA-gnost hTSH, Cis bio international, Cedex, France or Dynotest TSH 1, Brahms, Berlin, Germany). The normal range was 0.3–4 mU/l. TSH values ≤0.1 mU/l were considered to be suppressed. Free thyroxine (fT_4) and free triiodothyronine (fT_3) levels were measured with the Amerlex-FT4-MAB and Amerlex-FT3-MAB kits (Demeditec Diagnostica GmbH, Kiel, Germany). Reference ranges were 9–27 pmol/l (fT_4) and 3–7.7 pmol/l (fT_3). Laboratory kits and reference ranges were identical at both centres.

Thyroid sonography was performed with a 7.5-MHz linear transducer on a Hitachi CS 9000 sonography device and a 5-MHz linear transducer or a 7.5-MHz sector transducer on a Philips SSD-630 sonography device. The formula of Brunn and co-workers [13] was applied for sonographic estimation of total thyroid volume. This formula is based on the formula of a rotation ellipsoid and has an average inaccuracy of 15%.

Thyroid scintigraphy was performed by means of a high-resolution gamma camera (Siemens Basicam). Images were obtained over 5 min starting 20 min after intravenous injection of 37 MBq ^{99m}Tc-pertechnetate. A method originally described by Mahlstedt and Czirik was used for quantitative evaluation of scintigrams [14]. In brief, the count rate density was measured in a region of interest over the entire thyroid and corrected for the activity remaining in the syringe, activity at the site of injection and background activity. The camera and imaging procedure were identical at both centres. A $TcTU_s$ value of ≥1.5% was used to define functional thyroid autonomy [7, 11].

Urinary iodine excretion was measured in all patients of the study group either with a modified ceric ammonium sulphate method originally described by Wawschinek and co-workers [15] or with the Urojod®-Test (Merck, Darmstadt, Germany). These two methods are reported to produce comparable results [16].

Radioiodine therapy. Dosimetry was performed in all patients within 2 weeks prior to RIT by means of a radioiodine uptake test with 2 MBq iodine-131 lasting 3–5 days. The activity applied was calculated using Marinelli's formula [17]. Activities of 817± 329 MBq (185–2,220 MBq) were applied to achieve tissue absorbed doses of 150 Gy in 168 patients (38.4%), 200 Gy in 93 patients (21.2%), 250 Gy in 81 patients (18.5%) and 300 Gy in 96 patients (21.9%). Tissue absorbed doses were selected according to the pretreatment $TcTU_s$: 150 Gy for a $TcTU_s$ of 1.5%–2.49%, 200 Gy for a $TcTU_s$ of 2.5%–3.49%, 250 Gy for a $TcTU_s$ of 3.5%–4.49% and 300 Gy for a $TcTU_s$ of ≥4.5% [10]. Thyroidal radioiodine uptake was measured every day during therapy using a collimated gamma dose-rate probe to determine the maximum uptake and effective half-life of radioiodine. Calibration of the probe for the high activities of radioiodine was done with therapy capsules at the same distance as the patient.

Evaluation. Sonographic thyroid volume, fT_4 and fT_3, thyrotropin and ^{99m}Tc-pertechnetate thyroid uptake were measured when the radioiodine test was performed and again between 6 and 24 months after treatment. The results of radioiodine therapy in the four different dose groups were compared with regard to normalisation of $TcTU_s$, increase in TSH level, reduction of goitre volume and thyroid function.

Statistics. Data are expressed as mean values ±1 standard deviation (SD) and, if appropriate, as maximum and minimum values. The distribution-free rank sum test of Wilcoxon-Mann-Whitney was used to test whether the population distribution functions corresponding to the random samples were identical or whether they differed by location. The chi-square test was performed for comparison of proportions. A Bonferroni correction was applied for multiple comparisons. *P* values of less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS 9.0 for Windows software.

Results

The pretreatment data of the 438 patients with diffuse or nodular toxic goitre are shown in Table 1. As stated above, tissue absorbed doses of 150 Gy, 200 Gy, 250 Gy or 300 Gy were selected on the basis of the pretreatment $TcTU_s$. Mean radioiodine uptake was 44.7%±12.8% with a range from 16% to 84%. Despite some overlap

Table 1. Thyroid volume, $TcTU_s$ and iodine kinetics of 438 borderline hyperthyroid patients with multifocal and disseminated thyroid autonomy prior to RIT

	Tissue absorbed dose (Gy)				Total
	150	200	250	300	
Patients (no.)	168	93	81	96	438
Thyroid volume (ml)	52±25 (19–140)	52±22 (24–100)	51±29 (20–150)	60±26 (20–130)	54±26 (19–140)
TcTUs (%)*	2.02±0.29 (1.5–2.49)	3.02±0.28 (2.5–3.49)	3.93±0.33 (3.5–4.49)	7.23±2.07 (4.5–14.6)	3.73±2.22 (1.5–14.6)
Radioiodine uptake (%)*	36.9±10.6 (16–69)	42.1±11.4 (17–74)	48.4±8.2 (28–62)	57.7±12.1 (25–84)	44.7±12.8 (16–84)
Effective half-life (days)	6.3±0.8 (3.5–7)	5.8±1.2 (3–7)	6.2±0.7 (4–7)	6.5±0.8 (4–7)	6.2±0.9 (3–7)
Activity applied (MBq)	751±237 (185–1,480)	892±355 (220–2,220)	765±242 (295–1,480)	903±244 (370–1,665)	817±269 (185–2,220)

Ranges are shown in parentheses
* Significant differences between groups, $P<0.05$ (Wilcoxon-Mann-Whitney test)

Table 2. Results 15 months after RIT in 438 patients with multifocal and disseminated thyroid autonomy using a $TcTU_s$-adapted dosimetric approach

	Absorbed dose (Gy)				Total
	150	200	250	300	
Patients (no.)	168	93	81	96	438
Follow-up (months)	14.4±8.2	15.4±9.6	13.9±9.7	15.7±8.9	14.8±8.8
$TcTU_s$ <1.5% (no.)[a]	163 (97.0%)	89 (95.7%)	78 (96.3%)	91 (94.8%)	421 (96.1%)
TSH >0.3 mU/l (no.)	155 (92.3%)	87 (93.6%)	73 (90.1%)	88 (91.7%)	403 (92.0%)
Thyroid volume (ml)[b]	30.1±19.7 (6–115)	35.5±18.8 (9–94)	32.4±17.8 (6–70)	40.4±19.4 (10–82)	34.3±19.6 (6–115)
Hypothyroid (no.)[c]	3 (1.8%)	1 (1.1%)	0	0	4 (0.9%)
Euthyroid (no.)	157 (93.4%)	89 (95.7%)	77 (95.1%)	91 (94.8%)	414 (94.5%)
Hyperthyroid (no.)[d]	8 (4.8%)	3 (3.2%)	4 (4.9%)	5 (5.2%)	20 (4.6%)

[a] Six patients with $TcTU_s$ >2.5% and 11 patients with $TcTU_s$ 1.5%–2.5%
[b] Range in parentheses
[c] Three patients with subclinical hypothyroidism and one patient who was euthyroid under thyroid hormone substitution
[d] Fifteen patients with borderline hyperthyroidism, three patients who were euthyroid under antithyroid medication and two patients with overt hyperthyroidism

between groups, the mean radioiodine uptake increased significantly from 36.9%±10.6% in the 150-Gy group to 57.7%±12.1% in the 300-Gy group ($P<0.05$, Wilcoxon-Mann-Whitney test). There was a significant difference in radioiodine uptake between all treatment groups. However, no significant difference was observed between the four groups with respect to thyroid volume, effective half-life of radioiodine or applied activity. Sonographic mean thyroid volume was 54±26 ml, ranging from 19 to 140 ml. Effective half-life of radioiodine was 6.2±0.9 days, with a wide range from 3 to 7 days. Activities of 817±269 MBq radioiodine were applied with a minimum of 185 MBq and a maximum of 2,220 MBq.

The results of RIT are shown in Table 2. Mean follow-up period was 15±9 months, with no differences between groups. Post-treatment $TcTU_s$ was below 1.5% in 96.1% of cases, ranging from 97% in the 150-Gy group to 94.8% in the 300-Gy group. The frequency of TSH-normalisation was 92%, not significantly lower than that of $TcTU_s$ normalisation. The decrease in thyroid volume ranged between 10% and 60% with a mean reduction of 37%. Three of four cases of post-treatment hypothyroidism occurred in the 150-Gy group and one in

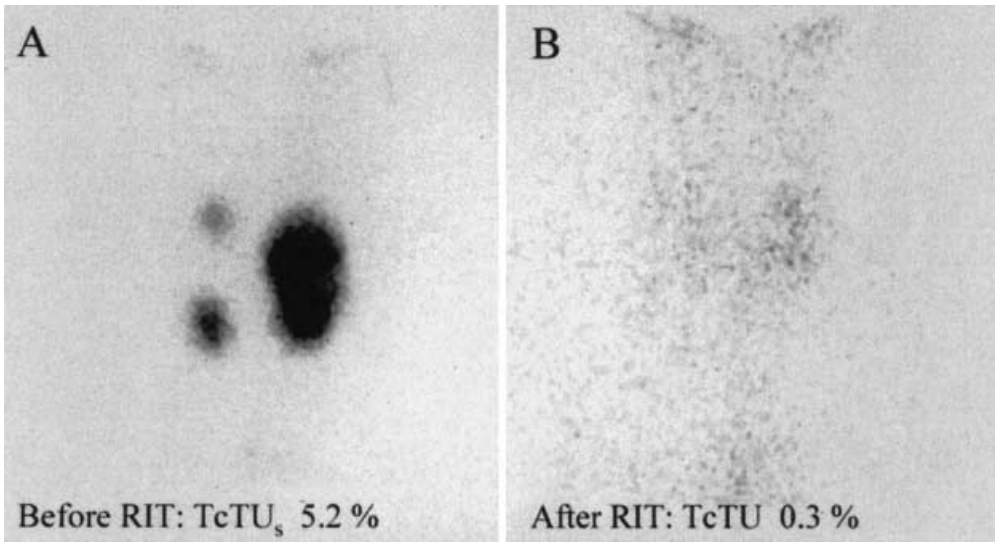

Fig. 1. Scintigraphy of multifocal thyroid autonomy before (**A**) and 9 months after (**B**) RIT. Due to a $TcTU_s$ of >4.5%, 1,295 MBq ^{131}I was administered to deliver a tissue absorbed dose of 300 Gy to the total thyroid volume. With a single RIT the patient became euthyroid (TSH 0.3 mU/l), the thyroid volume decreased by about 40% (from 72 ml to 44 ml) and functional autonomy was completely eliminated (TcTU after RIT: 0.3%)

the 200-Gy group. Only one patient was manifestly hypothyroid; the remaining three patients were subclinically hypothyroid.

One of five cases of recurrent hyperthyroidism occurred in the 200-Gy group, and two in each of the 250-Gy and the 300-Gy group. These five patients received a repeat treatment within 1 year after primary RIT. The frequency of borderline hyperthyroidism did not exceed 5%. Symptom relief was achieved in most of these 15 patients. The $TcTU_s$ decreased to below 1.5% in three of them, and to between 1.5% and 2.5% in 11 patients; only one patient had a $TcTU_s$ of >2.5% after RIT. Of 15 patients with borderline hyperthyroidism after RIT, just two were scheduled for repeat treatment with radioiodine.

There were no significant differences between the four treatment groups concerning any of the parameters evaluated in the follow-up.

An example of successful RIT is shown in Fig. 1. A 67-year-old patient suffered from recurrent hyperthyroidism on two occasions. Successful therapy of overt hyperthyroidism with anti-thyroid medication was discontinued when the patient was borderline hyperthyroid, 6 weeks before RIT. At the time of the radioiodine test and therapy, the patient continued to be borderline hyperthyroid and the $TcTU_s$ was 5.2%. Therefore, a 300-Gy tissue absorbed dose was selected and a sole RIT was performed with 1,295 MBq ^{131}I. Nine months later, the patient was euthyroid (TSH 0.3 mU/l) and scintigraphy showed a TcTU of 0.3%. This value was well below the threshold of reference range of $TcTU_s$ (<1.5%) and confirmed multifocal thyroid autonomy to be completely eliminated. Goitre size was significantly reduced by 40%.

Discussion

Follicular epithelial cells with autonomous iodine turnover are found inside and outside of thyroid nodules and also independent of the existence of nodules [18, 19, 20]. Thus, the target volume for RIT, i.e. the functional autonomous volume, can be determined with sufficient accuracy only in selected cases of unifocal autonomy, when the autonomous follicles are concentrated in a sonographically detectable area within the gland [8]. A more heterogeneous distribution of autonomously functioning epithelial cells renders sonographic volumetry almost impossible for the determination of the target volume. The non-suppressible ^{99m}Tc-pertechnetate uptake can be used as a measure of the mass of functional autonomous cells in the thyroid [7, 8]. Nevertheless, pretreatment thyroid volume and pretreatment $TcTU_s$ values have been identified as most significant independent factors influencing the outcome of RIT in multifocal and disseminated thyroid autonomy [21]. Both have to be considered when selecting a dosimetric approach. When the clinical applicability of a linear derivation of the autonomous volume from the $TcTU_s$ was tested in a small series of patients, a target dose of ≥350 Gy was necessary to achieve a $TcTU_s$ normalisation in 90% and a TSH normalisation in 70% [22]. When the patient database was increased, this merely $TcTU_s$-based dosimetric approach had to be corrected for the thyroid volume since large goitres need higher target doses [21]. Conversely, the older, merely volume-based approach [4] had to be corrected for higher $TcTU_s$ values [5].

As a consequence of the findings described above, a combined volume- and $TcTU_s$-based approach has been introduced that takes into consideration the total thyroid volume and entails a stepwise dose adaptation to the pretreatment $TcTU_s$ [9, 10]. The results achieved in the current series of 438 patients 15 months after a single RIT, i.e. a $TcTU_s$ normalisation rate of 96% and a TSH nor-

malisation rate of 92%, show that stepwise dose adaptation is a highly effective dosimetric approach for non-unifocal-distributed functional autonomous epithelial cells in enlarged thyroids. Even with a different graduation of the dose steps [23], the results of RIT in multifocal and disseminated thyroid autonomy are similar to those presented in the current study.

It may be a matter of debate whether such a sophisticated dosimetric approach for RIT is really necessary [1]. There are several issues to consider. In areas where most cases of hyperthyroidism are of a non-immunogenic origin, the majority of patients are above 60 years of age and many of them suffer from several other diseases which require diagnostic or therapeutic application of iodine-containing contrast media, disinfectants or drugs. These patients often cannot wait for years until repeated application of radioiodine will finally succeed. In the presented series of patients, the mean age was 70±9 years.

A very recent analysis of factors predicting the outcome of two fixed activity regimens with 185 or 370 MBq in patients with toxic nodular goitre reported an overall cure rate of 71.4% (66.6% after 185 MBq and 84.6% after 370 MBq) [24]. The same study identified more severe hyperthyroidism and medium or large goitres to be highly significant factors which make the patient less likely to respond to a single dose of radioiodine [24]. Most of our patients would belong to that subgroup: almost 80% had a thyroid volume above 30 ml (the mean thyroid volume was 54±26 ml), while the frequency of documented previous overt hyperthyroidism was 60%, similar to the frequency of pretreatment $TcTU_s$ of >3%, namely 62%. A $TcTU_s$ value of 3% is supposed to represent the "critical" autonomous volume, i.e. the volume at which overt hyperthyroidism will occur [8].

A standard activity of 740 MBq radioiodine has been reported to be highly effective in the treatment of toxic solitary autonomous nodules [25]. However, the same group reported that calculated activities adjusted for thyroid weight and radioiodine uptake were more effective than repeated standard activities in toxic multinodular goitre (relief of hyperthyroidism being achieved in 88% vs 73%) and that the percentage of patients who were adequately treated with a single application of radioiodine was more than twice as high for the calculated activity as for the standard activity (66% vs 27%) [26]. On the other hand, application of a cumulative activity of 2.22 GBq over 4 months with 555 MBq per month in patients with large multinodular goitres was reported to have produced hypothyroidism in 66% of cases after 18 months [27]. Nonetheless, a fixed activity method may strongly over-irradiate the smaller glands as well [28]. The hypothyroidism rate with our dosimetric approach was just 0.9% 15 months after RIT.

Beside the clinical success, RIT is supposed to enhance convenience for the patient and to facilitate early resumption of a normal lifestyle. Reducing the risk of recurrent hyperthyroidism following an occasional iodine exposure in the form of iodine-containing contrast agents or disinfectants is especially valuable for the older patient with concomitant disease. All this can be achieved with high efficiency by using the presented dosimetric approach: the percentage of patients adequately treated in the present study, 96%, is considerably higher than the 66% rate achieved with a less sophisticated approach [26]. As differences in radioiodine kinetics may occur in approximately 10% of cases between uptake test and therapy, a 100% success rate is scarcely possible with a single therapy. However, careful measurement of the therapeutic thyroidal radioiodine uptake permits detection of occasional underdosage and a subsequent correction by a second dose within the same in-patient treatment [29].

There are only a few requirements when using Marinelli's formula for absorbed dose calculations, and all the preparations may be completed within 24 h: sonographic volumetry of the thyroid, quantitative thyroid scintigraphy with ^{99m}Tc-pertechnetate and a radioiodine uptake test with a 24-h measurement of thyroidal radioiodine uptake. The effective half-life of radioiodine in benign thyroid disease is strongly correlated with the thyroid function and therefore may be derived from the TSH, fT3 and fT4 levels [30]. Whether, considering their logarithmic correlation [23], the 24-h radioiodine uptake may be replaced by the $TcTU_s$, or vice versa, might be a topic for further studies.

Conclusion

Stepwise adaptation of the tissue absorbed dose to the pretreatment uptake of ^{99m}Tc-pertechnetate by the thyroid under thyrotropin suppression and use of the total thyroid volume for calculation of the applied activity by means of Marinelli's formula can be recommended for complete elimination of multifocal and disseminated autonomous thyroid tissue with a sole radioiodine therapy at a very low rate of hypothyroidism. This approach would be especially beneficial in patients of advanced age or with enlarged goitres in whom iodine exposure by use of contrast media or disinfectants is intended and who are at risk of developing iodine-induced hyperthyroidism.

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