Dose selection for radioiodine therapy of borderline hyperthyroid patients according to thyroid uptake of ^{99m}Tc-pertechnetate: applicability to unifocal thyroid autonomy?

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Abstract. *Purpose:* The aim of this study was to evaluate the feasibility of applying a previously described dose strategy based on ^{99m}Tc-pertechnetate thyroid uptake under thyrotropin suppression ($TcTU_s$) to radioiodine therapy for unifocal thyroid autonomy.
Methods: A total of 425 consecutive patients (302 females, 123 males; age 63.1±10.3 years) with unifocal thyroid autonomy were treated at three different centres with ^{131}I, using Marinelli's formula for calculation of three different absorbed dose schedules: 100–300 Gy to the total thyroid volume according to the pre-treatment $TcTU_s$ (n=146), 300 Gy to the nodule volume (n=137) and 400 Gy to the nodule volume (n=142).
Results: Successful elimination of functional thyroid autonomy with either euthyroidism or hypothyroidism occurred at a mean of 12 months after radioiodine therapy in 94.5% of patients receiving 100–300 Gy to the thyroid volume, in 89.8% of patients receiving 300 Gy to the nodule volume and in 94.4% receiving 400 Gy to the nodule volume. Reduction in thyroid volume was highest for the 100–300 Gy per thyroid and 400 Gy per nodule strategies (36±19% and 38±20%, respectively) and significantly lower for the 300 Gy per nodule strategy (28±16%; p<0.01).
Conclusion: A dose strategy based on the $TcTU_s$ can be used independently of the scintigraphic pattern of functional autonomous tissue in the thyroid.

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Introduction

Three years ago, we reported a novel dosimetric approach to radioiodine therapy (RIT) of toxic nodular goitre with multifocal and disseminated thyroid autonomy [1]. This approach, based on ^{99m}Tc-pertechnetate thyroid uptake under TSH suppression ($TcTU_s$), used Marinelli's formula for calculation of the activity of ^{131}I to be administered. It entailed stepwise adaptation of the tissue absorbed dose to the thyroid (150, 200, 250 or 300 Gy) on the basis of the pre-treatment $TcTU_s$ as a measure of the entire functional autonomous mass in the thyroid [2, 3]. The pathophysiological basis of this strategy is the heterogeneous distribution of functional autonomous follicles in the entire thyroid, i.e. inside and outside of thyroid nodules and also independently of the existence of nodules [4–8]. It has to be pointed out that these autoradiographic findings apply not only to scintigraphically multifocal and disseminated autonomy but also to the majority of cases of unifocal thyroid autonomy [9]. Consequently, the above-mentioned dose strategy based on the $TcTU_s$ should be applicable to unifocal thyroid autonomy as well as to multifocal and disseminated thyroid autonomy. Thus, the aim of the present study was to evaluate the feasibility of applying this strategy to unifocal thyroid autonomy by comparing it with established approaches delivering absorbed doses of 300 or 400 Gy to the nodule volume.

Materials and methods

Patients

Consecutive patients (n=425; 302 females, 123 males; age 63.1±10.3 years, range 33–87 years) who were referred to three centres for RIT of an autonomously functioning thyroid nodule and who had a complete follow-up for 6 months or more were included in this prospective analysis. Indication for RIT was one documented episode of overt hyperthyroidism or symptomatic borderline hyperthyroidism and scintigraphically confirmed unifocal thyroid autonomy with a $TcTU_s$ ≥1.0%. A total of 228 patients (53.7%) had at least one documented previous episode of overt hyperthyroidism, while the remaining 197 patients (46.3%) had been borderline hyperthyroid. None of the patients had undergone a previous surgical intervention to the thyroid or RIT. All patients presented with suppressed thyrotropin (TSH_{basal} <0.1 mU/l) and peripheral euthyroidism [normal values for free triiodothyronine (FT_3) and free thyroxine (FT_4)] during radioiodine test and therapy. TSH suppression was achieved exogenously in 62 patients by administration of levothyroxine in doses between 100 and 150 µg/day over 4–6 weeks before and during RIT, and 363 patients presented with endogenously suppressed TSH. Occasional thionamide medication was withdrawn at least 4 weeks prior to RIT. Patients who were overtly hyperthyroid at the time of RIT were excluded from the present evaluation.

Methods

TSH was determined using an immunoradiometric assay (BRAHMS TSH 1 RIA, Brahms Bioassays GmbH, Henningsdorf, Germany or TSH Magnum Rapid, Medipan GmbH, Dahlewitz, Germany). Normal range was 0.3–4.0 mU/l. TSH values ≤0.1 mU/l were considered to be suppressed. Free thyroid hormones were measured with the Liaison FT_3 and Liaison FT_4 kits (DiaSorin Deutschland GmbH, Dietzenbach, Germany) or the SELco FT_4 and SELco FT_3 kits (Medipan GmbH, Dahlewitz, Germany). Reference ranges were 10–24 pmol/l (FT_4) and 2.5–7 pmol/l (FT_3).

Thyroid and nodule volumes were measured sonographically. Ultrasound was performed with a 7.5-MHz linear transducer on a Siemens Sonoline Sienna or a Toshiba Nemio sonography device. The formula of Brunn and co-workers [10] was applied for estimation of total thyroid volume. This formula is based on the formula of a rotation ellipsoid and has an average inaccuracy of 15%. Sphere-shaped nodules were measured using the formula for a sphere volume.

Thyroid scintigraphy was performed by means of a high-resolution gamma camera (Basicam, Siemens AG, Erlangen, Germany). Images were obtained over 5 min, 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 [11]. 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, the site of injection and background activity. Camera and imaging procedure were identical at all centres.

Radioiodine therapy

The patient's individual radioiodine kinetics was determined by means of a radioiodine uptake test with 2 MBq ^{131}I performed within 2 weeks of treatment. The activity applied was calculated using Marinelli's formula [12]. Each of the three centres performed a different dosimetric schedule: centre 1 used a dose strategy based on the $TcTU_s$, with tissue absorbed doses of 100, 150, 200, 250 or 300 Gy to the total thyroid volume as described previously [1]; centre 2 administered a 300-Gy absorbed dose to the hyperfunctioning nodule volume; and centre 3 administered a 400-Gy dose to the nodule. A few minor adjustments were made to the dose strategy based on the $TcTU_s$ for RIT of patients with unifocal autonomy: because goitres comprising unifocal autonomy were often smaller than those with multifocal and disseminated autonomy, the threshold of $TcTU_s$ for definition of functional thyroid autonomy was set at 1.0%, corresponding to a thyroid volume of 15 ml, and the tissue absorbed dose for patients with a $TcTU_s$ of 1.0–1.5% was reduced to 100 Gy.

Evaluation

Patients were followed after RIT at least until satisfactory elimination of thyroid autonomy had been achieved or repeat treatment was scheduled. Sonographic thyroid volume, free thyroid hormones, TSH and $TcTU/TcTU_s$ were measured at the time of the radioiodine test and again at a mean of 12 months after treatment. Follow-up included additional measurements of TSH and thyroid hormones at 4–6 weeks after RIT and again after 3 and/or 6 months in order to detect early changes in thyroid function and to initiate medical treatment as appropriate.

The results of RIT were compared among the three dose groups with respect to thyroid function and reduction in goitre volume. Therapeutic success was defined as elimination of unifocal thyroid autonomy with either euthyroidism or hypothyroidism.

Statistics

Data were expressed as mean values ±1 standard deviation (SD) and as maximum and minimum values. The distribution-free rank sum test of Wilcoxon-Mann-Whitney was used for comparison of means. Fisher's exact test was performed for comparison of proportions. A Bonferroni correction was applied for multiple comparisons. Probability (p) values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS 12.0 for Windows software.

Results

The pre-treatment data of the 425 patients with unifocal thyroid autonomy are shown in Table 1. About 140 patients were treated with each of the three dosimetric approaches.

Patients receiving a 300-Gy dose per nodule had a smaller mean goitre volume and patients receiving a 400-Gy dose per nodule had a larger mean nodule volume than the other treatment groups. Nonetheless, the ranges of thyroid and nodule volumes were identical in all groups (thyroid volume 15–94 ml; nodule volume 3–60 ml). The ratio of nodule to thyroid volume showed a significant difference for the 400 Gy per nodule group compared with the 300 Gy per nodule and the 100–300 Gy per thyroid group (i.e. the group in which the dose strategy was based on the $TcTU_s$). It may be noted that the range of the nodule to thyroid volume ratio was higher for the 300 Gy per nodule group than for the 100–300 Gy per thyroid group.

Table 1. Thyroid and nodule characteristics and ^{131}I kinetics in 425 patients with unifocal thyroid autonomy prior to RIT

	Absorbed dose (Gy)			Total
	100–300/thyroid	300/nodule	400/nodule	
Patients (no.)	146	137	142	425
Thyroid volume (ml)[a]	39±17 (16–84)	33±19 (15–90)	37±18 (18–94)	36±19 (15–94)
Nodule volume (ml)[b]	9.2±7.6 (4–60)	8.4±8.0 (3–56)	12.3±7.8 (5–60)	10.0±7.9 (3–60)
Nodule to thyroid volume ratio[b]	0.32±0.19 (0.18–0.75)	0.34±0.24 (0.10–0.87)	0.42±0.22 (0.22–0.90)	0.36±0.21 (0.10–0.90)
$TcTU_s$ (%)[b]	2.5±1.9 (1.0–7.8)	2.1±1.5 (1.0–7.2)	3.3±1.8 (1.5–7.5)	2.6±1.7 (1.0–7.8)
24-h ^{131} I uptake (%)[c]	26.3±12.2 (11–69)	24.7±11.6 (10–59)	37.3±11.2 (14–72)	29.4±12.6 (10–72)
Effective half-life (days)	6.0±0.9 (3.5–7)	6.3±0.8 (4–7)	5.9±1.1 (3–7)	6.1±0.9 (3–7)
Activity applied (MBq)[d]	618±258 (260–1480)	452±266 (150–1240)	569±253 (185–1300)	546±276 (150–1480)

Ranges are shown in parentheses

[a]100–300 Gy/thyroid and 400 Gy/nodule versus 300 Gy/nodule: $p<0.05$

[b]100–300 Gy/thyroid and 300 Gy/nodule versus 400 Gy/nodule: $p<0.01$

[c]100–300 Gy/thyroid and 300 Gy/nodule versus 400 Gy/nodule: $p<0.001$

[d]100–300 Gy/thyroid and 400 Gy/nodule versus 300 Gy/nodule: $p<0.001$

Despite almost identical measured ranges, the mean $TcTU_s$ and the mean 24-h ^{131}I uptake in the 400 Gy per nodule group were also higher than in both other groups, corresponding to the larger mean nodule volume in the 400 Gy per nodule group. The activity to be applied ranged between 150 and 1,480 MBq; it was not significantly higher for the 100–300 Gy per thyroid group than for the 400 Gy per nodule group but was significantly lower for the 300 Gy per nodule group.

The results of RIT are shown in Table 2. All three dosimetric approaches resulted in a reduction in the mean thyroid volume to about 25 ml 1 year after treatment. Nonetheless, the decrease was highest for the 100–300 Gy per thyroid and the 400 Gy per nodule groups, with reductions of 36±19% and 38±20%, respectively. The frequency of normalised TSH was 88.5%, without significant differences between the three dosimetric approaches. The overall rate of post-treatment hypothyroidism was 6.1%, again without significant differences among the groups. Only nine patients (2.1%) became overtly hypothyroid, and 17 (4.0%) were subclinically hypothyroid. The frequency of post-therapeutic euthyroidism was significantly lower for the 300 Gy per nodule group than for the other two treatment groups (82.5% versus 89.0% and 88.8%; $p<0.05$). The rate of residual or recurrent hyperthyroidism was 7.1%, without significant differences among the three dosimetric approaches. In detail, overt hyperthyroidism requiring a repeat treatment with antithyroid drugs followed by a second RIT occurred in only two patients (0.47%), both in the 300 Gy per nodule group, within 3–6 months after first RIT. All 28 patients with borderline hyperthyroidism after RIT (6.6%) had $TcTU_s$ values below 2.0%, and symptom relief was achieved in 75% of them. Seven patients (1.65%) with post-therapeutic $TcTU_s$ values between 1.5% and 2.0% and incomplete symptom relief (two in the 100–300 Gy per thyroid group, two in the 400 Gy per nodule group and three in the 300 Gy per nodule group) were scheduled for a second RIT within 6–15 months after first RIT. Most of these patients received anti-thyroid drug treatment for 1–2 months between first and second RIT.

Discussion

Our study demonstrates the feasibility of applying a dose strategy based on the $TcTU_s$ to unifocal thyroid autonomy. Consequently, the presented strategy can be used independently of the scintigraphic pattern of autonomous iodine turnover in the thyroid. The efficacy of the $TcTU_s$-based approach was equal to that of the 400 Gy per nodule approach, achieving an elimination rate for functional thyroid autonomy with a single RIT of nearly 95%. Almost identical results were reported some years ago for RIT using 400 Gy per nodule [13]. Those authors suggested for the first time the application of a $TcTU_s$-based approach to unifocal thyroid autonomy after virtual calculation of the dose delivered to the total thyroid volume considering the relation between the nodule and the paranodular volume [13]. According to our data, the $TcTU_s$-based approach resulted in a significantly higher rate of post-therapeutic hypothyroidism in unifocal autonomy than in multifocal and disseminated autonomy (5.5% versus 0.9%), while the rate of residual hyperthyroidism was about the same (4.6% versus 5.5%) [1]. A higher rate of post-therapeutic hypothyroidism is usually a result of over-treatment. The ratio of autonomous to non-autonomous thyroid tissue might play a significant role in this context. However, the ratio of the nodule to the goitre volume in the present series of patients was so widely distributed (range 0.1–0.9, median 0.35) that it was impossible to select a sufficient number of patients with similar conditions regarding the nodule to goitre ratio and $TcTU_s$. However, most of the patients with unifocal autonomy who became hypothyroid using the $TcTU_s$-based approach were characterised by a goitre volume below 35 ml and a $TcTU_s$ above 2.5%, and

Table 2. Results 12 months after RIT in 425 patients with unifocal thyroid autonomy using a dose of 300 Gy or 400 Gy per nodule or 100–300 Gy per thyroid (strategy based on the $TcTU_s$)

	Absorbed dose (Gy)			Total
	100–300/thyroid	300/nodule	400/nodule	
Patients (no.)	146	137	142	425
Follow-up (months)	11.8±9.6	12.4±10.3	13.3±12.1	12.5±10.8
Thyroid volume (ml)[a]	25±14 (9–60)	26±18 (8–70)	24±16 (10–65)	25±17 (8–70)
Volume change (%)[b]	36±19	28±16	38±20	34±18
TSH >0.3 mU/l (no.)	131 (89.7%)	120 (87.6%)	125 (88.0%)	376 (88.5%)
Hypothyroid (no.)[c]	8 (5.5%)	10 (7.3%)	8 (5.6%)	26 (6.1%)
Euthyroid (no.)[d]	130 (89.0%)	113 (82.5%)	126 (88.8%)	369 (86.8%)
Hyperthyroid (no.)[e]	8 (5.5%)	14 (10.2%)	8 (5.6%)	30 (7.1%)

[a]Range in parentheses

[b]100–300 Gy/thyroid and 400 Gy/nodule versus 300 Gy/nodule: $p<0.01$

[c]Including 6, 4 and 7 patients with subclinical hypothyroidism, respectively (100–300 Gy/thyroid, 300 Gy/nodule, 400 Gy/nodule)

[d]100–300 Gy/thyroid and 400 Gy/nodule versus 300 Gy/nodule: $p<0.05$

[e]Including 8, 12 and 8 patients with borderline hyperthyroidism, respectively (100–300 Gy/thyroid, 300 Gy/nodule, 400 Gy/nodule)

the nodule to thyroid volume ratio was above the median of the respective group. It may be hypothesised that the activity of ^{131}I should be reduced by 10–15% in such patients with significant unifocal autonomy but a smaller paranodular thyroid volume [13]. This hypothesis will be verified in an upcoming prospective study.

In comparing the results of the 300 Gy per nodule group and the 400 Gy per nodule group, some differences between the two groups should be considered. The 400 Gy per nodule group comprised goitres with larger nodules, higher nodule to thyroid volume ratios, higher $TcTU_s$ and higher ^{131}I uptake, i.e. patients in this group had a higher amount of autonomous thyroid tissue than those in the 300 Gy per nodule group. A higher amount of autonomous thyroid tissue requires a higher tissue absorbed dose for satisfactory elimination of thyroid autonomy [1, 13]. Therefore the rate of post-therapeutic hypothyroidism did not increase with the higher dose of 400 Gy. In fact, the results were about the same as those in the 100–300 Gy per thyroid group ($TcTU_s$-based approach).

The further analysis of the higher rate of post-therapeutic hypo- and hyperthyroidism in patients treated with the 300 Gy per nodule dose suggested a potential limitation of a nodule-based dose strategy. It turned out that the 300 Gy per nodule group included more extreme cases than both other groups, which resulted in the largest standard deviations of all three groups for thyroid volume, nodule volume and nodule to thyroid volume ratio. Although the mean thyroid volume in the 300 Gy per nodule group was the smallest of all the treatment groups, this group included some patients with large goitres and nodules and high $TcTU_s$ values comparable to those in the 400 Gy per nodule group as well as some patients with small goitres and low $TcTU_s$ values but high nodule to thyroid volume ratios, as in the $TcTU_s$-adapted dose group. Most patients who became hypothyroid after a 300 Gy per nodule dose had a pre-treatment $TcTU_s$ below 1.5% and a

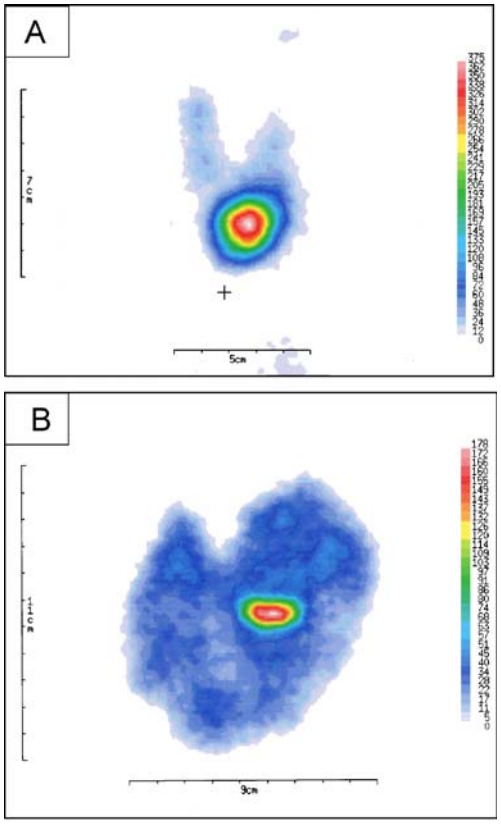

Fig. 1. Two examples of over- and under-treatment with a 300 Gy per nodule dose. **a** Thyroid scintigraphy of a 62-year old female patient with a small goitre volume of 19 ml and a nodule volume of 10 ml. The $TcTU_s$ of the total thyroid was 1.4% and that of the nodule was 1.0%. The patient became subclinically hypothyroid 6 months after RIT with a dose of 300 Gy per nodule. **b** Thyroid scintigraphy of a 71-year old female patient with a goitre volume of 75 ml and a single nodule in the left lobe with a volume of 9 ml. The $TcTU_s$ of the total thyroid was 6.8% and that of the nodule was 1.5%. RIT with a 300 Gy per nodule dose resulted in insufficient elimination of functional thyroid autonomy

thyroid volume below 20 ml, but a nodule to thyroid volume ratio above the median of the group. A typical example is shown in Fig. 1a. On the other hand, most patients who suffered from residual or recurrent hyperthyroidism after a 300 Gy per nodule dose were characterised by the combination of a goitre volume above 40 ml and a $TcTU_s$ above 3.5%, but a nodule to thyroid volume ratio below the median of the group. It has to be considered that a certain amount of autonomously functioning thyroid tissue can often be found outside of a hyperfunctioning thyroid nodule in such patients [4–9]. An example of a goitre with unifocal autonomy that was insufficiently treated with a 300 Gy per nodule dose is shown in Fig. 1b.

Thus it can be hypothesised that over- and under-treatment in the 300 Gy per nodule group would have been avoidable to some extent if consideration had been given to the $TcTU_s$ and the nodule to thyroid volume ratio when determining the dose [13]. The pre-treatment $TcTU_s$ and the thyroid volume have already been identified as the most significant independent predictors of the outcome of RIT in patients with functional thyroid autonomy [14].

Conclusion

Unifocal thyroid autonomy can be effectively treated with ^{131}I using a $TcTU_s$-based approach with delivery of doses of 100–300 Gy to the total thyroid volume. If a dose per nodule strategy is employed, 400 Gy per nodule may be favourable for large goitres with large nodules and higher $TcTU_s$ values and 300 Gy per nodule or less may be favourable for smaller goitres with smaller nodules and lower $TcTU_s$ values.

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