Endocrine (2015) 48:902–908
DOI 10.1007/s12020-014-0398-4

ORIGINAL ARTICLE

Clinical efficacy of radioiodine therapy in multinodular toxic goiter, applying an implemented dose calculation algorithm

Mara Schiavo · Maria Claudia Bagnara · Laura Camerieri · Elena Pomposelli · Massimo Giusti · Giampaola Pesce · Cristina Reitano · Mauro Caputo · Marcello Bagnasco

Received: 21 June 2014 / Accepted: 14 August 2014 / Published online: 24 August 2014

Abstract Radioiodine is a common therapeutic option for Multinodular Toxic Goiter (MTG). We evaluated an algorithm for personalized radioiodine activity calculation. Ninety-three (28 male, 65 female; 43–84 years) patients with MTG eligible for radioiodine treatment (^{131}I-iodide) were studied. The quantity of ^{131}I-iodide to be administered was estimated by Thyroid Volume Reduction (TVR) algorithm, developed for Graves' disease. It takes into account ^{131}I uptake, its effective half-life ($T_{1/2eff}$), thyroid volume, and its expected reduction during treatment. A comparison with the activity calculated by other dosimetric protocols and the "fixed" activity method was performed. ^{131}I uptake was measured by external counting, thyroid volume by ultrasonography (US), thyroid stimulating hormone (TSH), and thyroid hormones by standard immunometric methods. In a follow-up of 6–120 months, remission of hyperthyroidism after a single ^{131}I-iodide treatment was observed in 76 patients (64 euthyroid, 12 hypothyroid). The thyroid volume reduction observed by US after the treatment fairly correlated with what predicted by our model; $T_{1/2eff}$ was highly variable and critically affected dose calculation. The administered activities (median 526 MBq, range 156–625 MBq) were slightly lower than the "fixed" activities (600 MBq) and with respect to the other protocols' prescriptions (−15/38 %); the median ^{131}I activity administered to relapsed patients (605 MBq) was significantly greater ($P = 0.01$) with respect to the dose administered to cured patients (471 MBq). Our study shows that an effective cure of MTG can be obtained with relatively low ^{131}I activities and probably with a relatively low incidence of hypothyroidism, using TVR method.

Keywords Thyroid · Hyperthyroidism · Radioiodine · Dosimetry · Goiter

Introduction

Multinodular Toxic Goiter (MTG) is a hyperthyroid syndrome due to thyroid hormones overproduction by one or more autonomously functioning nodules. MTG as a cause of hyperthyroidism is strictly related to the prevalence of multinodular goiter, which in turn depends upon iodine deficiency (prevalence averaging 5 % of hyperthyroidism in areas with sufficient iodine intake and 20 % in areas of iodine deficiency). Iodine deficiency stimulates thyroid cell proliferation, eventually resulting in development of somatic activating mutations of TSH receptor [1]. Genetic background and female gender, in addition to iodine deficiency, are risk factors for its development.

A large prospective epidemiological study, recently conducted in Denmark, in an area with mild to moderate iodine deficiency, reported the following prevalence among the most frequent causes of hyperthyroidism: MTG 44 %,

M. Schiavo · L. Camerieri · G. Pesce · M. Bagnasco (✉)
Endocrinology Unit and Autoimmunity Laboratory, IRCCS AOU Sa Martino – IST, Di.M.I. Genoa University, Viale Benedetto XV, 6 I-16132 Genoa, Italy
e-mail: bagnasco@csita.unige.it; bagnasco@unige.it

M. C. Bagnara · C. Reitano
Medical Physics Unit, IRCCS AOU San Martino – IST, Genoa, Italy

E. Pomposelli · M. Caputo
Nuclear Medicine Unit, IRCCS AOU San Martino – IST, Genoa University, Genoa, Italy

M. Giusti
Endocrinology Unit, IRCCS AOU San Martino – IST, Di.M.I. Genoa University, Genoa, Italy

Graves' disease (GD) 37 %, and toxic adenoma (TA) 6 % [2].

Radioiodine therapy with ^{131}I-iodide is one of the treatments of choice of MTG, together with surgery [3–5]. In fact, antithyroid drugs, as a rule, are unable to achieve hyperthyroidism cure. Radioiodine is selectively taken up by thyroid tissue, resulting in volume and function reduction.

Two different approaches are used to choose the ^{131}I-iodide activity to be administered: a fixed "maximal" activity (typically 600 MBq) or an activity derived from a dosimetric calculation, that is, the computation of the lowest activity which is able to deliver an acceptable radiation dose to the target tissue [6–8]. Although these methods are both effective, the As Low As Reasonably Achievable (ALARA) principle should be always pursued, avoiding unjustified radioactivity exposition to the patient himself, to people living/working near him and to environment.

Dosimetric calculation implies the measurement of ^{131}I-iodide uptake by external counting after administration of a tracer activity and evaluation of functioning target tissue volume.

In this study, we applied a multi-parameter dosimetric approach to a group of patients with MTG. This algorithm was created and clinically validated for GD [9–11]. We successfully applied this protocol to single hyperfunctioning thyroid nodule patients [12]; yet there are no published studies about its use in the MTG treatment. The present study highlighted a fair therapeutic efficacy with a relatively low incidence of hypothyroidism.

Materials and methods

Patients

We prospectively evaluated a group of 93 consecutive patients (28 males and 65 females, aged between 43 and 84, median 71 years) with MTG and functionally autonomous areas as detected by thyroid $^{99m}TcO_4^-$ scintigraphy. In all of them, the thyroid scan showed a partial or complete functional inhibition of extra-nodular tissue. Patients with a single autonomously functioning thyroid nodule, without other clinically relevant US-detectable nodules, were excluded from the study.

Among them, 22 patients (24 %) had overt hyperthyroidism and 71 (76 %) subclinical hyperthyroidism.

All the patients with subclinical hyperthyroidism who underwent radioiodine treatment had TSH below 0.1 mU/L. They complained of cardiovascular symptoms/signs, such as tachycardia or arrhythmias, or had progressively worsening osteopenia or osteoporosis. In some cases, an additional indication was to obtain a clinically significant total thyroid volume reduction. Patients with clinical hyperthyroidism underwent, as a rule, a short course of low-dose methimazole therapy (10–20 mg daily) before radioiodine: antithyroid drugs were discontinued at least 3 weeks before measurement of thyroid ^{131}I-iodide uptake (see below). Follow-up visits were systematically performed at 7, 15, 30 days and 6 months after radioiodine therapy, and thereafter every 6 or 12 months (according to clinical conditions and thyroid function). Patients who were still hyperthyroid following the first administration of radioiodine were given a second administration 6 months later, which invariably resulted in hyperthyroidism cure (not shown).

Methods

Free thyroid hormones and TSH were measured in basal conditions (i.e., immediately before treatment), and during follow-up. TSH (3rd generation ultrasensitive assay) and free T_3 and T_4 assays were carried out through standard immunometric methods.

Shortly before treatment, thyroid ^{131}I uptake was evaluated by direct external measurements at 4th, 24th and between 96th and 120th h following administration of a trace activity (about 370 kBq of ^{131}I-iodide) with a $2'' \times 2''$ thallium-activated sodium iodide scintillator [NaI(Tl)] probe; an acrylic-water phantom was used for probe calibration.

Total thyroid and nodules volumes were evaluated by means of US [13] in basal conditions and at different times from ^{131}I-iodide therapy (after 1–6–12 months). In order to exclude iodine excess, 24-hour urinary iodine excretion was measured by the Sandell–Kolthoff method [14]. The prescribed absorbed dose to the hyperfunctioning tissue ranged between 250 and 300 Gy for MTG.

Dosimetry and statistical analysis

In order to estimate the activity (A, measured in MBq) to be prescribed for each patient, we referred to the method developed by Traino et al. [9] and reported in the above guidelines, specifically developed for GD treatment. This method takes into account, in addition to ^{131}I kinetics, the volume reduction of functioning thyroid tissue after radioiodine administration (TVR). We applied such a method also to the radioiodine therapy for MTG. The algorithm for TVR is the following:

$$A(MBq) = \frac{D_T \cdot m_0}{U_{max} \cdot T_{1/2eff}} \left(5,656 - 5,08 \times 10^{-5} \frac{D_T \cdot m_0}{U_{max}}\right), \quad (1)$$

where D_T is the target absorbed dose (Gy); m_0 the target (MTG) initial mass (g) evaluated by US (ellipsoid

approximation); U_{max} the maximum uptake of intra-thyroid radioiodine kinetics (fraction) and $T_{1/2eff}$ is the effective half-life.

As a rule, total thyroid volume derived from US was used for estimating m_0. In 27 MTG patients, who showed only one or two "hot" nodules at thyroid scintigraphy, with near-total functional inhibition of the remaining tissue, we considered only the volume of the hyperfunctioning nodule(s) to estimate the target mass m_0: this volume actually accounted for 8–56 % of total thyroid volume.

When the calculated prescribed activity exceeded the maximum allowed for outpatients by our national law (600 MBq), a standard upper threshold activity (600 ± 5 % MBq) was administered; when it was lower than what can be considered a clinical minimum, a lower threshold activity (about 150 MBq) was administered.

This implied, in some cases, a nodule absorbed dose lower/higher with respect to the one that had been calculated by the algorithm. Another imprecision factor was the exact time of radiopharmaceutical administration: ^{131}I was provided as sodium iodide caps with standard activities, and physical decay was used to reach the desired activity. As a rule, however, dose imprecision did not exceed 10 %.

Each prescribed activity was compared with both the following, more common, dosimetric approaches.

(a) Medical Internal Radiation Dose (MIRD) algorithm based on Snyder formula [15], which supposes a mono-exponential intra-thyroid radioiodine kinetics (symbols as before)

$$A(MBq) = 5,829 \cdot \frac{D_T \cdot m_0}{U_{max} \cdot T_{1/2eff}}. \quad (2)$$

(b) Simplified Marinelli–Quimby algorithm (MQ), based on the previous one, with a basic intra-thyroid radioiodine kinetics. U is approximated by a single 24th h radioiodine uptake measurement (U_{24}), and a standardized effective half-life (132 h) is considered [9]. Both Spearman and Mann–Whitney tests were used when appropriate for statistical analysis. The Life-Table method [16, 17] was used to estimate the expected prevalence of hypothyroidism. This method allows the calculation of a cumulative incidence of hypothyroidism at various time intervals, among cured patients, taking into account the variability in the length of follow-up period.

Results

After a follow-up of 6–120 months (median 60), 76 out of 93 patients (82 % of total, 23 male, 53 female) achieved hyperthyroidism cure, including both patients who reached normal thyroid function and those who developed hypothyroidism.

Among them, 59 patients achieved euthyroidism 1–6 months after treatment, while six patients were initially hyperthyroid and achieved euthyroidism later (8–24 months, respectively, one after 8 months; three after 12 months; one after 15 months and one after 24 months). In the subgroup who developed hypothyroidism, five patients started to display reduced thyroid function in the first 6 months after treatment, while seven patients became hypothyroid 10–48 months after treatment (two after 10 months, one after 12 months, one after 18 months, one after 28 months, one after 36 months, and one after 48 months). Seventeen patients (18 % of total, 5 male and 12 female) had persistent or recurrent disease.

In summary, we observed hypothyroidism (both early and late) in 12 patients out of 93 (13 %), euthyroidism in 64 patients (69 %), and persistent disease or relapse in 17 patients (18 %). The prevalence of hypothyroidism was greater in females than in males (11 females vs. 1 male).

Using the Life-Table method to estimate the cumulative incidence of hypothyroidism among cured patients, a 21 % incidence at 8.5 years after treatment was estimated (10 years maximum follow-up period, 79 ± 6 % SD average percentage of euthyroid patients, Table 1).

Despite the inhomogeneous distribution of radioiodine in the thyroid gland, ultrasonographic follow-up after approximately 1 month demonstrated a volume reduction significantly correlated ($R^2 = 0.77$, $P < 0.001$) to what predicted by TVR (see Fig. 1); no significant correlation between administered activity and volume reduction was found. We did not observe significant differences in median thyroid volume reduction at 1 month, since it resulted 12 % (7–51 %) in patients who achieved euthyroidism, 25 % (22–50 %) in patients become hypothyroid, and 21 % (19–41 %) in patients with persistent/relapsed disease. Similarly, no significant differences among the three groups of patients were observed 6 months (8–71 % in patients become euthyroid, 11–75 % in patients become hypothyroid, 11–70 % in patients still hyperthyroid) and 12 months following therapy (10–71 % in patients become euthyroid, 11–85 % in patients become hypothyroid, data on patients with persistent hyperthyroidism are not available, as they were given a further radioiodine treatment). The correlation between observed and expected thyroid volume was maintained at the long-term controls (data not shown).

The median activity to be administered, calculated with TVR method, was 526 MBq (156–600 MBq), lower than the activities that would have been obtained using other methods (median reductions: −13 % compared to fixed activity method, −38 % compared to MQ, and −15 % compared to MIRD), as shown in Fig. 2. In 25 patients, the

Table 1 Life-Table method evaluation of euthyroidism probability over time in cured patients

L_i	Year	n_i	w_i	d_i	n_i'	q_i	p_i	Eu_i (%)	Var Eu_i	SD Eu_i (%)	Hp_i (%)
L_0	0–0.5	76	0	5	76	0.066	0.934	100	0.0009	3	0
L_1	0.5–1.5	71	22	4	60	0.067	0.933	93	0.0018	4	7
L_2	1.5–3	45	11	2	39.5	0.051	0.949	87	0.0026	5	13
L_3	3.1–5	32	16	1	24	0.042	0.958	83	0.0036	6	17
L_4	5.1–7.5	15	8	0	11	0.000	1.000	79	0.0033	6	21
L_5	7.5–8.5	7	3	0	5.5	0.000	1.000	79	0.0033	6	21
L_6	>8.5	4	4	0	2	0.000	1.000	79	0.0033	6	21

See text for details

L_i = follow-up time interval, median value is taken as reference time; 8.5 year for the last interval (amplitude of each interval selected on the basis of patients' number), n_i = total number of patients with MTG in the time interval, w_i = patients lost to follow-up, d_i = patients become hypothyroid after therapy with ^{131}I-iodide, n_i' = total number of patients corrected for hypothyroidism risk, q_i = estimated probability of hypothyroidism, p_i = estimated probability of euthyroidism, Eu_i (%) = estimated percentage of euthyroidism at the beginning of the interval, Hp_i (%) = estimated percentage of hypothyroidism at the beginning of the interval, *Var* Eu_i = Variance of Eu_i, *SD* Eu_i = standard deviation of

Eu_i, $n_i' = n_i - ½\ w_i$, $q_i = d_i/n_i'$, $p_i = 1 - q_i$, $Eu_i = Eu_0 \bullet p_0 \bullet p_1 \bullet \ldots\ldots\ldots\ldots\bullet p_{i-1}$, $\mathrm{Var}(Eu_i) = (Eu_i)^2 \sum_{k=0}^{i-1} \frac{d_k}{n_k'(n_k' - d_k)}$

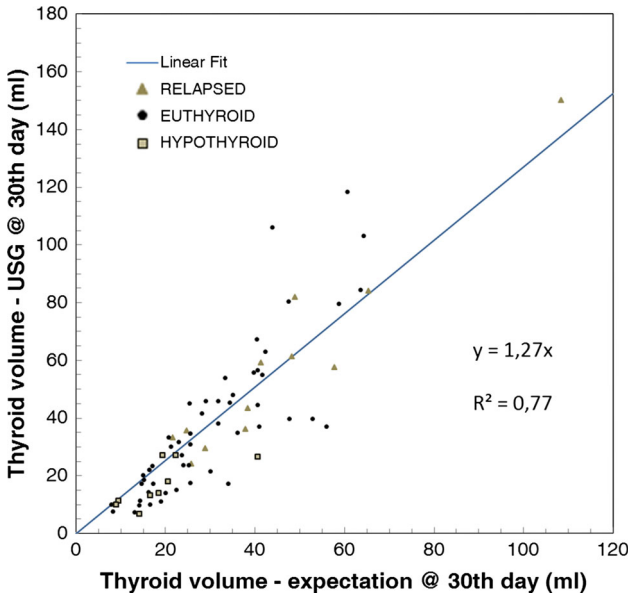

Fig. 1 Correlation between expected (model predicted) and observed (US measures) glandular volume, 30 days after ^{131}I-iodide therapy, in patients with MTG ($P < 0.001$, Spearman test)

activities calculated for administration with TVR method exceeded the activity threshold for outpatients established in Italy, so they were treated with a standard activity (600 ± 5 % MBq), thus receiving a dose lower than 250–300 Gy; among these, 19 patients were cured and only six relapsed, with no significant difference in received dose.

In our study, a widespread distribution of ^{131}I-iodide individual effective half-life is noticeable, although most of the patients' $T_{1/2eff}$ was in the range 150–200 h (6–8 days) (Fig. 3). An estimated effective half-life higher than the physical half-life of ^{131}I (192 h) is in fact a paradox, due to the fact that it results from a semi-log fitting based on two points only (2nd and 3rd in vivo measurements), in the hypothesis of a single-order kinetics and a maximum uptake around the 24th h (see also discussion).

Furthermore, we compared the outcome of patients with relapsed or persistent disease after radioiodine therapy with those who were cured after the first treatment, to assess whether there was any difference in terms of kinetics of radioiodine and risk factors for recurrence.

The median $T_{1/2eff}$ was 174 h (121–330 h) in relapsed patients and 175 h in cured patients (84–511 h), the median maximum uptake was 51.2 % (15.6–67.1 %) in relapsed patients and 37 % (9.4–68 %) in the cured ones. There were no significant differences in female/male ratio (relapsed 2.4/cured 2.3), in age (mean male age: relapsed 72 years/cured 71.8 years; mean female age: relapsed 69 years/cured 64.4 years), in smokers/ex-smokers prevalence (relapsed 63 %/cured 65 %) and in clinical presentation. The pre-treatment glandular volume calculated with the rule of the ellipsoid was significantly greater ($P < 0.0001$) in relapsed patients (median initial volume: 72.2 cc) than in patients cured after the first treatment (median initial volume: 32.0 cc) (Table 2).

The ^{131}I-iodide activity administered to relapsed patients (median 605 MBq; range 307–625 MBq) was significantly greater ($P = 0.01$) than the dose administered to cured patients (median 471 MBq; range 156–615 MBq); this is probably related to the gland volume differences described above. Of note, three patients, after 6–12 months of treatment, showed a slight positivity of TSH receptor antibodies (TRAb): two of them relapsed and one achieved euthyroidism later (18 months after treatment).

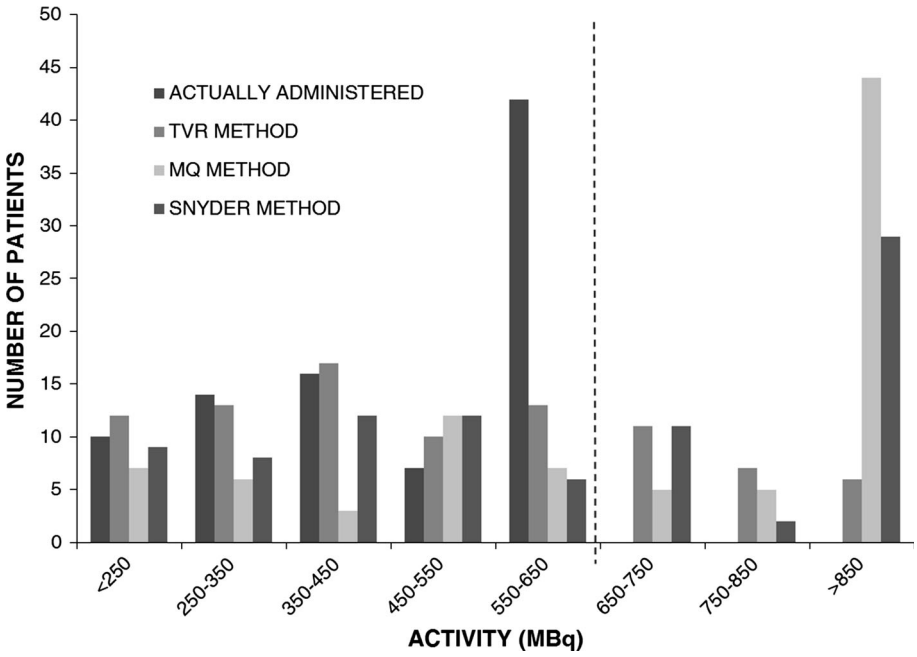

Fig. 2 Distribution of radioiodine activity prescription, according to different algorithms (MQ, MIRD, TVR) and actually administered. *Dotted line* indicates the 600 MBq hystogram class, corresponding to upper limit activity

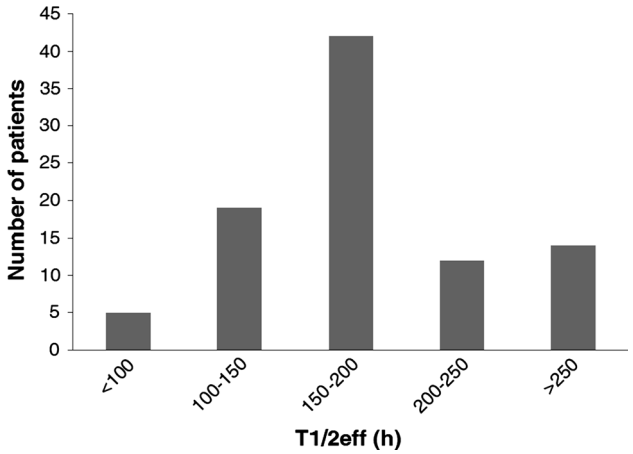

Fig. 3 Distribution of estimated ^{131}I-iodide effective half-life ($T_{1/2eff}$), calculated from patients measurements, using a single-order kinetics approximation (see text for further details)

Table 2 Relapsed/cured patients features after treatment with ^{131}I-iodide

	Relapsed	Cured
N Patients	17	76
F/M	2.4	2.3
All mean age	69	68
F mean age	69	64
M mean age	72	72
Smokers/no smokers	0.63	0.65
Sub hyperthyroidism	0.53	0.64
Severe hyperthyroidism	0.4	0.34
Median initial thyroid volume (cc)	72*	32*
Median greatest nodule volume (cc)	10.4	5.5
F greatest nodule vol (cc)	12.3*	5.3*
M greatest nodule vol (cc)	7.2	10.1

* $P < 0.05$ relapsed versus cured

Discussion

In this study, we applied a multiparametric dosimetric approach (TVR), developed by Traino in 2001 for the treatment of GD [8], in patients with MTG and evaluated the results in terms of therapeutic efficacy.

This dosimetric approach does not take into account only the intra-thyroid radioiodine kinetics (uptake and elimination phase) for the calculation of the activity to be administered, but it also includes the volume reduction during and after the treatment of 'target organ' (hyperfunctioning tissue), which significantly affects the absorbed dose.

The application of this approach would imply a homogeneous radioiodine distribution within the gland. While this assumption is acceptable for the single hyperfunctioning thyroid nodule, it is much less plausible for MTG considered in the present series, where areas with different radioiodine uptake coexist within the gland. Despite this theoretical limit, the correlation between thyroid volume reduction estimated by applying this method and thyroid volume reduction observed by US, was highly significant and a great majority of patients were cured. In addition, the results obtained show that the use of TVR allows to administer radioiodine activities slightly lower than the

"fixed" activities without any decrease of therapeutic effectiveness [18].

In patients (27) who showed only one or two hyperfunctioning nodules at thyroid scintigraphy and a near-total functional inhibition of surrounding tissue, we attempted to obtain a more accurate dosimetry, by taking into account only the nodular volume in the dose estimation calculation. Despite this, four patients relapsed, the effectiveness of the treatment being comparable to that observed for the entire series; to date, none of them developed hypothyroidism.

Half-life determination results crucial for activity estimation, and it is probably in most part responsible for the important differences observed among the aforementioned algorithms (namely, between MQ, that does not take it into account, and the others). Its determination implies at least one additional measuring session for the patient, and this is the main reason behind the use of simplified protocols.

As previously mentioned, the finding of effective half-life higher than the physical half-life of ^{131}I (192 h) is a paradox, due to the use of a single-order kinetics. This is obviously a simplification, that in some cases leads to inaccuracy. In fact, in some cases, a second-order kinetics should be more suitable to describe the actual behavior. This is also evident from the iodide biological uptake, which turns out to be still rising after 24 h. In these cases, a better fit should involve more than two points and a "second order effective half-life" should be considered. However, this is hardly feasible in the daily clinical practice, even if this concept has been applied in selected cases; the improvement of accuracy in the activity calculation did not substantially impact the planned therapy. Thus, in our opinion, a delayed last measurement in the range 96th–120th h minimizes, as a rule, the need for further measurements. In fact, the cumulated activity integral, hence the dose, depends mostly on the first-order exponential.

Our endpoint was the achievement of stable euthyroidism; this objective was attained in the majority of patients (69 %), at least during the observed period. Additional 12 patients (13 %, 11 female, 1 male) were cured from hyperthyroidism, but developed hypothyroidism during follow-up. The estimated perspective cumulative risk of hypothyroidism was performed by the Life-Table method, and showed a risk of 20.7 % at 8.5 years after treatment.

Altogether, these results, both in terms of effectiveness with a single administration (main endpoint) and in terms of minimizing the risk of hypothyroidism (secondary endpoint), are fair, when compared with those reported in literature [3–5] In one long-term follow-up study on patients treated with radioiodine, a prevalence of hypothyroidism of 3 % at 1 year and 64 % at 24 years was shown [19]. It is likely that the administration of lower activities with respect to other dosimetric methods can also offer advantages in terms of reduction of the long-term hypothyroidism incidence.

Twenty-five patients were treated with lower activity than predicted by the TVR method, as the calculated activities exceeded the maximum for outpatients: of them, 19 were cured and only six relapsed, with a similar percentage of cure as the whole set; thus, it is possible to achieve permanent clinical remission with radiation doses lower than what established/scheduled. As a matter of fact, on the basis of our results, it is possible to cure the majority of patients with MTG in an outpatients setting.

As mentioned above, the dosimetric protocol we applied in the present study was originally set up for GD treatment: both the proposers [9, 10] and our group [11] obtained good clinical results in terms of GD cure, that is, functional thyroid ablation and hypothyroidism. In a more recent study, we used the same protocol in single hyperfunctioning thyroid nodule [12]. In such condition, the clinical endpoints (hyperthyroidism cure, preservation of thyroid function) are the same as in the present study, and the results have been even more favorable in terms of hyperthyroidism cure; hypothyroidism incidence was apparently low, although a reliable prospective incidence estimate was not possible due to the low number of patients actually hypothyroid. This is not unexpected, since the model assumes a homogeneous radioiodine distribution within the functioning tissue and fits far better with single hyperfunctioning nodule than with MTG.

Furthermore, we comparatively evaluated two groups: cured and relapsed/resistent (after a single treatment) patients to analyze the possible causes of treatment resistance. We did not find any significant difference in age at the time of therapy, in female/male ratio (for both there is a higher female prevalence), smoking habits, or in presence of comorbidities.

Conversely, pre-treatment thyroid volume was significantly higher in relapsed patients (both genders) than in cured ones; in addition, we did not identify any significant difference in intra-thyroid radioiodine kinetics ($T_{1/2\text{eff}}$ and maximum uptake). As a consequence, the median-administered activity to relapsed patients was significantly higher due to a greater measured target volume, rather than to disadvantageous intra-thyroid radioiodine kinetic.

In order to improve the therapeutic effectiveness, it may be considered to increase the prescribed dose only for greater goiters (namely >70 cc, the median relapsed patients' volume), although some of them would require an inpatient treatment.

In addition, it should be noted that three patients (two relapsed and one with clinical remission after 18 months) developed positivity for TSH receptor antibodies that may have concurred to the poor response to therapy, as it is described in literature [20].

In any case, the individual radiosensitivity of thyroid gland is probably a critical variable affecting the clinical outcome of radioiodine therapy in single patient, although we are not able to quantify it, and may be responsible, at least in part, of the observed variability.

In conclusion, considering that the radioiodine therapy of hyperthyroidism is definitely the most widely employed nuclear medicine therapy, the results of this study show that an effective cure of MTG can be obtained with relatively low ^{131}I-iodide activities, and probably with a relatively low incidence of hypothyroidism, using the TVR algorithm. We think this approach should be preferred, when possible, to the administration of fixed ^{131}I-iodide amounts.

Acknowledgments This work was partially supported by a Grant from Fondazione CARIGE, Genoa, Italy.

References

1. C. Liu, J. Yang et al., United detection GNAS and TSHRS mutations in subclinical toxic multinodular goiter. Eur. Arch. Otorhinolaryngol. **267**, 281–287 (2010)
2. A. Carlè, I. Bulow Pedersen, N. Knudsen et al., Epidemiology of subtypes of hypertiroidism in Denmark. A population-based study. Eur. J. Endocrinol. **164**, 801–809 (2011)
3. C.T. Sawin, D.V. Becker, Radioiodine and the treatment of hyperthyroidism: the early history. Thyroid **7**, 163–176 (1997)
4. B. Tarantini, C. Ciuoli, G. Di Cairano, E. Guarino, P. Mazzucato, A. Montanaro, L. Burroni, A.G. Vattimo, F. Pacini, Effectiveness of radioiodine (131-I) as definitive therapy in patients with autoimmune and non-autoimmune hyperthyroidism. J. Endocrinol. Invest. **29**, 594–598 (2006)
5. P. Szumowski, F. Rogowski, S. Abdelrazek, A. Kociura-Sawicka, A. Sokolik-Ostasz, Iodine isotope (131I) therapy for toxic nodular goitre: treatment efficacy parameters. Nucl. Med. Rev. Cent. East Eur. **15**(1), 7–13 (2012)
6. L.D. Marinelli, E.H. Quimby, G.J. Hine, Dosage determination with radioactive isotopes; practical considerations in therapy and protection. Am. J Roentgenol. Radium Ther. **59**, 260–281 (1948)
7. M.G. Stabin, MIRDOSE: personal computer software for internal dose assessment in nuclear medicine. J. Nucl. Med. **37**, 538–546 (1996)
8. M.C. Gotthardt, A. Bauhofer, F. Berce, W.J.G. Oyen, J. Goecke, A. Pfestroff, A. Schlieck, F.H. Corstens, M. Béhé, T.M. Behr, What is the best pre-therapeutic dosimetry for succesful radioiodine therapy of multifocal autonomy? Nuklearmedizin **45**, 206–212 (2006)
9. A.C. Traino, F. Di Martino, M. Lazzeri, M.G. Stabin, Study of the correlation between administered activity and radiation committed dose to the thyroid in 131I therapy of Graves' disease. Radiat. Prot. Dosimetry. **95**, 117–124 (2001)
10. A.C. Traino, M. Grosso, G. Mariani, Possibility of limiting the un-justified irradiation in (131)I therapy of Graves' disease: a thyroid mass-reduction based method for the optimum activity calculation. Phys. Med. **26**, 71–79 (2010)
11. M. Schiavo, M.C. Bagnara, I. Calamia, I. Bossert, E. Ceresola, F. Massaro, M. Giusti, A. Pilot, G. Pesce, M. Caputo, M. Bagnasco, A study of the efficacy of radioiodine therapy with individualized dosimetry in Graves' disease: need to retarget the radiation committed dose to the thyroid. J. Endocrinol. Invest. **34**, 201–205 (2011)
12. M. Schiavo, M.C. Bagnara, E. Pomposelli, V. Altrinetti, I. Calamia, L. Camerieri, M. Giusti, G. Pesce, C. Reitano, M. Bagnasco, M. Caputo, Radioiodine therapy of hyperfunctioning thyorid nodules: usefulness of an implemented dose calculation algorithm allowing reduction of radioiodine amount. Q J Nucl. Med. Mol. Imaging. **57**, 301–307 (2013)
13. F. Massaro, L. Vera, M. Schiavo, C. Lagasio, M. Caputo, M. Bagnasco, F. Minuto, M. Giusti, Ultrasonography thyroid volume estimation in hyperthyroid patients treated with individual radioiodine dose. J. Endocrinolol. Invest. **30**, 318–322 (2007)
14. E.B. Sandell, I.M. Kolthoff, Micro determination of iodine by a catalytic method. Mikrochemica. Acta. **1**, 9–25 (1937)
15. W. Snyder, M. Ford, G. Warner, S. Watson, *"S" absorbed dose per unit cumulated activity for selected radionuclides and organs, MIRD Pamphlet No. 11* (Society of Nuclear Medicine, New York, 1975)
16. B. Fontana, G. Curti, A. Biggi, G. Fresco, The incidence of hypothyroidism after radioactive iodine (131I) therapy for autonomous hyperfunctioning thyroid nodule evaluated by means of life-table method. J. Nucl. Med. Allied Sci. **24**, 85–91 (1980)
17. S.J. Cutler, Edere F Maximum utilization of the life table method in analyzing survival. J. Chron. Dis **8**, 699 (1958)
18. S.K. Gupta, S. McGrath, K. Rogers, J. Attia, G. Lewis, S. Viswanathan, M. Saul, L. Allen, Fixed dose (555 MBq; 15 mCi) radioiodine for the treatment of hyperthyroidism: outcome and its predictors. Intern. Med. J. **40**, 854–857 (2010)
19. L.E. Holm, G. Lundell et al., Incidence of hypothyroidism occurring long after iodine-131 therapy for hyperthyroidism. J. Nucl. Med. **23**, 103–107 (1982)
20. B. Nygaard, J. Faber, A. Veje et al., Transition of nodular toxic goiter to autoimmune hyperthyroidism triggered by 131I therapy. Thyroid **9**, 477–481 (1999)