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Effectiveness of radioiodine (131-I) as definitive therapy in patients with autoimmune and non-autoimmune hyperthyroidism

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ABSTRACT. We evaluated the outcome of radioiodine (RAI) therapy in 100 consecutive patients treated in the period 2000-2001 for hyperthyroidism due to Graves' disease (GD), toxic adenoma (TA) and toxic multinodular goiter (TMG). Thyroid function was measured before and after therapy every 3-6 months up to 3 yr. Three years after therapy, 75% of TA patients were euthyroid, 18.7% were hypothyroid and 6.3% hyperthyroid. Of the TMG patients, 62.2% were euthyroid, 18.9% were hypothyroid and 18.9% hyperthyroid. In GD patients euthyroidism was achieved in 12.9% of the patients, hypothyroidism in 74.2% and hyperthyroidism persisted in 12.9%. Definitive hypothyroidism was significantly higher in GD ($p<0.0001$) than in TA and TMG patients. Overall, positive effect of RAI (definitive hypothyroidism or euthyroidism) was very high: 93.7% in TA, 81.1% in TMG and 87.1% in GD patients. Thyroid volume reduction was observed in all patients, but was higher in GD patients (mean reduction of 76%) and in TA patients (mean nodule reduction of 69%). In TMG, mean reduction was of 32%. The median activity of RAI received by the 86 cured patients was 555 MBq (15 mCi) compared to 407 Mbq (11 mCi) received by the 14 patients who remained hyperthyroid. No influence was found between outcome and clinical parameters at the moment of 131-I therapy. In conclusion, our results indicate that RAI therapy is highly effective and safe for the control of hyperthyroidism.
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INTRODUCTION

Radioiodine (RAI) therapy was introduced in clinical practice in 1964 (1) and it is increasingly used as treatment of choice for Graves' disease (GD) and nodular hyperthyroidism, unless surgery is mandatory. It is an easy, harmless and inexpensive procedure with no age restriction even in young adults. RAI treatment of hyperthyroidism has very high rate of definitive success, although controversies still exist regarding the dose of RAI to be administered. The aim of the present retrospective study was to assess the outcome of 100 hyperthyroid patients treated with RAI at our institute in 2000-2001.

Key-words: Hyperthyroidism, Graves' disease, toxic adenoma, multinodular goiter, radioiodine.

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MATERIALS AND METHODS

We retrospectively reviewed all patients treated in our endocrine unit for clinical or subclinical hyperthyroidism during 2000-2001. Excluding patients that had already been treated with RAI in other institutions or that had been submitted to partial thyroidectomy, we had 100 patients treated with RAI in our institution as the first treatment option. This group was made up of 26 males and 74 females. The clinical diagnosis as assessed by the results of thyroid ultrasound, thyroid scintigraphy and measurement of serum free T_4 (FT_4), free T_3 (FT_3), TSH and thyroid antibodies (anti-thyroglobulin, anti-thyroperoxidase and anti-TSH receptor antibodies) was toxic multinodular goiter (TMG) in 37 patients, Graves' disease (GD) in 31 and toxic adenoma (TA) in 32.

Patients

The epidemiological and clinical features of the patients are reported in Table 1. Mean (±SD) age was 62.9±11.6 yr, range 27-83 yr, with GD patients being significantly younger than TA and TMG patients ($p<0.0001$).

At presentation, 63 patients (63%) had overt hyperthyroidism (suppressed serum TSH values and elevated FT_3 and FT_4) and 37 patients (37%) had subclinical hyperthyroidism defined as serum TSH levels <0.1 μU/ml or suppressed with normal FT_3

Table 1 - *Epidemiological and clinical features of the patients.*

	TA	TMG	GD	*p*
Patients (no. 100)	32	37	31	ns
Female/male	18/14	28/9	28/3	0.008
Mean (±SD) age (yr)	68.5±7.0	66.2±8.1	53.3±13.1	<0.0001*
Hyperthyroidism: overt/subclinical	17/15	20/17	26/5	0.01*
AbTg and AbTPO+	1/32 (3.1%)	7/37 (18.9%)	21/31 (67.7%)	<0.0001*
TRAb+	0/32 (0%)	0/37 (0%)	22/31 (70.9%)	<0.0001*
Hypothyoroid patients at 36 months (%)	18.7	18.9	74.2	<0.0001*
Mean (±SD) 131-I (MBq) Range Median	448±84.5 333-592 444	480±80 370-592 481	533.5±54 370-592 555	0.36

*Statistical significance is related to Graves' group vs toxic adenoma/multinodular goiter groups. TA: toxic adenoma; TMG: toxic multimodular goiter; GD: Graves' disease; TRAb: anti TSH-receptor antibodies; AbTg: antithyroglobulin antibodies; AbTPO: antithyroperoxidase.

and FT_4. Overt hyperthyroidism was significantly more frequent in GD patients (p=0.01). In this group, 5 patients had subclinical hyperthyroidism. All of them had been previously treated with a course of anti-thyroid drugs and after discontinuation of the drugs developed subclinical hyperthyroidism.

The prevalence of anti-thyroglobulin (ATG) and/or anti-thyroperoxidase (ATPO) antibodies was significantly lower in the two groups of nodular hyperthyroidism than in GD patients (p<0.0001) and, when present, the antibody levels were lower than in GD patients. Anti TSH-receptor antibodies (TRAb) were present only in patients with GD (70.9%).

The mean (±SD) thyroid volume by ultrasound was 43.2±16.3 ml (range 23-68 ml) in TMG patients and 22±13 ml (range 5.3-50 ml) in GD patients; the mean (±SD) autonomous nodule volume was 14.4±8.6 ml (range 3-32 ml) in TA patients.

Patients with GD were treated with anti-thyroid drug (methimazole) before RAI treatment, which was withdrawn 4-5 days before RAI treatment. All GD patients were euthyroid at the moment of RAI administration. In case of TA and TMG, anti-thyroid drugs were withdrawn at least 20 days before RAI therapy. TA and TMG patients with subclinical hyperthyroidism were not pre-treated with antithyroid drugs, but GD patients with subclinical hyperthyroidism were normalized with anti-thyroid drugs.

Nine patients with Graves' disease had Graves' mild to severe ophthalmopathy; these patients were treated with steroids (per os or by bolus injection) to prevent exacerbation of Graves' ophthalmopathy, starting ten days after RAI administration.

Before treatment, all patients gave written informed consent to RAI therapy.

The activity of RAI administered to GD and TMG was similar, ranging 370-592 MBq (median 555 and 481 MBq, respectively). Patients with TA received slightly lower activities (median 444 MBq) since in these patients the aim was to destroy only the autonomous functioning nodule while preserving the normal thyroid tissue.

Patients were followed-up to 3 yr, at 3-6 month intervals. In case of persistent hyperthyroidism after RAI, patients were treated with anti-thyroid drugs. Patients developing subclinical or clinical hypothyroidism were started on L-T_4 replacement therapy.

Methods

Serum TSH and FT_4 were measured using a commercial chemiluminescent immunometric assay (Diagnostic Products Corp., Los Angeles, CA); serum FT_3 was measured using an immunometric assay (Biomerieux SA, 69280 Marcy l'Etoile, France); a chemiluminescent immunometric assay (Diagnostic Products Corp., Los Angeles, CA) was used for anti-thyroglobulin and anti-thyroperoxidase antibodies, while a radioimmuno-assay (Brahms Aktiengesellschaft, Neuendorfstrasse 25, D-16761 Hennigsdorf) was used for TRAb.

The statistical analysis was performed by Mann Whitney, Kruskal Wallis test and chi-square test, as appropriate, using the Graph Pad Prism version 3.0.

RESULTS

As shown in Figure 1, six months after treatment, 65.7% of TA patients (panel A) were euthyroid, 15.6% were still hyperthyroid and 18.7% hypothyroid. At 12 months, the percentage of euthyroid patients increased to 71.9% and that of persistent hyperthyroidism was reduced to 9.4%. The number of hypothyroid patients was unchanged. These results were confirmed at 18 and 24 months. At 3 yr after therapy, 75% of TA patients were euthyroid, 6.3% were still hyperthyroid and 18.7% hypothyroid. A similar trend was observed in TMG patients (panel B): at 6 months from RAI therapy, 51.4% were euthyroid, 32.4% were still hyperthyroid and 16.2% were hypothyroid. At 12 months, euthyroid patients increased to 56.8%, hyperthyroid patients were reduced to 27% and hypothyroid patients remained unchanged. At 24 months the euthyroid patients represented 59.5%, hyperthyroid patients 21.6% and hypothyroid patients 18.9%. At 36 months (last follow-up) the percentage of euthyroid patients in-

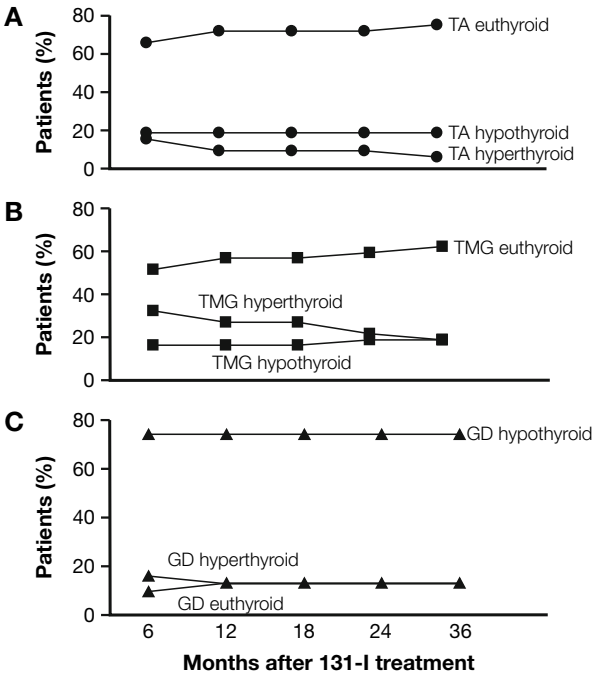

Fig. 1 - *Outcome of patients treated with radioiodine (RAI) expressed as percentage of patients becoming hypothyroid, euthyroid or remaining hyperthyroid at each period of observation. Panel A: toxic adenoma (TA) patients; panel B: toxic multinodular goiter (TMG) patients; panel C: Graves' disease (GD) patients.*

creased to 62.2%, of hyperthyroid patients it fell to 18.9% and that of hypothyroid patients was 18.9%.
At variance with the results obtained in TA and TMG, a high proportion of GD patients (panel C) was hypothyroid (74.2%) or euthyroid (9.7%) at 6 months after therapy and persistent hyperthyroidism was found in 16.1% that dropped to 12.9% in all subsequent observations up to 36 months. The rate of hypothyroid patients was significantly higher in GD patients ($p<0.0001$) than in TA and TMG patients.
Overall, the rate of positive effect of RAI (definitive hypothyroidism or euthyroidism) was very high in the three groups: 93.7% in TA, 81.1% in TMG and 87.1% in GD patients, accounting for a total of 86 patients cured.
The success of therapy was marginally, but significantly ($p=0.04$) influenced by the dose of RAI administered: the median activity received by the 86 cured patients was 555 Mbq (15 mCi) compared to 407 Mbq (11 mCi) received by the 14 patients who remained hyperthyroid. No influence was found between age, gender, serum TSH (in GD patients) at the moment of 131-I therapy and outcome of the disease.
At the end of follow-up (3 yr) (Fig. 2), the mean (±SD) thyroid volume was reduced from 43.2±16.3 to 30.4±18 ml (range 5-56 ml) in TMG patients with

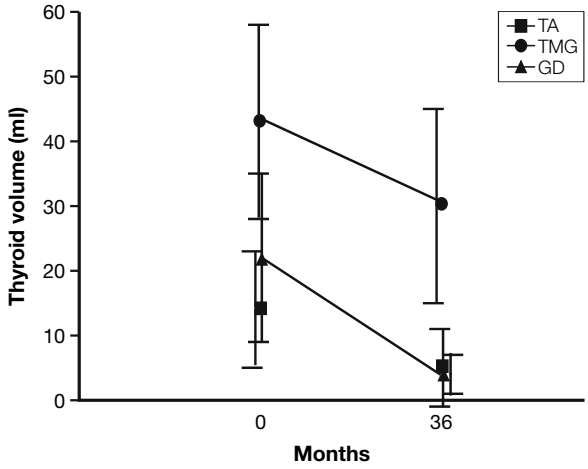

Fig. 2 - *Reduction of thyroid volume in toxic multinodular goiter (TMG) and Graves' disease (GD) patients, and of the functioning thyroid nodule in toxic adenoma (TA) patients at the end of follow-up.*

a mean (±SD) reduction of 32.8%±30.8% (range 3-78%) and from 22±13 to 4.2±3 ml (range 0.7-9 ml) in GD patients with a mean (±SD) reduction of 76±14.5% (range 44-92%); in TA patients the mean (±SD) volume of the autonomous nodule was reduced from 14.4±8.6 ml (range 3-32 ml) to 5.5±6 ml (range 0-18 ml) with a mean (±SD) percent reduction of 69±27% (range 18-100%). The reduction of thyroid volume was significantly higher in GD patients than in TMG and TA patients ($p<0.007$).
Side effects were rare and limited to transient nausea and scialoadenitis in a few patients. Post-treatment thyrotoxicosis was observed in about 10% of the patients mainly with GD and was always well controlled by β-blockers.

DISCUSSION

When treating hyperthyroidism with RAI, the main goal is to achieve permanent and rapid resolution of hyperthyroidism. A second objective should be to avoid the development of hypothyroidism at least in patients with nodular, not autoimmune, hyperthyroidism, both due to single toxic adenoma or toxic multinodular goiter. In case of GD, hypothyroidism is no longer considered an unwanted complication, but rather the desirable end point of treatment in view of the high rate of relapse observed in GD patients who remain euthyroid. In thyroid cancer patients associated with autoimmune disease, evidence has been provided (2) that persistence of residual thyroid tissue or metastases after initial treatment is sufficient to perpetuate the autoimmune process. By analogy,

one can hypothesize that also in GD patients, incomplete ablation of the thyroid gland may perpetuate the production of thyroid stimulating antibodies, and thus expose the patient to later recurrence of hyperthyroidism.

Our retrospective study shows that definitive cure is achieved in most hyperthyroid patients treated with RAI, regardless of the underlying condition causing hyperthyroidism.

As in other series (3), we were not able to find any correlation between the outcome of RAI treatment and clinical or biochemical features such as sex, age, serum TSH at the moment of treatment, medical pretreatment or serum anti-thyroid status. The only factor significantly affecting the outcome was the activity of RAI administered: when all patients were considered, higher RAI doses were associated with higher success rate. However, as reported by others (4), within the GD group no dose effect was observed.

RAI therapy was associated with a significant shrinkage of the thyroid gland in GD patients and or the nodular component in TMG and TA patients. TMG were those exhibiting the lower volume reduction (nearly 1/3 reduction); this is not surprising in view of the pathophisiology of the multinodular goiter, where nodular areas of intense 131-I uptake are associated with non-functioning nodular areas not responding to RAI therapy. Nevertheless, most of the time the goiter shrinkage was sufficient to eliminate local compressive symptoms. In TA patients the rate of hypothyroidism at 1 yr of follow-up was higher in our series compared to a recent study by Ceccarelli et al. (5) (18.7 *vs* 7.6%). However, in Ceccarelli 's series the rate of hypothyroidism at 2 and 5 yr was 12.6 and 28%, respectively, close to the 18.7% found by us at 3 yr of follow-up.

Another controversial issue of RAI treatment is the medical preparation prior to therapy. RAI failure has been reported in GD patients treated with anti-thyroid medication (either propylthiouracil or methimazole) for more than 4 months before therapy (6), while no effect of methimazole pre-treatment has been found by others (7, 8). Our patients were all treated with methimazole before RAI and were euthyroid at the moment of therapy, nevertheless they responded very well to RAI treatment and only a minority (12.9%) remained hyperthyroid. Our findings are consistent with the reports by Andrade et al. (7), Marcocci et al. (8) and Imseis et al. (9), who found propylthiouracil, but not methimazole, able to reduce the therapeutic efficacy of subsequent RAI administration.

At variance with Mariotti et al. (10), we did not observe an influence of positive anti-thyroid antibody status on the development of hypothyroidism in patients with toxic adenoma. However, very few patients in our series had positive anti-thyroid antibodies, thus reducing the statistical power of our finding. In addition, as reported in a recent review by Reiners and Schneider (11), we did not observe exacerbation of pre-existing thyroid autoimmunity in GD patients or the development of thyroid autoimmunity in non-autoimmune hyperthyroidism. Chiovato et al. (12) have shown that in GD high levels of thyroid-stimulating antibodies may be associated with a relative resistance to RAI therapy. With our method of detection, we can measure thyroid-receptor antibodies without distinction between thyroid-stimulating or thyroid-blocking antibodies; however we could not find any correlation between the antibody level and the RAI outcome.

In conclusion, RAI therapy is highly effective and safe for the permanent control of autoimmune or nodular hyperthyroidism. Fixed activities of 555 MBq (15 mCi) are sufficient to achieve the desirable goal of permanent hypothyroidism in most patients with GD and euthyroidism in nearly two thirds of those with nodular hyperthyroidism. For its simplicity and effectiveness, RAI therapy is increasingly used as the treatment of choice by several centers, particularly in USA. A comparison of the therapeutics strategies for the management of GD among ATA and ETA members had shown a predilection of RAI therapy by 69% of ATA members *vs* only 22% of ETA members (13).

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REFERENCES

1. Sawin CT, Becker DW. Radioiodine and the treatment of hyperthyroidism: the early history. Thyroid 1997, 7: 163-76.
2. Chiovato L, Latrofa F, Braverman LE, et al. Disappearance of humoral thyroid autoimmunity after complete removal of thyroid antigens. Ann Intern Med 2003, 139: 346-51.
3. Allahabadia A, Daykin J, Sheppard MC, Gough SCL, Franklyn JA. Radiodine treatment of herthyroidism-prognostic factors for outcome. J Clin Endocrinol Metab 2001, 86: 3611-7.
4. Leslie WD, Ward L, Salamon EA, Ludwig S, Rowe RC, Cowden EA. A randomized comparison of radioiodine doses in Graves' hyperthyroidism. J Clin Endocrinol Metab 2003, 83: 978-83.
5. Ceccarelli C, Bencivelli W, Vitti P, Grasso L, Pinchera A. Outcome of radioiodine-131 therapy in hyperfunctioning thyroid nodules: a 20 years' retrospective study. Clin Endocrinol (Oxf) 2005, 62: 331-5.
6. Alexander EK, Reed Larsen P. High dose 131I therapy for the treatment of hyperthyroidism caused by Graves' disease. J Clin Endocrinol Metab 2002, 87: 1073-7.

7. Andrade VA, Gross JL, Maia AL. The effect of methimazole pretreatment on the efficacy of radioactive iodine therapy in Graves' hyperthyroidism: one-year follow-up of a prospective, randomized study. J Clin Endocrinol Metab 2001, 86: 3488-93.
8. Marcocci C, Gianchecchi D, Masini I, et al. A reappraisal of the role of methimazole and others factors on the efficacy and outcome of radioiodine therapy of Graves' hyperthyroidism. J Endocrinol Invest 1990, 13: 513-20.
9. Imseis RE, Vanmiddlessworth L, Massie JD, Bush AJ, Vanmiddlessworth NR. Pretreatment with propylthiouracil but not methymazole reduces the therapeutic efficacy of iodine-131 in hyperthyroidism. J Clin Endocrinol Metab 1998, 83: 685-7.
10. Mariotti S, Martino E, Francescani M, et al. Serum thyroid autoantibodies as a risk factor for development of hypothyroidism after radioactive iodine therapy for single thyroid "hot" nodule. Acta Endocrinol (Copenh) 1986, 113: 500-7.
11. Reiners C, Schneider P. Radioiodine therapy of thyroid autonomy. Eur J Nucl Med 2002, 29 (Suppl 2): S471-8.
12. Chiovato L, Fiore E, Vitti P, et al. Outcome of thyroid function in Graves' patients treated with radioiodine: role of thyroid-stimulating and thyrotropin-blocking antibodies and of radioiodine-induced thyroid damage. J Clin Endocrinol Metab 1998, 83: 40-6.
13. Wartofsky L, Glinoer D, Solomon B, Lagasse R. Differences and similarities in the treatment of diffuse goiter in Europe and the United States. Exp Clin Endocrinol 1991, 97: 243-51.