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Greater Efficacy of Total Thyroidectomy versus Radioiodine Therapy on Hyperthyroidism and Thyroid-Stimulating Immunoglobulin Levels in Patients with Graves' Disease Previously Treated with Antithyroid Drugs

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Key Words
Hyperthyroidism · Graves' disease · Radioiodine therapy · Total thyroidectomy · Thyroid-stimulating immunoglobulin

Abstract
Aims: We compared the effects of total thyroidectomy (TTx) and radioiodine (RAI) administration on the course of thyroid hormones and thyroid-stimulating immunoglobulins (TSI) in patients with Graves' disease. ***Methods:*** We retrospectively studied 80 patients initially treated with antithyroid drugs and requiring either RAI (8.3 ± 1.7 mCi of ^{131}I; n = 40) or TTx (n = 40) as second-line therapy. ***Results:*** The TTx and RAI groups were not different, except for larger goiter, higher FT_3 and more frequent Graves' orbitopathy at diagnosis in the surgery group ($p < 0.05$). A persistent remission of hyperthyroidism was observed in 97% of operated patients versus 73% of the RAI patients at 3 years ($p < 0.01$). TTx was followed by a rapid and steady decrease in TSI during the first 9 months, while a surge of antibodies was observed during the first 6 months after RAI, followed by a slow decrease over the next 18 months. At the last visit, high TSI levels were still observed in 18 and 60% of patients in the surgery and RAI groups, respectively ($p < 0.001$). ***Conclusions:*** TTx is more efficient than RAI to induce a rapid and permanent correction of hyperthyroidism and TSI decrease in patients previously treated with antithyroid drugs.

Introduction

Graves' disease (GD) is a common autoimmune disorder mainly characterized by an abnormal production of antibodies binding to and activating TSH receptor, referred to as thyroid-stimulating immunoglobulins (TSI), thereby leading to the development of a goiter and hyperthyroidism. Treatment should aim at inducing a rapid and permanent remission of hyperthyroidism and a disappearance of TSI with minimal morbidity. Thyroid surgery and radioiodine (RAI) therapy are both used as second-line treatments, at least in Europe, in case of unsuccessful therapy with antithyroid drugs (ATD), disease relapse, or drug intolerance [1]. Surgery should consist of a near total thyroidectomy (TTx), which leads to a reduced risk of relapse, as compared with sub-TTx [2], but results in systematic hypothyroidism that will require

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lifelong L-thyroxine substitution. RAI is also effective on hyperthyroidism, less expensive and less traumatic than surgery, but often followed by delayed hypothyroidism and by a transient flare-up in TSI levels which is not observed under medical treatment or after surgery [3–5].

Another matter of concern is the course of Graves' orbitopathy (GO) which partly depends on the treatment chosen [4, 6–9], but also on other factors such as smoking [10], the degree of thyroid dysfunction [7] and the persistence of high TSI levels [8, 11, 12]. A recent systematic review clearly demonstrated an increased risk of new GO or worsening of preexisting GO in patients treated with RAI compared with those treated medically, while there was no significant difference between RAI and surgery (RR 1.6) [6].

There is no clear consensus yet regarding the best radical treatment of GD. Few studies have indeed compared the efficacy of surgery and RAI in terms of long-term cure of hyperthyroidism and remission of the autoimmune disease [5] and none has addressed the relative efficiency of TTx versus RAI as second-line treatment in these patients. We therefore performed this retrospective study in patients with GD previously treated with ATD, comparing the course of thyroid function tests and TSI levels after treatment with RAI or TTx.

Patients and Methods

Patients

The study included 80 patients with proven GD treated with RAI (n = 40) or TTx (n = 40) in our institution between 2000 and 2006. The following inclusion criteria were used: (a) the diagnosis of GD had been confirmed in all patients by the presence of overt hyperthyroidism, typical ultrasonographic and/or scintigraphic features, and positive TSI levels either at diagnosis or at any time during follow-up until radical treatment; (b) all patients had received ATD as first-line therapy, and (c) relevant clinical and biological parameters (TSH, free T_4 (FT_4), free T_3 (FT_3), anti-thyroglobulin antibodies (Tg Ab), anti-thyroperoxidase antibodies (TPO Ab) and TSI) had to be available before and at least 12 months after radical treatment. We intentionally excluded hyperthyroid patients without any evidence of TSH receptor autoimmunity during the course of the disease and patients with positive TSI and a toxic multinodular goiter, to avoid any selection bias related to baseline heterogeneity in the disease severity or pathogeny.

RAI and TTx had been proposed to patients relapsing after a well-conducted 18-month treatment with methimazole or propylthiouracil (PTU) (n = 48 patients; 60%), to patients with persisting or relapsing hyperthyroidism under ATD (n = 10; 12.5%), to patients with unacceptable side effects of ATD (urticaria/vasculitis in 7 and agranulocytosis in 1; 10%) or to patients with severe GD complications (n = 16; 17.5%). The choice of treatment was not randomized but mainly depended upon discussion and informed agreement between the patient and the referring physician.

Forty patients received a fixed low-to-medium dose of ^{131}I which was roughly individualized only on the basis of thyroid gland size estimation (which was <30 ml in most of these patients). The mean activity (±SD) was 8.3 ± 1.7 mCi (range 5–12) and activities of 8–10 mCi were used in the vast majority of patients (32/40), which are well in the range of doses used in other studies [13–15]. They were compared to a surgical group of 40 patients blindly selected in a chronological order from a cohort of patients who had undergone a TTx (i.e. a total macroscopic resection of the thyroid gland) by a single surgeon in our institution during the same period and who fulfilled the same inclusion criteria. These TTx patients received a saturated potassium iodide solution during 10 days before surgery and immediate hormonal substitution after surgery.

Out of the 46 patients relapsing after a first course of medical therapy, 36 were treated again with ATD at tapered doses for a period of 1–12 months before undergoing their respective radical treatment. In those receiving RAI, the drug was stopped 1 week before ^{131}I administration and if necessary restored at low doses 1 week after treatment until remission of hyperthyroidism.

Clinical and Biochemical Evaluation

Patients were seen at the outpatient clinic 6–8 weeks after radical treatment, then every 3–4 months for 1 year (n = 80), every 6 months for the second year (n = 72) and at 3 years posttreatment (n = 59). A clinical and biochemical evaluation was performed at each visit. The severity of GO could not be precisely evaluated due to the lack of precise information on the clinical activity score in many patients and to the non-standardized evaluation by different ophthalmologists. Therefore, we only assessed the presence or absence of active GO at diagnosis, before radical treatment and at last evaluation on the basis of detailed ophthalmologist reports.

Thyroid volume at diagnosis was measured by ultrasonography and calculated using the simplified elliptical formulae: length × width × thickness × 0.52 [16]. TSH, FT_4 and FT_3 concentrations were measured by an automated Elecsys® assay (Roche) and Tg Ab and TPO Ab were assayed by the automated Centaur® assay (Bayer Siemens). TSI concentrations were determined using a competitive radioreceptor assay measuring the ability of patient's serum to inhibit the binding of labeled TSH to human recombinant TSH receptors, hence measuring both stimulating and inhibiting TSH receptor antibodies (SELco® TRAb; Medipan GmbH, Dahlewitz/Berlin, Germany). This assay had a functional sensitivity of 2.5 U/l and intra- and interassay coefficients of variation of 6% at a concentration of 10 U/l. Normal range values for TSH (0.2–3.5 mU/l), FT_4 (10.3–25.7 pmol/l), FT_3 (3.4–6.2 pmol/l), Tg Ab (<100 kU/l), TPO Ab (<100 kU/l) and TSI (<12.5 U/l) were those used at the time of the evaluation.

Statistics

Statistical analyses were performed using PASW Statistics 18 (SPSS Inc., Chicago, Ill., USA). For comparisons of groups, we used non-parametric tests (Mann-Whitney, depending on the number of strata) and χ^2 test (comparison of percentages). The level of significance was set at 5%. To analyze the probability of thyroid function and TSI normalization during follow-up, Kaplan-Meier survival curves were calculated using as duration the

time interval between TTx or RAI and the first visit at which the variables were normalized, the last available visit or the time at which another treatment of GD had been required. Comparison between treatment groups was made using the log-rank test. The level of statistical significance was set at $p < 0.05$.

Results

General Characteristics of the Patients at Diagnosis and before Radical Treatment

At diagnosis, mean age and sex ratio were similar in both RAI and TTx groups. Thyroid hormone and antibody levels were also similar between the two treatment groups except for FT_3, which was twofold higher in the surgery group ($p = 0.01$) (table 1). Patients in the TTx group also had a larger goiter volume compared to the RAI group ($p < 0.05$), and a clear correlation was observed between thyroid volume and FT_3 levels ($r = 0.679$; $p < 0.01$). Out of 80 patients, 22 (28%) had GO at diagnosis, 15 of them (68%) being later directed towards TTx and 7 (32%) to RAI treatment ($p < 0.05$).

All patients had a first ATD therapy and most of them received methimazole. Only 12 patients (15%) had been treated with PTU and they were more often operated (9/11) than treated with RAI (2/11) ($p < 0.05$). The median time interval elapsed between diagnosis and radical treatment was 3.0 years (extreme values: 0.5–17) in the surgery group and 3.5 years (0.5–19) in the RAI group (table 2). At the time of definitive treatment, Tg Ab and TPO Ab levels remained positive in most patients without a significant difference between the two groups (table 2). Mean TSI concentrations were also not different between the surgery and RAI groups.

Table 1. Characteristics of the patients at the time of diagnosis

	TTx (n = 40)	RAI (n = 40)	p value
Age, years	38.8 ± 14.1	43.2 ± 16.0	NS
Female/male	35/5	33/7	NS
Goiter volume, ml	24.3 (7.8–181.0)	18.7 (6.0–50.2)	<0.05
FT_4, pmol/l	43.8 (10.3–191.8)	43.1 (16.2–89.4)	NS
FT_3, pmol/l	30.6 (10.3–40.3)	17.1 (5.4–44.2)	<0.05
Tg Ab, kU/l	100 (37–4,589)	67 (0–248)	NS
TPO Ab, kU/l	904 (50–19,780)	764 (0–19,100)	NS
TSI, U/l[a]	24.4 (2.0–200.0)	39.0 (9.6–255.0)	NS
No positive TSI[a]	17/22	20/21	NS
No GO	15/40	7/40	<0.05

Values are expressed as mean ± SD or as median (range). TTx = Near total thyroidectomy group; RAI = radioiodine group; GO = Graves' ophthalmopathy; NS = no significant difference between the TTx and RAI groups.

[a] TSI at diagnosis (i.e. before any treatment) were not available in 18 and 19 patients in the TTx and RAI groups, respectively.

Outcome of Thyroid Function Tests and TSI after TTX versus RAI

All TTx patients were in remission of their hyperthyroidism at the first visit 3 months after surgery. This remission was still present at the last available visit in 39/40 patients (97%). Hyperthyroidism relapsed in only 1 female patient 36 months after surgery. At that time she also exhibited high TSI levels and a significant thyroid remnant on both ultrasonographic and scintigraphic images and underwent repeat surgery. In contrast, only 29/40 patients treated with RAI (73%, $p < 0.01$ vs. TTx) had a permanent correction of hyperthyroidism with a median remission time of 3.8 (1.0–24.0) months, and the probability that a patient normalized hyperthyroidism was 30% at 3 months, 64% at 6 months, 77% at 1 year, and 85% at 2 and 3 years (fig. 1). The 11 remaining patients had persistence (n = 5) or relapse of their hyperthyroidism after a median time interval of 12 months (4–32) (n = 6), accompanied by a surge of TSI levels. Four of them benefited from thyroid surgery and 7 had a second dose of RAI to control hyperthyroidism. ATD treatment had to be restored again in 9 out of these 11 RAI patients to achieve euthyroidism before additional definitive treatment.

The course of TSI levels was analyzed over a total period of 36 months after radical treatment (fig. 2, 3). In the TTx group, a rapid and constant decrease of TSI levels was observed over the first 9 months. Median TSI level was 20.6 U/l (2.0–237.0) before surgery and was normalized to 2.6 U/l (2.0–11.0) after 9 months. In the RAI group, we observed a marked rise of TSI levels over the first 6 months. Median TSI levels were 15.6 U/l (2.0–200.0) before treatment and increased to 55.4 U/l (2.2–200.0) after 6 months, before decreasing slowly thereafter. A significant difference in TSI concentrations was observed between the two groups at 3, 6, 9 and 12 months but no longer at 24 and 36 months (fig. 2). The probability that a patient in the TTx group had normalized TSI levels was 75, 75 and 85% at 12, 24 and 36 months, respectively, while in the RAI group, the same probabilities were lower at 20, 50 and 65%, respectively ($p < 0.001$; fig. 3). At the last available visit, 60% of the patients in the RAI group still had positive TSI, as opposed to only 18% in the

Table 2. Characteristics of the patients at the time of radical treatment

	TTx	n	RAI	n	p
Time, years[a]	3.00 (0.50–17.0)		3.50 (0.50–19.0)		NS
Methimazole/PTU	31/9		37/3		<0.05
TSH, mU/l	0.07 (0.00–16.10)	40	0.01 (0.00–13.31)	40	NS
FT_4, pmol/l	16.7 (3.9–41.2)	26	16.7 (3.9–52.8)	39	NS
FT_3, pmol/l	5.2 (2.6–14.8)	17	5.2 (1.8–10.6)	27	NS
Tg Ab, kU/l	100 (2–8,080)	36	78 (50–1,175)	36	NS
TPO Ab, kU/l	589 (50–13,700)	39	305 (11–100,000)	39	NS
TSI, U/l	20.6 (2.0–237.0)	40	15.6 (2.0–200.0)	39	NS
No positive TSI	29/40 (73%)		23/39 (59%)		NS
No GO	13/40		4/40		<0.02

Values are expressed as median (range). n = Number of patients for whom parameters were available; TTx = total thyroidectomy group; RAI = radioiodine group; GO = Graves' ophthalmopathy; NS = no significant difference between the TTx and RAI groups.
[a] Time elapsed between diagnosis and radical treatment.

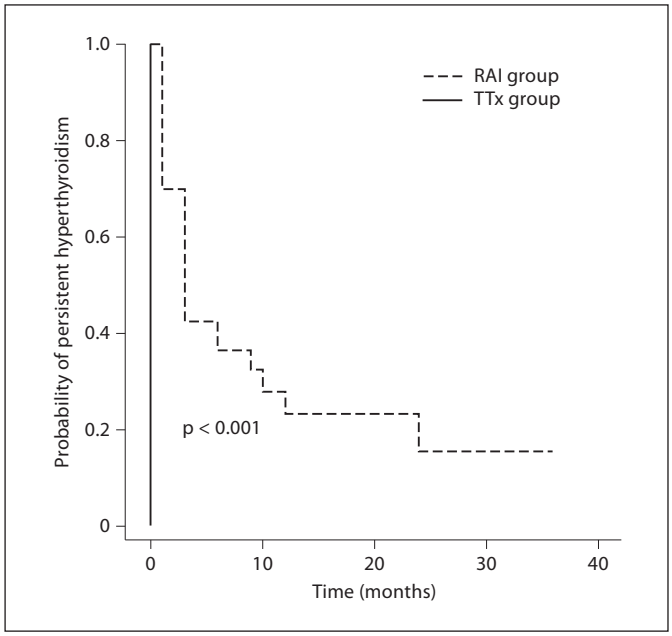

Fig. 1. Probability of persistent hyperthyroidism over the 36 months following TTx (n = 40) or RAI administration (n = 40). All TTX patients had immediate remission after surgery. In the RAI group, the probability that a patient normalized hyperthyroidism was 30% at 3 months, 64% at 6 months, 77% at 1 year, and 85% at 2 and 3 years.

surgery group ($p < 0.001$). The median time interval until TSI normalization was also significantly shorter in patients in the TTx group (3 months) as compared to RAI (18 months; $p < 0.001$).

Prevalence of Graves' Orbitopathy

At the time of diagnosis, 22 patients had active GO, which was still present in 17 at the time of radical treatment. Among them, 13 underwent TTx (33% of the surgery group) and 4 received RAI therapy (10% of the RAI group; table 2), with a prophylactic glucocorticoid treatment in 3 of them. At the last follow-up, GO was present in 4 patients in the TTx group (10% of total) and in 7 in the RAI group (18%, NS vs. TTX group). New GO appeared in 5 RAI patients after a median time interval of 10 months (1–36), while in the surgery group only 1 new case was noted in the patient who had also a relapse of GD 36 months after surgery.

Side Effects of Treatments

In the RAI group, 27 out of 40 patients (68%) developed permanent hypothyroidism after a median time delay of 3 months (extreme values: 1–36). Of the remaining 13 patients, 11 had persistent hyperthyroidism and only 2 patients recovered a normal thyroid function over time. Two patients developed severe side effects after RAI. One patient had an acute hyperthyroid crisis 3 months after RAI administration requiring surgery and another patient developed permanently high TSI concentrations inducing fetal and neonatal hyperthyroidism when the patient became pregnant 48 months after RAI administration. In the surgery group, all patients were by definition hypothyroid and 11 patients had transient postoperative hypocalcaemia but there was no case of permanent hypoparathyroidism or laryngeal nerve palsy.

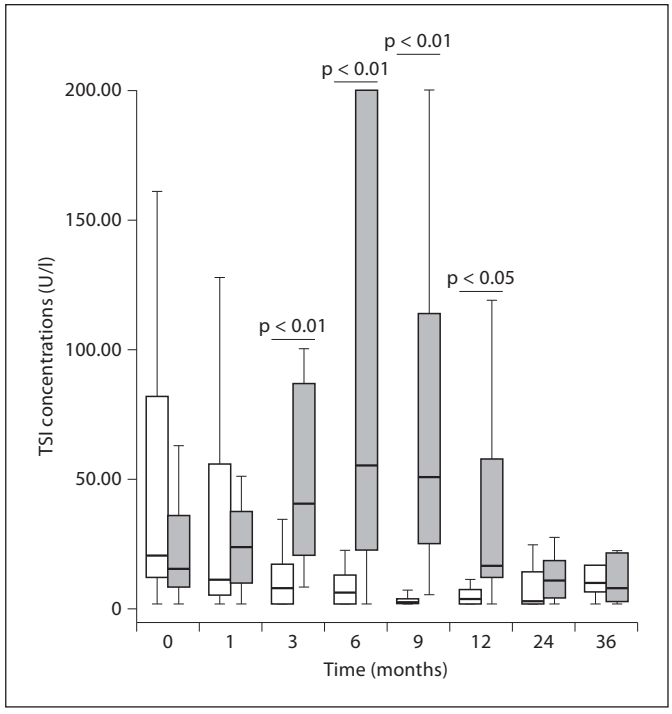

Fig. 2. Box-and-whisker plots showing median TSI concentrations (P25, P75 and extreme values) at 0, 1, 3, 6, 9, 12, 24 and 36 months after TTx (open boxes) or RAI treatment (shaded boxes). Significant differences between the two treatment groups are indicated in the graph.

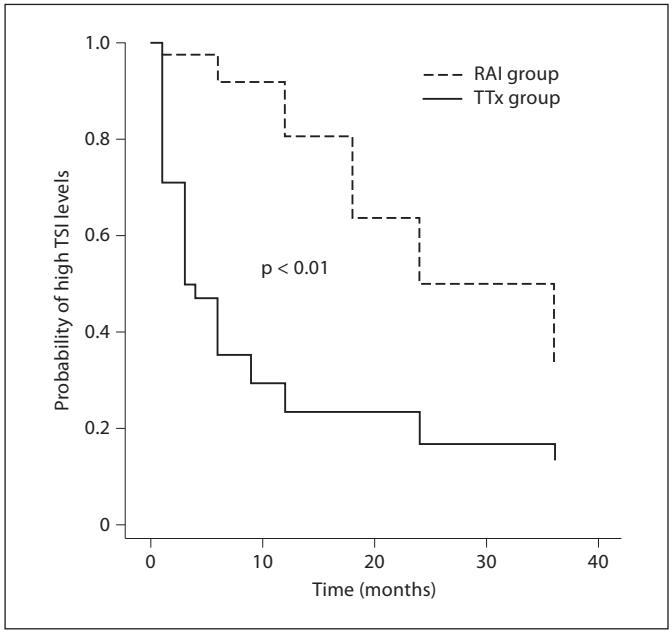

Fig. 3. Probability of persistent high TSI concentrations (>12.5 U/l) over the 36 months following TTx (n = 40) or RAI administration (n = 40).

Discussion

In this retrospective study on 80 patients treated for GD in our institution, we demonstrate that a near TTx is superior to RAI administration as second-line therapy to induce a permanent remission of hyperthyroidism as well as a rapid and sustained decrease of TSI concentrations in patients previously treated with antithyroid dugs. A trend to a lesser prevalence of Graves' ophthalmopathy after surgery was also observed, although the difference between both treatment arms was not statistically significant.

In about two-thirds of the cases radical treatment was proposed because of disease relapse after adequate ATD treatment, a finding similar to that reported by another study [17]. A larger number of operated patients had received PTU compared to those subsequently treated with RAI. Two factors could account for this observation. Most patients treated with PTU had shown side effects under previous methimazole treatment and were then preferentially directed towards surgery to ensure rapid and permanent remission of their hyperthyroidism. Alternatively, physicians might have preferred surgery as second-line treatment, being aware of the lesser efficiency of RAI in patients pretreated with PTU [18].

A permanent correction of hyperthyroidism was observed in 97% of patients after surgery, as compared to only 73% in the RAI group. The median time interval to correction of hyperthyroidism was also longer in the RAI group. Thus, in case of severe side effects encountered with ATD, surgery should be considered as the treatment of choice, as it will avoid the need for another ATD treatment in virtually all patients. It should be noted that a fixed, low-to-medium ^{131}I activity (mainly 8–10 mCi) was administered in our patients, roughly individualized on the basis of thyroid gland size estimation, in an attempt to preserve some thyroid function over time. More recently, higher doses of ^{131}I (10–15 mCi) have been advocated in GD to control hyperthyroidism by rendering the patient hypothyroid [19]. Thus, the lower doses of RAI used in this study might have contributed to a lower remission rate seen with RAI and perhaps to a different time course of TSI. However, significant failure rates (14–26%) are still observed when RAI is used at high doses to treat patients with GD [13–15] and in one study no advantage was found to use either a higher ^{131}I dose or an individualized regimen based on elaborate dosimetry [15].

The course of TSI concentrations was also markedly different between the two treatment groups during the first 12 months following radical treatment. In the sur-

gery group, there was a rapid and steady decrease of TSI levels, which were normalized after a time interval of 3 months in more than 50% of the patients. In the RAI group, there was an initial increase of TSI levels over the first 6 months, followed by a slow decrease with a long median time interval to normalization of 18 months. It is known that radioactive iodine administration can induce a temporary surge in all types of thyroid autoantibodies, probably due to a release of thyroid antigens following irradiation-induced follicular damage [5, 20, 21]. To the best of our knowledge, no study has yet looked at a possible influence of the RAI dose on the subsequent course of TSI concentrations.

Few studies have focused until now on the comparative time course of antibodies after the different treatment options for GD. Laurberg et al. [5] reported follow-up of TSI levels over 5 years in patients randomized to receive ATD, RAI or sub-TTx as first-line treatment. They showed a similar evolution of antibody levels as observed in our study, with both surgery and ATD inducing rapid decreases of TSI concentrations, in contrast with a marked initial increase observed after RAI administration. The median time interval at which TSI values peaked after RAI was however slightly shorter in their study (3 months), compared to 6 months in ours, suggesting that our patients might have benefited from a persistent immunosuppressive effect of previous ATD treatment, as reported previously [22, 23]. Laurberg et al. [5] also reported a median time interval of TSI normalization after surgery which was much longer than in our study. This difference could also be explained by persisting immunosuppressive effects of prior ATD treatment in our patients or by a more complete ablation of the thyroid gland practiced in our institution compared to a sub-TTx in the Danish study. A recent systematic review clearly highlighted the better efficacy of a near total versus sub-TTx for disease remission [2].

Surgery was obviously preferred when active GO was present either at diagnosis or at the time of radical treatment. We could also observe a less frequent persistence of active GO after TTx than after RAI, as reported by other studies [7, 8, 24]. However, the difference between both groups did not remain significant, likely because our study was not designed and powered enough to specifically address this question. It is now well established that worsening of GO may occur after RAI administration [6–9], but there is no clear consensus about the need for prophylactic use of glucocorticoids when RAI has to be given to patients with preexisting GO [25, 26]. Some advocate steroid administration only in the presence of risk factors such as smoking, high TSI levels, severe preexisting GO or high levels of FT_3 before treatment [8, 24, 27]. Other authors have also reported that persistently high TSI levels increase the risk of relapse or worsening of eye disease [8, 28]. Of note, the only patient with a relapse of hyperthyroidism 3 years after TTx had at the same time a surge of TSI together with the observation of a significant thyroid remnant at imaging.

Our study has limitations. First, the number of patients in each group is low and possible small differences in the baseline characteristics or in the clinical outcome between the two treatment groups might have been masked. Also, this was a retrospective analysis of patients who were not randomized to each treatment arm and several parameters such as goiter volume, FT_3 levels and prevalence of active GO were different between the TTx and RAI groups at diagnosis. However, other important characteristics such as age or gender were similar in both subgroups and no biological parameter (thyroid hormones or TSI) differed between the two groups at the time of radical treatment. Thus, we believe that our main conclusions remain valid because the differences observed between the two groups after radical treatment were impressive and largely outweighing potential small inclusion bias. Moreover, such bias would have clearly disadvantaged the surgery group as patients with a more active disease were preferentially oriented to surgery.

In conclusion, this study shows that a TTx is more efficient than low-to-medium doses of RAI therapy to induce rapid and permanent correction of hyperthyroidism and decrease in TSI levels. While the use of RAI remains indicated in GD, particularly in old patients with comorbidities and no or low-active GO, we suggest that surgery should be nowadays the treatment of choice in cases with a high disease immune activity as reflected by TSI levels, in patients at high risk for persistent or new severe ophthalmopathy, and in all cases where a rapid and permanent remission of hyperthyroidism is needed.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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