Percutaneous Ethanol Injection plus Radioiodine Versus Radioiodine Alone in the Treatment of Large Toxic Thyroid Nodules

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Therapeutic options for toxic thyroid nodules (TTNs) are surgery, radioiodine (RAI), and percutaneous ethanol injection (PEI). Surgery is generally considered for TTNs larger than 4 cm. However, some patients may be at high surgical risk. The purpose of the study was to evaluate the efficacy of 2 nonsurgical modalities for these TTNs. **Methods:** Twenty-two patients with TTNs larger than 4 cm were randomly assigned to 2 different treatments: to 11 (subgroup A), RAI was administered at a dose of 12,580 kBq/mL of nodular volume (NV) and was corrected for 100% 24-h ^{131}I uptake (RAIU); to 11 (subgroup B), 2–4 PEI sessions (ethanol injected = 30% NV) preceded 2 mo of 24-h RAIU and RAI dosing. Inclusion criteria were clinical and biochemical hyperthyroidism; a single palpable, hot nodule at ^{99m}Tc scintigraphy; and high surgical risk or refusal to have surgery. Patients gave informed consent. Local symptoms were evaluated by a previously validated score (symptom score, or SYS). **Results:** Both treatments were well tolerated. Subgroup B showed a significant reduction of NV 2 mo after PEI: 33.6 ± 18.5 versus 60.8 ± 29.5 mL. Their 24-h RAIU was similar to that of subgroup A: 53.9 ± 13.9 versus 61.8% ± 11.0%. Consequently, the administered RAI dose was significantly lower for subgroup B (730 ± 245 MBq) than for subgroup A (1,048 ± 392 MBq). Twelve months after RAI, subgroup B had a higher NV reduction and a lower SYS than did subgroup A. In subgroup A, 1 patient was subclinically hyperthyroid, 2 showed a slight increase of thyroid-stimulating hormone, and 1 was clinically hypothyroid. In subgroup B, 1 patient had a slight increase of thyroid-stimulating hormone. **Conclusion:** We demonstrated that RAI, alone or with PEI, can be considered a valid alternative for TTNs larger than 4 cm when surgery is either refused or contraindicated. PEI plus RAI can be considered when marked shrinkage of a nodule is required or when reduction of the RAI dose can prevent hospitalization.

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Treatment modalities of toxic thyroid nodules (TTNs) include thyroidectomy, radioiodine (RAI) ablation, and percutaneous ethanol injection (PEI) (*1*).

The choice of an appropriate treatment for TTNs is not easy because unequivocal criteria for therapy selection have not yet been established (*1–3*), on account of the lack of long-term prospective randomized studies comparing different treatment modalities. However, a surgical approach for patients with TTNs larger than 3–5 cm is generally suggested (*1–4*). In fact, the higher the RAI dose requested to ablate TTNs, the greater is the concern about radiation exposure to the surrounding normal thyroid tissue (*5*). In contrast, on the basis of a reduced effectiveness of PEI for TTNs greater than 30 mL (approximately 4 cm in diameter), most authors do not recommend its use for large nodules (*1,6–9*).

We previously published a retrospective study evaluating long-term outcome in 43 patients with TTNs (3–4 cm in diameter) treated with either RAI or PEI and suggesting both treatments to be applicable and useful (*10*). On the basis of this previous work (*10*), our group has further and more deeply investigated the issue of nonsurgical treatment of large TTNs.

In this prospective study, we had the opportunity of evaluating a set of patients with TTNs larger than 4 cm, who either were at high surgical risk or refused surgery. They were randomly assigned to 2 different nonsurgical treatment modalities: The first subgroup was treated with RAI alone, whereas in the second subgroup RAI administration was preceded by a limited number of PEI sessions to reduce nodular volume (NV).

The goals of the study were to compare the 2 treatment modalities in terms of clinical, hormonal, scintigraphic, and ultrasonographic outcome and to assess the impact of both on local symptomatology.

MATERIALS AND METHODS

Patients

From January 1997 to December 1999, 22 patients who were referred to our hospital for previously untreated TTNs were included in this study on the basis of a clinical picture of thyrotoxicosis; high levels of free triiodothyronine (FT_3) or free thyroxine (FT_4) and suppressed values of thyroid-stimulating hormone (TSH); normal circulating levels of antithyroglobulin and antithyroperoxidase autoantibodies; the finding of a single thyroid nodule at palpation, consistent with echographic evidence of a solid or mixed, well-delimited thyroid nodule either without other nodules or with nodules less than 1 cm; NVs, calculated at ultrasonography by an ellipsoid formula, comprising 33.6 mL (corresponding to a 4.0-cm-diameter spheric nodule) and 113 mL (corresponding to a 6.0-cm-diameter spheric nodule); a ^{99m}Tc scintigraphic picture of a hot nodule without visualization of the contralateral lobe; and a post-treatment follow-up of at least 12 mo.

Methods

Group A (RAI Treatment). Ultrasonography was performed with a real-time scanner (Toshiba, Tosbee, Japan), using a 7.5-MHz transducer and a specific water-bag pad to allow measurements up to 8 cm. NV was calculated at ultrasonography by the ellipsoid formula using a previously validated algorithm (*11*).

Evaluation of local symptoms because of pressure in the neck, dysphagia, or aesthetic complaints was performed, attributing to each symptom a previously validated arbitrary score (0 = absent; 1 = moderate; 2 = severe) and then calculating the sum of single scores (symptom score, or SYS) (*12*).

FT_4 (normal range, 9–24.5 pmol/L), FT_3 (normal range, 2.9–6.5 pmol/L), and TSH (normal range, 0.2–4 mU/L) were measured with commercial kits (Elecsys; Roche Diagnostics, Mannheim, Germany). Antithyroglobulin and antithyroperoxidase autoantibodies were measured with commercial kits (Immulite; Euro-DPC, Gwynedd, U.K.).

In accord with other authors (*2*,*5*,*13*), we administered RAI at a fixed dose of 12,580 kBq (340 μCi)/mL NV, corrected for 100% of 24-h radioiodine uptake (RAIU).

RAIU was calculated using a previously described method (*14*). A capsule containing 1.85 MBq of RAI was measured in an acrylic neck phantom by a probe (distance, 30 cm) and was promptly administered to the fasting patient. Room background activity was also measured. Neck and thigh (for circulating activity) uptake was measured at 2, 6, and 24 h after the administration; the probe, positioned at 30 cm, recorded the activity for 1 min. Neck counts, after background and circulating activity subtraction and physical decay correction, were divided for capsule activity and gave the percentage uptake in the thyroid.

Group B (PEI + RAI Treatment). Ultrasonographic picture, local symptoms, and hormonal status were evaluated as for group A patients. The total ethanol volume to be injected by PEI was calculated in 30% of NV to be subdivided into 2–4 different injections. PEI was accomplished under sonographic guidance by one of us as previously described (*10*–*12*); sterile 95% ethanol (Salf, Bergamo, Italy) was injected by a free disposable syringe through a 20-gauge needle at weekly intervals divided into 4- to 8-mL doses. The cystic portion of the nodule, when visible, was preliminarily aspirated by a 18-gauge needle fitted to a 20-mL disposable syringe, and then ethanol was injected into the cystic portion and the surrounding solid portion through the same needle. The effect of PEI was optimized through repositioning of the needle when permeation of the ethanol into the nodule was inhomogeneous.

Ultrasonography with NV reevaluation, RAIU, and RAI administration were performed 2 mo after the last PEI session.

In both groups, 7.5 mg of methimazole per day were administered for 2 mo after the first evaluation, with the administration stopped 15 d before RAIU evaluation and subsequent RAI administration. TSH values at the time of RAI administration were still suppressed in all patients.

Antithyroid drugs were not used after RAI administration. According to clinical conditions, 20–40 mg of propranolol were used 3 times a day for 1–2 mo after RAI dosing. In selected patients, when the use of β-blockers was contraindicated, 80 mg of verapamil were administered 3 times a day during the same period.

Follow-up modalities were identical in the 2 groups. At 6 and 12 mo after RAI administration, we performed a clinical evaluation, calculated SYS, and determined serum FT3, FT4, and TSH levels and NV using ultrasonography. A new scintigraphic picture was obtained for all patients 6 mo after treatment.

Data are expressed as mean ± SD, with range in parentheses; an unpaired Student *t* test was used to compare mean values.

RESULTS

Twenty-two subjects entered the study: 11 in subgroup A and 11 in subgroup B. Baseline data for the 2 subgroups are reported in Table 1.

Comparison Between Subgroups

At the 12th month, the percentage of NV reduction was lower ($P < 0.05$) in subgroup A than in subgroup B (Table 2).

Two months after PEI treatment, subgroup B showed a significant reduction of NV ($P < 0.05$) in comparison with basal NV: 33.6 ± 18.5 mL (15.8–78.1 mL) versus 60.8 ± 29.5 mL (33.5–112 mL). The 24-h RAIU percentage for subgroup B was not different from that for subgroup A: 53.9% ± 13.9% (42.0%–78.3%) versus 61.8% ± 11.0% (43.9%–77.5%). As a consequence, the administered RAI dose (calculated on the basis of NV and RAIU) was higher ($P < 0.05$) for subgroup A (1,048 ± 392 MBq [555–2,035 MBq]) than for subgroup B (730 ± 245 MBq [444–1,110 MBq]).

In both subgroups, treatment was well tolerated; in 15 of 37 sessions, PEI induced a mild, self-limiting pain, radiating to the neck or jaw.

In subgroup A at the 12th month, 10 of 11 patients were clinically euthyroid: 2 had suppressed TSH values and another 2 showed a slight increase of TSH (4.2 and 8.8 mU/L). Finally, in a 69-y-old man treated with 2,035 MBq of RAI for a large (103 mL) TTN, clinically overt hypothyroidism developed, requiring L-thyroxin therapy.

In subgroup B at the 12th month, 11 of 11 patients were clinically euthyroid: 1 showed a slight increase of TSH (4.2 mL).

TABLE 1
Some Characteristics of the 2 Subgroups Under Basal Conditions

Characteristic	Subgroup A: 11 subjects (RAI)	Subgroup B: 11 subjects (PEI + RAI)
Age (y)	61 ± 7 (48–69)	61 ± 8 (52–75)
Female/male	6/5	6/5
SYS	3.4 ± 0.9 (2–6)	3.5 ± 0.8 (2–6)
Nodule volume (mL)	53.1 ± 22.3 (34.9–103)	60.8 ± 29.5 (33.5–112)
FT_4 (pmol/L)	35.8 ± 12.4 (26.2–54.9)	33.4 ± 9.4 (18.3–48.6)
FT_3 (pmol/L)	14.2 ± 5.1 (8.7–23.5)	13.0 ± 4.3 (6.8–22.5)
TSH (mU/L)	0.01 ± 0.00 (0.00–0.01)	0.01 ± 0.00 (0.00–0.01)
RAIU (24-h %)	61.8 ± 11.0 (43.9–77.5)	53.9 ± 13.9 (42.0–78.3)
RAI dose (MBq)	1,048 ± 392 (555–2,035)	730 ± 245* (444–1,110)

*$P < 0.05$.

Data are given as mean ± SD, with range in parentheses. Normal ranges were 9–24.5 pmol/L for FT_4, 2.9–6.5 pmol/L for FT_3, and 0.2–4.0 mU/L for TSH. SYS includes pressure symptoms in neck, dysphagia, and aesthetic complaints.

None of the patients with subclinical hypothyroidism started L-thyroxin therapy.

At the 6-mo scintiscan, the persistence of an autonomous nodule with complete or partial suppression of the extranodular parenchyma was disclosed in 5 of 11 subjects in subgroup A and in 6 of 11 subjects in subgroup B.

Evaluation of Local Symptomatology

In both groups, SYS was significantly ($P < 0.01$) lowered at the 12th month as compared with basal values. Local symptomatology improvement was significantly ($P < 0.01$) worse in subgroup A than in subgroup B (Table 2).

DISCUSSION

In this study, we demonstrated that a nonsurgical approach may successfully be used in the treatment of large TTNs (between 4 and 6 cm) when surgery is refused or contraindicated. In fact, we showed that RAI treatment, alone or in combination with PEI, is able to cure hyperthyroidism, obtaining a remarkable shrinkage of the nodule with amelioration of local symptomatology, particularly when RAI treatment was associated with PEI.

TTNs are an infrequent cause of hyperthyroidism in North America, but in Europe they account for 9% of all thyrotoxicosis (*15*); furthermore, they are almost twice more common in iodine-deficient than in iodine-sufficient areas (*16*). The risk of developing thyrotoxicosis in autonomous functioning thyroid nodules is higher in older patients and in patients living in areas of relatively low iodine intake (*16*). Not infrequently, older patients with TTNs refuse surgery or are at high surgical risk because of atrial fibrillation and heart failure, so that nonsurgical procedures are mandatory.

In a recent retrospective study, efficacy was shown for both RAI and PEI in the treatment of TTNs between 3 and 4 cm, with both treatments obtaining remarkable shrinkage of the nodule (*10*); we concluded that RAI was more effective than PEI for treating hyperthyroidism, although with minimal sequelae of subclinical hypothyroidism. On the

TABLE 2
NV and Thyroid Function in the 2 Subgroups at the 12th Month

Characteristic	Subgroup A: 11 subjects (RAI)	Subgroup B: 11 subjects (PEI + RAI)
Nodule volume (mL)	21.9 ± 12.3 (8.1–41.5)	13.2 ± 12.9 (1.2–49.3)
Percentage of NV reduction	57.2 ± 16.3 (30.0–82.9)	79.3 ± 14.7* (56.0–96.5)
SYS	2.3 ± 0.6 (1–4)	1.4 ± 0.3* (0–4)
FT_4 (pmol/L)	12.7 ± 2.7 (8.6–18.3)	14.5 ± 1.9 (12.4–19.2)
FT_3 (pmol/L)	4.4 ± 0.9 (3.0–5.9)	4.2 ± 0.7 (3.1–5.7)
TSH (mU/L)	3.64 ± 5.52 (0.01–18.4)	1.9 ± 1.2 (0.2–4.2)

*$P < 0.01$ vs. group A.

Data are given as mean ± SD, with range in parentheses. Normal ranges were 9–24.5 pmol/L for FT_4, 2.9–6.5 pmol/L for FT_3, and 0.2–4 mU/L for TSH. SYS includes pressure symptoms in neck, dysphagia, and aesthetic complaints. Percentage of NV reduction is calculated as NV (mL) 12 mo after treatment/NV (mL) at baseline × 100.

basis of this previous work (*10*), our group has further and more deeply investigated the issue of nonsurgical treatment of TTNs larger than 4 cm by the combined approach of PEI plus RAI.

Recently, PEI has successfully been used to treat 12 patients with large (>30–108 mL; mean, 48.5 mL) TTNs, obtaining a stable euthyroidism during a 4- to 48-mo follow-up (*17*). The described procedure for PEI treatment was complex and time expensive. In fact, 1 or 2 cycles of PEI sessions (mean, 7) were performed and each session required multiple punctures in different portions of the nodule (*17*).

To the best of our knowledge, no study has been specifically aimed at evaluating the effectiveness of RAI in the treatment of TTNs larger than 4 cm, although other studies have reported successful RAI treatment in cohorts that included some large TTNs (*18–20*). We have demonstrated that RAI can be considered a valid alternative to surgery in these conditions.

During our previous experiences with the use PEI treatment for TTNs, we observed impressive shrinkage of the nodule soon after the first 2 or 3 sessions, particularly when "complex" (cystic–solid) nodules were treated. For this reason, in the combined approach of the present study, we chose to perform PEI before rather than after RAI. We scheduled the ethanol injection, in an amount of 30% of total NV, to occur 2 mo before RAI administration to obtain significant shrinkage of the nodule, possibly without reducing RAIU. Consequently, the administered dose was decreased. The results of the present study showed that, when RAI treatment was preceded by few sessions of PEI, the RAI dose to be administered was reduced and that greater NV shrinkage and amelioration of local symptomatology were nonetheless observed. The combined treatment was therefore at least as effective as treatment with RAI alone for hyperthyroidism.

In both groups, post-treatment scintigraphy showed the persistence of autonomous tissue with suppression of normal extranodular tissue in approximately 50% of patients, despite normal TSH values; these data confirm previous reports (*10*,*21*).

CONCLUSION

Our data, to be confirmed in further investigations with larger sample sizes and longer follow-ups, suggest that RAI can be used for TTNs larger than 4 cm when surgery is either refused or contraindicated; the combination of PEI plus RAI can be considered when marked shrinkage of the nodule is required to relieve local symptoms or when the reduction of the RAI dose can prevent hospitalization.

REFERENCES

1. Ferrari C, Reschini E, Paracchi A. Treatment of the autonomous thyroid nodule: a review. *Eur J Endocrinol.* 1996;135:383–390.
2. Corvilain B, Dumont JE, Vassart G. Toxic adenoma and toxic multinodular goiter. In: Baverman LE, Utiger RD, eds. *Werner and Ingbar's The Thyroid.* Philadelphia, PA: Lippincott Williams & Wilkins; 2000:564–572.
3. Mazzaferri EL. Management of a solitary thyroid nodule. *N Engl J Med.* 1993; 328:553–559.
4. Giuffrida D, Gharib H. Controversies in the management of cold, hot and occult thyroid nodules. *Am J Med.* 1995;99:642–650.
5. Gorman CA, Robertson JS. Radiation dose in the selection of ^{131}I or surgical treatment for toxic thyroid adenoma. *Ann Intern Med.* 1978;89:85–90.
6. Livraghi T, Paracchi A, Ferrari C, Reschini E, Macchi RM, Bonifacino A. Treatment of autonomous thyroid nodules with percutaneous ethanol injection: 4-year experience. *Radiology.* 1994;190:529–533.
7. Verde G, Papini E, Zingrillo M, et al. Long term effects of percutaneous ethanol injection in the treatment of autonomous functioning thyroid nodules. In: Abstract book of 10th International Congress of Endocrinology; June 12–15, 1996; San Francisco, CA. Page 380.
8. Lippi F, Ferrari C, Manetti L, et al. Treatment of solitary autonomous thyroid nodules by percutaneous ethanol injection: results of an Italian multicenter study. The Multicenter Study Group. *J Clin Endocrinol Metab.* 1996;81:3261–3264.
9. Monzani F, Caraccio N, Goletti O, et al. Five-year follow up of percutaneous injection for the treatment of hyperfunctioning thyroid nodules: a study of 117 patients. *Clin Endocrinol (Oxf).* 1997;46:9–15.
10. Zingrillo M, Torlontano M, Ghiggi MR, et al. Radioiodine and percutaneous ethanol injection in the treatment of large toxic thyroid nodule: a long-term study. *Thyroid.* 2000;10:985–989.
11. Bruneton JS. *Ultrasonography of the Neck.* Berlin, Germany: Springer-Verlag; 1987:6.
12. Zingrillo M, Collura D, Ghiggi MR, Nirchio V, Trischitta V. Treatment of large cold benign thyroid nodules not eligible for surgery with percutaneous ethanol injection. *J Clin Endocrinol Metab.* 1998;83:3905–3907.
13. Kaplan MM, Meier DA, Dworkin HJ. Treatment of hyperthyroidism with radioactive iodine. *Endocrinol Metab Clin North Am.* 1998;27:205–223.
14. O'Connor MK. *The Mayo Clinic Manual of Nuclear Medicine.* Philadelphia, PA: Churchill Livingston; 1996:222–226.
15. Reinwein D, Benker G, Konig MP, et al. The different types of hyperthyroidism in Europe: result of a prospective survey of 924 patients. *J Endocrinol Invest.* 1988;11:193–200.
16. Belfiore A, Sava L, Runello F, et al. Solitary autonomously functioning thyroid nodules and iodine deficiency. *J Clin Endocrinol Metab.* 1983;56:283–287.
17. Tarantino L, Giorgio A, Mariniello N, et al. Percutaneous ethanol injection of large autonomous hyperfunctioning thyroid nodules. *Radiology.* 2000;214:143–148.
18. Mariotti S, Martino E, Francesconi 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;113:500–507.
19. Huysmans DA, Corstens FH, Kloppenborg PW. Long-term follow-up in toxic solitary autonomous thyroid nodules treated with radioactive iodine. *J Nucl Med.* 1991;32:27–30.
20. Nygaard B, Hegedus L, Nielsen KG, Urliksen P, Hansen JM. Long-term effect of radioactive iodine on thyroid function and size in patients with solitary autonomously functioning toxic thyroid nodules. *Clin Endocrinol (Oxf).* 1999;50:197–202.
21. Nygaard B, Jarlov AE, Hegedus L, Schaadt B, Kristensen LO, Hansen JM. Long-term follow-up of thyroid scintigraphies after ^{131}I therapy of solitary autonomous thyroid nodules. *Thyroid.* 1994;4:167–171.