INVITED COMMENTARY

Role of Percutaneous Ethanol Injection in Management of Nodular Lesions of the Thyroid Gland

Percutaneous ethanol injection (PEI) has traditionally been used in the management of small hepatocellular carcinomas, metastatic liver lesions, primary or secondary parathyroid adenomas, and, sporadically, other benign endocrine neoplasms such as aldosterone-producing adrenocortical adenomas (*1–5*).

The use of PEI in the management of autonomous functioning thyroid nodules (AFTNs) was introduced into clinical practice by Livraghi et al. (*6*) in 1990. Since then, several other series (*7–14*) have shown that PEI represents an effective alternative to surgery and radioiodine for the treatment of AFTNs. Normal thyroid function is restored in nearly 100% of patients with subclinical hyperthyroidism and in 52%–80% of those with overt hyperthyroidism. In addition, significant nodule shrinkage (21%–88% of the pretreatment volume) is obtained in most cases, and follow-up data indicate a low rate of recurrence and of permanent hypothyroidism. Side effects are frequent but are generally mild, consisting of local pain, sometimes radiating to the upper neck, but on certain occasions the pain is so severe that the patient refuses further treatment. In sporadic cases, major complications, such as transient vocal cord palsy and venous thrombosis, have been reported.

The most important factor affecting the rate of success seems to be the skillfulness of the operator, together with an accurate selection of cases. The therapeutic effect is better in small nodules (3 cm or less), but large nodules have occasionally been treated with success (*15–18*). The article by Zingrillo et al. (*19*) in this issue of *The Journal of Nuclear Medicine* selectively studied the indication of PEI in large toxic thyroid nodules. The authors randomly assigned 22 patients with toxic thyroid adenomas larger than 4 cm to receive radioiodine therapy alone or radioiodine therapy preceded by 2–4 sessions of PEI. The results of the study showed that, after 12 mo of follow-up, all patients achieved adequate control of hyperthyroidism, and those treated with PEI plus radioiodine had a significantly higher reduction of nodule volume and of local symptoms compared with patients treated with radioiodine alone.

The merit of this new approach is evident: It allows one to avoid a surgical procedure in patients with locally symptomatic large thyroid nodules whose response to radioiodine alone is poor, at least in terms of nodule shrinkage. Another obvious advantage is that side effects from PEI are limited to a few sessions, since the intent of PEI in this context is not to cure the nodule but just to offer a shrunken nodule to the subsequent action of radioiodine. Furthermore, pretreatment with PEI shrinks the nodules before radioiodine therapy, thus allowing the administration of lower doses of ^{131}I. The caveat is that, despite normalization of serum thyroid-stimulating hormone concentrations, the posttreatment scan showed evidence of autonomous nodular tissue suppressing the function of the extranodular tissue in nearly 50% of patients (as observed also in patients treated with radioiodine alone). This finding should alert one to the possibility of later relapse of hyperthyroidism and calls for further confirmatory studies with longer follow-up.

PEI has also been proposed for the treatment of cold benign thyroid nodules (*20,21*) and thyroid cysts (*22,23*). A randomized study from Bennedbaek et al. (*24*) showed that a single injection of ethanol in a mean dose equal to 21% of the nodule volume produced a mean reduction in nodule volume of 47%, compared with 9% in the control group treated with L-thyroxine–suppressive therapy. Relief of compressive symptoms was experienced by 56% of the PEI-treated patients versus 32% in the group treated with L-thyroxine. In another study from the same authors (*25*), increasing the number of PEI sessions did not result in additional benefit.

Cold thyroid nodules are treated in many centers by surgery, if indicated, or by long-term administration of thyroid-stimulating hormone–suppressive therapy. The benefits of the latter treatment are controversial, at least in the case of single thyroid nodules without goiter. The possibility of alternative therapies such as PEI is attractive but must be balanced against 2 main concerns: the eventuality that cold nodules may harbor an incidental cancer and the frequency of side effects. Although thyroid malignancy may be ruled out by fine-needle aspiration cytology before PEI, Monzani et al. (*26*) reported the presence of papillary cancer in 1 of 12 PEI-treated nodules that were treated by surgery because of PEI fail-

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ure. Major side effects consisting of permanent ipsilateral facial dysesthesia, an increased flow of tears, and paranodular fibrosis resulting from subsequent surgery have been reported (*25*). Of course, side effects depend on the selection of patients, the number of injections, and the skillfulness of the operator.

More convincing is the use of PEI in patients with thyroid cysts. In this case, the presence of a fibrous capsule surrounding the cysts and the absence of sensitive nerves prevents accidental leakage of ethanol into the surrounding normal thyroid tissue and avoids pain. The technique is simple (a single session is usually effective), shrinkage of the nodule is impressive, and recurrences are limited and can be treated with a second injection. The general impression is that PEI treatment may be the first-line procedure for the definitive treatment of thyroid cysts.

In conclusion, the article by Zingrillo et al. (*19*) proposes some kind of "adjuvant" PEI treatment to assist radioiodine therapy. If confirmed in subsequent studies, this approach may become a useful tool for the management of large toxic thyroid nodules. In contrast, the use of PEI as the single form of treatment of thyroid nodules remains indicated only in selected patients: those who have small, easily accessible hot nodules; those who refuse radioiodine therapy; and those who are at high risk of surgical morbidity. According to these restrictions, the final number of candidates for PEI treatment is limited and will probably be further reduced by the advent of new therapeutic strategies that carry limited surgical risks, such as video-assisted thyroid lobectomy (*27*), or are more comfortable for patients, such as interstitial laser photocoagulation, cryoablation, radiofrequency thermal ablation, and microwave destruction.

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REFERENCES

1. Livraghi T. Treatment of hepatocellular carcinoma by interventional methods. *Eur Radiol.* 2001;11:2207–2219.
2. Giovannini M. Percutaneous alcohol ablation for liver metastasis. *Semin Oncol.* 2002;29:192–195.
3. Karstrup S, Transbol I, Holm HH, Glenthoj A, Hegedus L. Ultrasound-guided chemical parathyroidectomy in patients with primary hyperparathyroidism: a prospective study. *Br J Radiol.* 1989;67:1037–1042.
4. Solbiati L, Giangrande A, De Pra L, Bellotti E, Cantù P, Ravetto C. Percutaneous ethanol injection of parathyroid tumors under US guidance: treatment for secondary hyperparathyroidism. *Radiology.* 1985;155:607–610.
5. Rossi R, Savastano S, Tommasselli AP, et al. Percutaneous computed tomography-guided ethanol injection in aldosterone-producing adrenocortical adenoma. *Eur J Endocrinol.* 1995;132:302–305.
6. Livraghi T, Paracchi A, Ferrari C, et al. Treatment of autonomous thyroid nodules with percutaneous ethanol injection: preliminary results. *Radiology.* 1990;175:827–829.
7. 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.
8. Martino E, Murtas ML, Loviselli A, et al. Percutaneous intranodular ethanol injection for treatment of autonomously functioning thyroid nodules. *Surgery.* 1992;112:1161–1165.
9. Papini E, Panunzi C, Pacella CM, et al. Percutaneous ultrasound-guided ethanol injection: a new treatment of toxic autonomously functioning thyroid nodules? *J Clin Endocrinol Metab.* 1993;76:411–416.
10. Livraghi T, Paracchi A, Ferrari C, Reschini E, Macchi RM, Bonifacino A. Treatment of autonomous thyroid nodules by percutaneous ethanol injection: 4-year experience. *Radiology.* 1994;190:529–533.
11. Caraccio N, Goletti O, Lippolis PV, et al. Is percutaneous ethanol injection a useful alternative for the treatment of the cold benign thyroid nodule? Five years' experience. *Thyroid.* 1997;7:699–704.
12. Cerbone G, Spiezia S, Colao A, et al. Percutaneous ethanol injection under power Doppler ultrasound assistance in the treatment of autonomously functioning thyroid nodules. *J Endocrinol Invest.* 1999;22:752–759.
13. Spiezia S, Cerbone G, Assanti AP, Colao A, Siciliani M, Lombardi G. Power Doppler ultrasonographic assistance in percutaneous ethanol injection of autonomously functioning thyroid nodules. *J Ultrasound Med.* 2000;19:39–46.
14. Brkljacic B, Sucic M, Bozikov V, Hauser M, Hebrang A. Treatment of autonomous and toxic thyroid adenomas by percutaneous ultrasound-guided ethanol injection. *Acta Radiol.* 2001;42:477–481.
15. Del Prete S, Russo D, Caraglia M, et al. Percutaneous ethanol injection of autonomous thyroid nodules with a volume larger than 40 ml: three years of follow-up. *Clin Radiol.* 2001;56:895–901.
16. Janowitz P, Ackmann S. Long-term results of ultrasound-guided ethanol injections in patients with autonomous thyroid nodules and hyperthyroidism. *Med Klin.* 2001;96:451–456.
17. Zingrillo M, Torlontano M, Ghiggi MR, et al. Radioiodine and percutaneous ethanol injection in the treatment of large toxic nodule: a long-term study. *Thyroid.* 2000;10:985–989.
18. Tarantino L, Giorgio A, Mariniello N, et al. Percutaneous ethanol injection of large autonomous hyperfunctioning thyroid nodules. *Radiology.* 2000;214:143–148.
19. Zingrillo M, Modoni S, Conte M, Frusciante V, Trischitta V. Percutaneous ethanol injection plus radioiodine versus radioiodine alone in the treatment of large toxic thyroid nodules. *J Nucl Med.* 2003;44:207–210.
20. Goletti O, Monzani F, Lenziardi M, et al. Cold thyroid nodules: a new application of percutaneous ethanol injection treatment. *J Clin Ultrasound.* 1994;22:175–178.
21. 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.
22. Monzani F, Lippi F, Goletti O, et al. Percutaneous aspiration and ethanol sclerotherapy for thyroid cysts. *J Clin Endocrinol Metab.* 1994;78:800–802.
23. Zingrillo M, Torlontano M, Chiarella R, et al. Percutaneous ethanol injection may be a definitive treatment for symptomatic thyroid cystic nodules not treatable by surgery: five-year follow-up study. *Thyroid.* 1999;9:763–767.
24. Bennedbaek FN, Nielsen LK, Hegedus L. Effect of percutaneous ethanol injection therapy versus suppressive doses of L-thyroxine on benign solitary solid cold thyroid nodules: a randomized trial. *J Clin Endocrinol Metab.* 1998;83:830–835.
25. Bennedbaek FN, Hegedus L. Percutaneous ethanol injection therapy in benign solitary solid cold thyroid nodules: a randomized trial comparing one injection with three injections. *Thyroid.* 1999;9:225–233.
26. Monzani F, Caraccio N, Basolo F, Iacconi P, Livolsi V. Miccoli P. Surgical and pathological changes after percutaneous ethanol injection therapy of thyroid nodules. *Thyroid.* 2000;10:1087–1092.
27. Miccoli P, Berti P, Raffaelli M, Materazzi G, Baldacci S, Rossi G. Comparison between minimally invasive video-assisted thyroidectomy and conventional thyroidectomy: a prospective randomized study. *Surgery.* 2001;130:1039–1043.