

# Therapeutic Indications for Autonomous Adenoma of the Thyroid: 71 cases



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## Introduction

Autonomous adenoma (AA) represents around 10% of thyroid pathologies of surgical interest (1-4). In recent years, radioiodine therapy (5-6) and percutaneous ethanol injections (7-10) have been proposed as an alternative to surgery. However, the undesired long-term effects of radioiodine therapy (hypothyroidism), the comparatively high incidence of therapeutic failure after PEI, and the lack of histologic comparison for the lesion have brought surgical treatment back to the fore.

In this article we submit the data relative to PEI and surgical treatment of AA in a series of cases at the Institute of Experimental Surgery of the Second University of Naples (S.U.N.).

## Patients and methods

In the period between May 1987 and December 1998, 644 patients with thyroid diseases were surgically treated at the Institute of Experimental Surgery of the S.U.N.

Among these, 71 (11%) had an autonomous adenoma; 55 (78%) were female and 16 (22%) male. The average age was 52; the age range went from 28 to 71. In terms of degree of autonomy, as defined by Andreoli (11), 10 (14%) were partially inhibiting autonomous nodules, 38 (54%) non-toxic autonomous nodules, and 23 (32%) toxic autonomous nodules (Tab. I). The dimensions of the nodules varied from 13 mm to 5 cm, with an average of 2.8 cm: 18 (11 of which had undergone PEI, which we started in 1995) were smaller than 2 cm.

## Abstract

*The Authors, on the basis of personal experience relative to 71 cases of Autonomous Adenoma of the thyroid treated by surgery or percutaneous ethanol injections (PEI), analyze the results in terms of complications and function. After comparing their results with the data in the literature relative to radioiodine therapy, the Authors conclude that surgery should be the primary treatment for plurifocal nodules or nodules greater than 2 cm in diameter, while PEI can be used for single nodules smaller than 2 cm.*

*The point is that radioiodine often induces hypothyroidism, while our knowledge of the results of percutaneous ethanol injections is still limited in terms of number of cases and length of observation periods. Therefore, the authors think that the treatment of Autonomous Adenomas should be surgical, while non-surgical therapy should be limited to specific cases (dimensions, age, or general contraindications to the operation).*

Key words: Thyroid, autonomous adenoma.

Tab. I – DIRECT EXPERIENCE (STAGED ACCORDING TO ANDREOLI)

|         | Total | Partially<br>inhibiting | Non toxic | Toxic    |
|---------|-------|-------------------------|-----------|----------|
| Surgery | 60    | 5 (8%)                  | 33 (55%)  | 22 (37%) |
| PEI     | 11    | 5 (45%)                 | 5 (45%)   | 1 (10%)  |

Tab. II – CHOICE OF TREATMENT OVER THE YEARS

|             | Before 1994 |       | After 1994 |         |
|-------------|-------------|-------|------------|---------|
| Resections  | 27          | (38%) | 1          | (1.4%)  |
| Lobectomies | 9           | (13%) | 23         | (32%)   |
| PEI         | –           | –     | 11         | (15.6%) |

The most frequent symptoms were tachycardia, irritability, anxiety, insomnia, and the presence of a swelling in the anterior region of the neck. Cutaneous and ocular symptoms, which are not typical of this affection, were

always absent. In 8 cases the initial symptom was cardiac (tachycardia, atrial fibrillation).

In all the patients, symptoms began at least 6 months before diagnosis and, in one case, many years before. In all the cases, the thyroid scintiscan showed an area of increased uptake requiring, in the non-inhibiting cases, the carrying out of a suppression test to evaluate functional autonomy.

TSH was lower than normal range values, even in cases of AA that were not yet inhibiting the rest of the thyroid parenchyma to the scintiscan. In all the patients, the TRH test confirmed the presence of hyperthyroidism with a block in the secretion of the thyrotrope hormone.

Eleven patients underwent PEI as outpatients. They had a single nodule measuring 2 cm or less (the average was 16 mm).

We used antithyroidal drugs to prepare the patients for surgical treatment and, in case of plain hyperthyroidism, beta-blockers as well.

The choice of surgical intervention depended on the dimensions and position of the autonomous nodule, as well as the state of the residual thyroid parenchyma. We performed: 12 monolateral almost total resections for small adenomas located in the body and at the base of the thyroid lobe; 16 almost total resections combined with subtotal contralateral resections; 26 monolateral extracapsular lobectomies with or without isthmectomy; 6 monolateral extracapsular lobectomies combined with subtotal resection of the contralateral lobe. All of these techniques involved the preliminary localization of the recurrent nerve of the treated side. In our experience, over the years lobectomies took the place of resections.

The p.o. hospital stay was regular in 56 out of 60 patients. In 4 patients we had a short thyreotoxic crisis with hyperthermia and tachycardia which regressed in a few days merely through the use of antipyrexial drugs and beta-blockers. We have not observed any case of lesion of the recurrent nerve or other complications of relief (hemorrhages, etc.).

After 2, 6 and 12 months we repeated the TRH test and the dosing of the thyroid hormones. We observed a constant increase of basal TSH in all patients. Normalization of the response to the thyrotropic stimulus was achieved in one year for 50 patients (70%). A year after, 18 patients (25%) showed an increased TSH stimulation response related to subclinical hypothyroidism, easily controllable with substitutive therapy. A thyroid scintiscan performed 6 months after the intervention confirmed the functional resumption of the previously inhibited thyroidal parenchyma in all the cases.

63 out of 71 patients are in our follow-up program. Presently, with a follow-up range from 10 months to 10 years (average 3.5), we have not observed relapses either in the residual parenchyma in case of resection, or in the contralateral lobe in case of lobectomy with or without resection of the other lobe.

Since we started PEI in 1995, 10 out of 11 patients treated

with this method are still under follow up and all are free from relapses.

## Discussion

The AA is a thyroid affection prevalently found among females aged 30 to 40 years.

According to the classification proposed by Andreoli (11), the AA evolves quite constantly from an autonomous form to a pretoxic one, and then finally to the so-called "toxic form", which is characterized by clinical, scintigraphic and hormonal manifestations of hypothyroidism.

This variability makes AA's difficult to interpret, especially in the first stage of the disease, which is why the incidence of AA varies considerably in different case records: from 0,9% according to Hamburger (4) to 15% according to Dulac (3).

Furthermore, it is well recognized that AA can have double evolution. In fact, it generally goes through three evolutionary stages related to the dimensions of the nodule, and culminates in toxicity. A full regression of the adenoma is also possible as a consequence of centronodular necrosis and hemorrhage determining a remission of clinical hyperthyroidism accompanied by the reappearance of the surrounding parenchyma and the transformation of the warm nodule into a cold one. Such an evolution, which can also be predictive of malignancy, can occur in 27.9% of the non-toxic AA's and in 10.3% of the toxic ones (11).

The evolution toward toxicity is almost compulsory, as the need to exclude a coexistent neoplasia, also in those rare forms of spontaneous involution, that still requires the diagnosis and therapy to run their full course.

It is essential to diagnose not only the degree of autonomy of the nodule, but also the plurifocality of the lesion and its benignity. In fact, it has been shown that about 8% of clinical and scintigraphic uninodular lesions are in reality plurifocal (12), with a high impact on therapeutic strategy. Ultrasonography, while not allowing a functional evaluation, still provides interesting information about the possible coexistence of lesions in the same or in the contralateral lobe that are still not evident in scintigraphy. The most important information that needs to be diagnosed is, without any doubt, whether the lesion is benign or not. It is documented that the association between hyperthyroidism and cancer is rare: 0.3% according to Loddi (13), 1.6% according to Dulac (3), 2.9% according to Wahl (14). Finally, a warm nodule can be itself a malignant tumor, the so called hyperfunctioning or hyperdifferentiated follicular cancer.

Cytology, whose limits are the procedure itself, the lack of samples, a misalignment of the nodule, and interpretation difficulties, is the only exam able to detect malignant alterations pre-operatively, and should therefore be constantly used, especially in anticipation of non-surgical therapy of the AA.

For many years, the treatment of choice for the AAs was exclusively surgical. More recently, alternative treatments have been proposed, such as therapy with antithyroid drugs, radioiodine therapy and percutaneous ethanol injections. Each of these treatments indubitably has its advantages and shortcomings. Their principal advantage is of course the minimization, if not the total elimination, of the risks of surgical intervention (generic risks, recurrent nerve lesions, hypoparathyroidism).

These alternatives to surgery, however, entail some disadvantages that condition their diffusion and limit their indication to selected cases.

Patients undergoing *therapy with antithyroid drugs* (excluding the rare cases of spontaneous resolution) must be treated for life since the treatment cannot induce a permanent remission of hyperthyroidism, and hence can only be used to prepare the patients for further treatment, whether surgical or not.

The authors' perplexities, with regard to *radioiodine* treatment, is that it requires high doses of I131 (15-25 mCus), even higher than those used for the Basedow disease, and hence frequently results in hypothyroidism (15); lower doses would not allow the destruction of the adenoma. It has been calculated that a dose of at least 350 Gy is needed on the AA to gain control over it (16). Some Authors hold the opposite view, since they feel that when the surrounding parenchyma is functionally at rest, it is less exposed to the action of I131, and hypothyroidism should therefore be less frequent than after therapy for the Basedow disease. Therapeutic success of treatment with I131 amounts to about 90% of cases. Another disadvantage of radioiodine therapy is that it requires a complex structure for the administration of radioactive substances, and a short hospitalization of the patient. Pretreatment with antithyroid drugs must be avoided since the paranodular tissue, stimulated by an increased TSH, will take up I131, which should only reach the solitary autonomous nodule (20).

PEI is best used with small adenomas (less than 20 mm) and has better results with the non-toxic forms. In an Italian multicentric experience, this treatment worked in 66.5% of the toxic AAs and in 83% of the non-toxic ones (17). Thyroid hormones go back to normal values in those patients who suffered from hyperthyroidism upon diagnosis in 77% of the cases, and in 69% TSH also returns to normal values; better results (100% of normal TSH values) are obtained in patients who had euthyroidism before the treatment (18). The PEI technique is undoubtedly simple and almost without complications (transitory dysphonia, rare jugular thromboses). Rare thyreotoxic crisis and transitory dysphonia were reported in the early post-treatment period. Injection of local anesthetic reduces the occurrence of local pain. At any rate, PEI needs to be evaluated on larger case records, even though the initial results seem to be favorable. This limits the range of applicability of the treatment: unifocality of the lesion, cytology negative for

malignancy, dimensions of the nodule and degree of toxicity. PEI is an interesting alternative to radioiodine therapy in younger patients and to surgery in case of small lesions or serious contraindications to operation. Furthermore, it doesn't cause evident alterations of the capsule. Therefore, a possible surgical intervention would not be difficult after PEI.

*Surgical treatment* undoubtedly introduces some advantages, due to the rapid and complete resolution of hyperthyroidism. Proposed treatments vary extremely from one author to another, ranging from simple enucleoresection to subtotal resection and extracapsular lobectomy. In recent literature, resections are less frequent, lobectomy being the treatment of choice, independently of the size and site of the adenoma. This appears logical, considering the possibility that other silent adenomatous lesions may coexist in proximity of the main nodule and, if left in situ, could give rise to a recurrence.

The results of surgical treatment are widely known. From the functional point of view, the incidence of hypothyroidism varies if we consider a condition characterized by clinical signs of thyroid hypofunction and low T3 and T4 values (from 1% to 5%), or if we include the more frequently observed hyperresponse of TSH to TRH (2). At any rate, in most cases this post-operative hypothyroidism evolves into a condition of functional normality within 12 months from the operation.

Surgical treatment carried out by experienced hands is not significantly burdened by complications of relief. In most case records there are no recurrent lesions. In adequately prepared patients, thyreotoxic crises only occur in 2% of the cases, and they are generally feeble and short lasting. Hypocalcemia, generally absent in most of the case records, appears to be transitory and is not associated with neuromuscular hyperexcitability.

Beside assuring the rapid resolution of hyperthyroidism, surgery is the only treatment able to reveal the possible coexistence of malign lesions. We have already mentioned that the association of hyperthyroidism with cancer, although limited, is certainly not impossible (0.3%-2.9%) (3, 13, 14). Surgery, however, is a high-cost treatment and necessarily requires the hospitalization of the patient.

## Conclusions

The treatment of the AA has undergone remarkable changes over the years. Most authors currently favour three strategies: radioiodine therapy, PEI and surgery. Each of these treatments has its indications and limits. Radioiodine therapy allows, almost unfailingly, control of hyperfunction in the totality of the cases, but it exposes patients to a substantial risk of delayed hypothyroidism. Furthermore, since the treatment with I131 is not recommendable in infancy and there are also contraindications for its use during pregnancy, radioiodine

therapy appears currently suitable essentially as an alternative to surgery in case of general contraindications to anesthesia, or recurrences after surgical treatment in which the risks of operating complications have increased considerably.

PEI has proved an effective technique, achieving its best results in the treatment of small and medium-sized lesions. It is not burdened by significant complications and it doesn't jeopardize further surgical treatment. However, it doesn't allow histology and doesn't seem to affect the silent adenomas frequently accompanying the main lesion.

Thus, in our experience, surgical treatment still retains its primary role, as it can quickly and radically resolve hyperthyroidism, and is not burdened, in experienced hands, by complications. In our opinion, the alternative therapeutic strategies are indicated for small adenomas or in patients with general contraindications; of these strategies, PEI is especially recommendable for the rapidity and facility of its execution and the good results it offers.

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