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# THYROTROPIN-SECRETING PITUITARY ADENOMAS

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## ABSTRACT

Thyrotropin-secreting pituitary tumors (TSH-omas or TSH-PitNET) are a rare cause of hyperthyroidism and account for about 1% of all pituitary adenomas. It is, however, noteworthy that the number of reported cases increased over the last few decades because of the improved awareness of this condition. Indeed, ultrasensitive TSH assays allow a clear distinction between patients with suppressed and those with non-suppressed circulating TSH concentrations, i.e., between patients with primary hyperthyroidism (Graves' disease or toxic nodular goiter) and those with central hyperthyroidism (TSH-oma or resistance to thyroid hormone beta, RTHβ). Failure to recognize the presence of a TSH-oma may result in dramatic consequences, such as improper thyroid ablation that may cause the pituitary tumor volume to further expand. The presence of compressive manifestations (visual defects, headache) or clinical features of concomitant hypersecretion of other pituitary hormones (acromegaly, galactorrhea/amenorrhea) strongly supports the diagnosis of TSH-oma. Nevertheless, the differential diagnosis between TSH-oma and RTHβ may be difficult when the pituitary adenoma is tiny, or in the case of unrelated lesions such as an empty sella or pituitary incidentalomas. First-line treatment of TSH-omas is pituitary adenomectomy followed by irradiation in the case of surgical failure. However, medical treatment with long-acting somatostatin analogues (e.g. octreotide and lanreotide), are effective in reducing TSH secretion in more than 90% of cases with consequent normalization of FT4 and FT3 levels and restoration of the euthyroid state.

## INTRODUCTION

Thyrotropin (TSH)-secreting pituitary adenomas (TSH-omas or TSH-PitNET) are a rare cause of hyperthyroidism. In this situation, TSH secretion is autonomous and refractory to the negative feedback of thyroid hormones (thus justifying the term of inappropriate TSH secretion), and results in the hyperstimulation of the thyroid gland and hypersecretion of T4 and T3 (1, 2). Therefore, this entity can be appropriately classified as a form of "central hyperthyroidism". The first case of TSH-oma was described in 1960 by measuring serum TSH levels with a bioassay (3). In 1970, Hamilton et al. (4) reported the first case of TSH-oma proved by measuring TSH by radioimmunoassay.

Classically, TSH-omas were diagnosed at the stage of invasive macroadenoma and were considered difficult to cure. However, the advent of ultrasensitive immunometric assays and the more widespread clinical awareness, prompted by the work of several

groups including our own, greatly increased the recognition of this entity. Nowadays, TSH-omas are more often diagnosed at an earlier stage, before they develop into macroadenomas, and an increased number of patients with normal or elevated TSH levels in the presence of high free thyroid hormone concentrations have been recognized. Signs and symptoms of hyperthyroidism along with values of thyroid function tests similar to those found in TSH-oma may be encountered in patients with resistance to thyroid hormone beta, RTHβ (5-7). Failure to differentiate these diseases may result in dramatic consequences, such as improper thyroid ablation in patients with central hyperthyroidism or unnecessary pituitary surgery in those with RTHβ. Conversely, early diagnosis and the correct treatment of TSH-omas may prevent the occurrence of the typical complications of chronic hyperthyroidism (e.g. tachyarrhythmias, osteoporosis) and pituitary macroadenomas (e.g. visual field defects, headache, and hypopituitarism) and increases the chance of achieving a definitive cure.

## EPIDEMIOLOGY

TSH-producing adenomas are rare and account for about 0.5% to 2% of all pituitary adenomas; the prevalence in the general population is thought to be 1 to 2 cases per million (1, 2, 8-86). However, this figure is probably an underestimate because TSH-omas can be missed with the widespread use of reflex TSH testing if the hormone is not frankly elevated. The Swedish Pituitary Registry (87) documented an increased incidence of TSH-omas over time (0.05 per 1 million per year in 1990-1994 to 0.26 per 1 million per year in 2005-2009), the national prevalence in 2010 being 2.8 per 1 million inhabitants. The increased number of reported cases principally results from improved general awareness by practitioners and endocrinologists. Based on the finding of non-suppressed or elevated serum TSH levels in the presence of elevated FT4 and FT3 concentrations, many patients are now correctly diagnosed with TSH-oma or with RTHβ (1, 2, 5-7).

The presence of a TSH-oma has been reported at ages ranging from 7 to 84 years (2, 58-60, 74), the mean age at diagnosis being 46 ± 6 years (61). TSH-omas occur with equal frequency in men and women, in contrast with the female predominance seen in other thyroid disorders, and a recent structured review of 535 adult cases of adult cases confirmed a female to male ratio of 1.07 (61). Familial cases of TSH-oma have been reported as part of multiple endocrine neoplasia type 1 (MEN1) (10), and in familial isolated pituitary adenoma (FIPA) families with an *AIP* mutation (52).

## PATHOLOGICAL ASPECTS

Immunostaining studies showed the presence of TSH beta subunit, either free or combined, in all adenomatous cells from every type of TSH-oma, with only a few exceptions (1, 2, 8, 9, 88, 89). Most TSH-secreting adenomas (72%) are secreting TSH alone, often accompanied by unbalanced hypersecretion of the alpha subunit of glycoprotein hormones (alpha-GSU) (Table 1). Interestingly, the existence of TSH-omas composed of two different cell types, one secreting alpha-GSU alone and another cosecreting alpha-GSU and the mature TSH molecule (mixed TSH/alpha-GSU adenomas), was documented by using double gold particle immunostaining (89). The presence of a mixed TSH/alpha-GSU adenoma is suggested by the finding of an extremely high alpha-GSU/TSH molar ratio and/or by the observation of dissociated TSH and alpha-GSU responses to TRH (1, 89). Classic mixed adenomas characterized by concomitant hypersecretion of other anterior pituitary hormones are found in about 25% of patients.

| Table 1. Recorded Cases of TSH-omas or TSH-PitNET of Different Type | | |
|---|---|---|
| | **Number** | **% of total** |
| Total TSH-omas | 764 | --- |
| Pure TSH-omas | 563 | 73.7 |
| TSH-omas with associated hypersecretion of other pituitary hormones (mixed TSH-omas) | 185 | 24.2 |
| Mixed TSH/GH-omas | 126 | 16.5 |
| Mixed TSH/PRL-omas | 51 | 6.7 |
| Mixed TSH/FSH/LH-omas | 8 | 1.0 |
| Ectopic TSH | 16 | 2.1 |

(Updated May 2025 including personal unpublished observations)

Hypersecretion of GH and/or PRL, resulting in acromegaly and/or amenorrhea/galactorrhoea syndrome, are the most frequent associations (1,61). This is likely due to the common Prop-1 and Pit-1-dependent origin of thyrotroph, somatotroph and lactotroph cells (90). Rare is the occurrence of mixed TSH/gonadotropin adenomas, while no association with ACTH hypersecretion has been documented to date. Importantly, positive immunohistochemistry for one or more pituitary hormone(s) does not necessarily correlate with its or their hypersecretion *in vivo* (9, 72, 91). Accordingly, clinically and biochemically silent thyrotropinomas have been reported (9, 92, 93). Moreover, true TSH-secreting tumors associated with Hashimoto's thyroiditis and hypothyroidism have been documented (2, 39, 94, 95). Finally, an isolated pituitary gangliocytoma producing TSH and TRH has also been reported (96).

Microadenomas, with a diameter <1 cm, were recorded in less than 15% of the cases before 1996 (22), but their prevalence among all the TSH-omas is progressively increasing due to improved testing of thyroid function and awareness among endocrinologists and general practitioners. Consistently, in the series published by our institution in 2014 and 2020 (97, 152), up to 30% of TSH-omas were microadenomas. A structured review of 533 cases of adult TSH-omas by De Herdt C et al. published in 2021 reported that 23.1% of them were microadenomas, and the remaining 76.9% were macroadenoma with a mean diameter of 21.5 ± 7.9 mm (61). The TSH-omas diagnosed at the stage of macroadenomas showed localized or diffuse invasiveness into the surrounding structures, especially into the dura mater (1, 8, 15, 22, 88). Extrasellar extension in the supra- and/or parasellar direction were present in the majority of cases. The occurrence of invasive macroadenomas is particularly high among patients with previous thyroid ablation by surgery or radioiodine (Figure 1) (2). This finding emphasizes the deleterious effects of incorrect diagnosis and treatment of these adenomas, because the resolution of thyrotoxicosis appears to release the brake exerted by the high circulating thyroid hormone levels on tumor growth. This potentially aggressive transformation of the tumor is reminiscent of Nelson's syndrome, the progressive growth and secretion of adrenocorticotropic hormone (ACTH) of corticotroph adenoma, after bilateral adrenalectomy for Cushing's disease. Finally, some data suggest that somatic mutations of the thyroid hormone receptor beta gene may be responsible for the defect in negative regulation of TSH secretion in some TSH-omas (56, 98-100). In addition, alteration in iodothyronine deiodinase enzyme expression and function may contribute to the resistance of tumor cells to the feedback mechanism of elevated thyroid hormone levels (101). However, these data were not confirmed by another study on this topic (102).

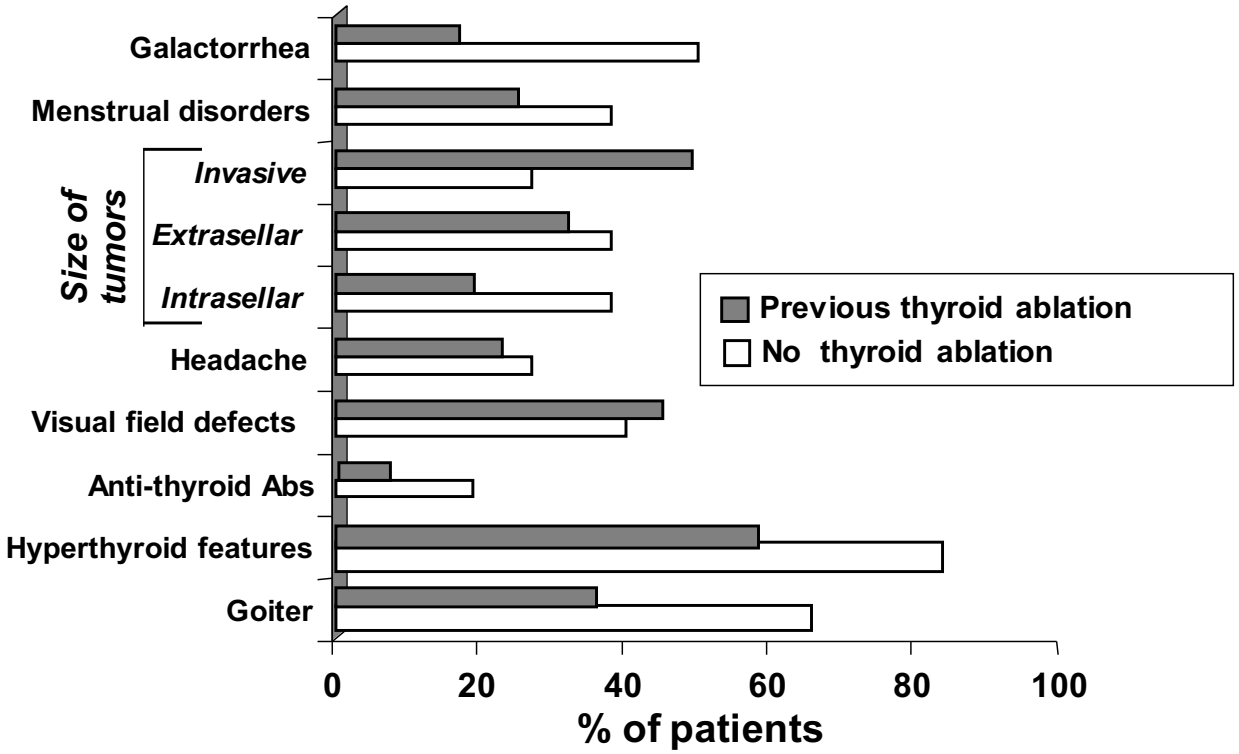


**Figure 1. Clinical manifestations in patients with TSH-secreting adenomas. Patients have been divided into two categories according to previous thyroid surgery. The presence of goiter is the rule, even in patients with partial thyroidectomy. Hyperthyroid features may be overshadowed by those of associated hypersecretion/deficiency of other pituitary hormones. Invasive tumors are seen in about half of the patients with previous thyroidectomy and in 1/4 of untreated patients (P<0.01 by Fisher's exact test). Intrasellar tumors show an opposite distribution pattern.**

The consistency of TSH-omas is usually very fibrous and sometimes so hard that they were described as a "pituitary stone" (103). Increased basic fibroblast growth factor (bFGF) levels were found in blood from two patients with invasive mixed PRL/TSH-secreting adenomas characterized by marked fibrosis (104). The tumoral origin of bFGF was confirmed by the finding of specific transcripts in the tissues removed at surgery, suggesting a possible autocrine role for this growth factor in tumor development.

By light microscopy and appropriate staining, adenoma cells usually have a chromophobe appearance. Cells are often organized in cords, and they frequently appear polymorphous and characterized by large nuclei and prominent nucleoli. Ultrastructurally, the well differentiated adenomatous thyrotropes resemble the normal ones, while the poorly differentiated adenomas are composed of elongated angular cells with irregular nuclei, poorly developed rough endoplasmic reticulum (RER), long cytoplasmic processes, and sparse small secretory granules (50-200 nm) usually lining up along the cell membrane (9, 88). Generally, no exocytosis is detectable (105). Cells with abnormal morphology or mitoses are occasionally found and may be mistaken for a pituitary malignancy or metastases from distant carcinomas (105). Of note, the transformation of a TSH-oma into a pituitary carcinoma with multiple metastases has only been reported rarely (35, 61, 62, 106). Future malignant behavior might be predicted by the finding of a concomitant, spontaneous and marked decrease of both TSH and alpha-GSU serum concentrations that might indicate that the tumor is becoming less differentiated. Finally, in a mouse model of TSH-oma, the activation of phosphatidyl-

inositol 3-kinase promoted aberrant pituitary growth that may induce transformation of the adenoma into a carcinoma (107).

## MOLECULAR AND *IN VITRO* SECRETION STUDIES

The molecular mechanisms leading to the formation of TSH-omas are presently unknown, as is true for most pituitary adenomas. X-chromosomal inactivation analysis demonstrated that most pituitary adenomas, including the small number of TSH-omas investigated, derive from the clonal expansion of a single initially transformed cell (43). Accordingly, the general principles of tumorigenesis, which assume the presence of a transforming event providing gain of proliferative function followed by secondary mutations or alterations favoring tumor progression, presumably also apply to TSH-omas.

A large number of candidate genes, including common proto-oncogenes and tumor suppressor genes as well as pituitary specific genes, have been screened for mutations that might confer a growth advantage to thyrotrope cells. In analogy with the other pituitary adenomas, no mutations in oncogenes commonly activated in human cancer, particularly *RAS*, have been reported in TSH-omas. In contrast, with GH-secreting adenomas in which the oncogene *gsp* (*GNAS* mutation) is frequently present, none of the TSH-oma screened has been shown to express activating mutations of genes encoding for G protein subunits (108). Similarly, no mutations in the TRH receptor or dopamine D2 receptor genes (108, 109) have been reported in 9 and 3 TSH-omas, respectively, while these tumors were not screened for alterations in protein kinase C alterations, previously identified in some invasive tumors. In consideration of the crucial role that the transcription factor Pit-1 exerts on cell differentiation and PRL, GH and TSH gene expression, the Pit-1 gene has been screened for mutations in 14 TSH-omas and found to be wild-type (2). By contrast, as occurs in GH-omas, Pit-1 was demonstrated to also be overexpressed in TSH-omas (2, 88, 90).

In addition to activating mutations or overexpression of protooncogenes, tumors may originate from the loss of tumor suppressor genes, but no loss of p53 was found in the only TSH-oma studied. Another candidate gene is *MEN1* coding for menin. In fact, 3-30% of sporadic pituitary adenomas show loss of heterozygosity (LOH) on 11q13, where *MEN1* is located, and LOH on this chromosome seems to be associated with the transition from the non-invasive to the invasive phenotype. A study carried out on 13 TSH-omas using polymorphic markers on 11q13 showed LOH in 3, but none of them showed a *MEN1* mutation after sequence analysis (110). Interestingly, hyperthyroidism due to TSH-omas has been reported in five cases within a familial setting of MEN1 (1, 2, 10). In addition, LOH and polymorphisms at the somatostatin receptor type 5 gene locus, seem to be associated with an aggressive phenotype and resistance to somatostatin analogue treatment (111). Moreover, germline mutations in the aryl hydrocarbon receptor interacting protein (*AIP*) are known to be involved in sporadic pituitary tumorigenesis, and mutations were found in two patients with TSH-omas (52, 112). Finally, a recent study based on whole-exome sequencing identified several candidate somatic mutations and copy number variations in 12 sporadic TSH-omas, but with a low number per tumor and without the mutations being observed in different cases (113). A publication by a French group analyzing a series of secreting and non-secreting pituitary adenomas (including 6 TSH-omas) demonstrated a higher frequency of chromosomal alterations in TSH-omas, but these alterations were not associated with aggressiveness (114). The same authors also demonstrated that POU1F1/PIT1-lineage tumors (including TSH-omas) were characterized by a global hypomethylation, possibly inducing chromosomal alterations through the activation of transposable elements. Finally, a transcriptomic analysis demonstrated that thyrotroph tumors cluster with sparsely granulated somatotroph adenomas and plurihormonal PIT1-positive adenomas, a group

characterized by a high interferon-α and -γ gene expression (114).

The extreme refractoriness of neoplastic thyrotropes to the inhibitory action of thyroid hormones suggests the presence of mutant forms of thyroid hormone receptors (TR) as potential candidate oncogenes. Absence of TR alpha1, TR alpha2 and TR beta1 expression was reported in two TSH-omas (100, 115), but aberrant alternative splicing of thyroid hormone receptor beta2 (*THRB*) mRNA encoding TR beta variant lacking T3 binding activity and other *THRB* mutations were shown as a mechanism for impaired T3-dependent negative regulation of both TSH and alpha-GSU in tumoral tissue (98,99). Moreover, aberrant expression of a novel thyroid hormone receptor β isoform (TRβ4) may partly contribute to the inappropriate secretion of TSH in TSH-omas (56). Several patients with RTHβ have been described to bear pituitary lesions at imaging of the sella region, raising diagnostic and therapeutic challenges (30, 115-118, 152). The results of dynamic testing of TSH secretion were consistent with RTHβ, rather than TSH-omas, indicating that these lesions are likely to be non-secreting pituitary incidentalomas, whose prevalence in unselected autopsy series reaches 20% (117).

Pharmacological manipulations in short-term cell cultures of TSH-omas indicate that these tumors express a large number of functioning receptors. Although *in vivo* TSH response to TRH is usually absent, several *in vitro* studies showed either the presence or the absence of TSH response, indicating that most tumors possess TRH receptors (2). Similarly, somatostatin binding experiments indicate that almost all TSH-omas express a variable number of somatostatin receptors, the highest somatostatin-binding site densities being found in mixed GH/TSH adenomas (57, 119,120). Since somatostatin analogues are highly effective in reducing TSH secretion by neoplastic thyrotropes (12, 13, 30, 75, 121-123), the inhibitory pathway mediated by somatostatin receptors appears to be largely intact in such adenomas. Consistently, there is a good correlation between somatostatin binding capacity and maximal biological response, as quantified by inhibition of TSH secretion and *in vivo* restoration of an euthyroid state (57, 121-124). The presence of dopamine receptors in TSH-omas was the rationale for therapeutic trials with dopaminergic agonists, such as bromocriptine (57, 125, 126). Several studies have shown a large heterogeneity of TSH responses to dopaminergic agents, either in primary cultures or *in vivo* (1, 41, 127, 128). The effects of these two inhibitory agents should be nowadays re-evaluated considering the demonstration of the possible heterodimerization of somatostatin receptor subtype 5 (sst5) and dopamine D2 receptor (129).

## CLINICAL FINDINGS

Patients with TSH-omas present with signs and symptoms of hyperthyroidism that are frequently associated with the compressive manifestations of the pituitary macroadenomas (Figure 1) (22, 49, 65, 130). TSH-omas may occur at any age and, in contrast with the common thyroid disorders, there is no preferential incidence in females (2, 8, 22, 61). Due to the long history of thyroid dysfunction, many patients had been mistakenly diagnosed as having primary hyperthyroidism (Graves' disease or multinodular goiter), and about one third had inappropriate thyroid ablation by thyroidectomy and/or radioiodine. True coexistence of Graves' disease and TSH-oma has been reported in about 20 cases (54, 80, 131-134). The majority of these cases were females, and the dual diagnosis was confirmed within 3 years from the original diagnosis in all cases. When Graves' disease is diagnosed initially, it has been speculated that antithyroid medications may promote the growth of a TSH-oma via the positive feedback system (133).

Clinical features of hyperthyroidism are present in up to 75% of patients (1,63), sometimes milder than expected given the level of thyroid hormones, probably due to their gradual increase and longstanding duration (135). Interestingly, only two cases of TSH-oma complicated by thyroid storm peri-

or post-operatively have been published (136,137). Consistently, several untreated patients with TSH-oma were described as clinically euthyroid (60, 138). Moreover, hyperthyroid features can be overshadowed by those of acromegaly in patients with mixed TSH/GH adenomas (61, 79, 139-143), thus emphasizing the importance of the systematic measurement of TSH and FT4 in patients with pituitary tumors. Acromegaly itself can often be associated with multinodular goiter, presenting a further confounding diagnostic scenario.

Thyrotoxic heart failure and atrial fibrillation were described in a considerable percentage of cases (11.1%) (61). Cardiac complications such as atrial fibrillation and cardiac failure have been seldom reported (144-147). Typical episodes of periodic paralysis have also been described in two patients (20, 148). A high prevalence of radiological vertebral fracture has been documented in a series of patients with TSH-omas (149) thus confirming the deleterious effects of thyrotoxicosis on bone health.

The presence of a goiter is the rule, even in the patients with previous partial thyroidectomy, since thyroid residue may regrow as a consequence of the chronic TSH hyperstimulation. The occurrence of uni- or multinodular goiter is frequent (about 72% of reported cases), and progression towards functional autonomy was sometimes observed (150-152). The monitoring of the thyroid nodule(s) and the performance of fine needle aspiration biopsy should be performed in TSH-omas following established guidelines (1, 11, 55, 61, 153-157). A recent publication evaluating 62 patients who underwent surgery for TSH-oma demonstrated an estimated incidence of thyroid carcinoma of 4.8%, thus suggesting a possible role of TSH hypersecretion in the development of thyroid cancer (155). The prevalence of circulating antithyroid autoantibodies (anti-thyroglobulin: Tg-Ab, and anti-thyroid peroxidase: TPO-Ab) is similar to that found in the general population, but some patients developed Graves' disease after pituitary surgery and a few others presented with bilateral exophthalmos due to the eye involvement of the autoimmune process (2, 55, 158), while unilateral exophthalmos due to orbital invasion by the pituitary tumor has also been reported (3, 159).

Dysfunction of the gonadal axis is not rare, with menstrual disorders present in one third of the reported cases, mainly in the mixed TSH/PRL adenomas. In this respect, a recent report described a case of a 37-year-old woman who had experienced galactorrhea and menstrual abnormalities; she underwent infertility treatment for one year before the TSH-oma was diagnosed (160). Central hypogonadism, delayed puberty and decreased libido were also found in some males with TSH-omas and/or mixed TSH/FSH adenomas (1, 127, 161,162).

Because of suprasellar extension or invasiveness, signs and symptoms of an expanding tumor mass are predominant in many patients. Partial or total hypopituitarism was seen in about 25% of cases, headaches have been reported in 20-25% of patients, and visual field defects are present in about 50% of patients (Figure 1).

## BIOCHEMICAL FINDINGS

High concentrations of circulating free thyroid hormones in the presence of inappropriately unsuppressed TSH levels, within the reference range or above, characterize the hyperthyroidism secondary to TSH-secreting pituitary adenomas. In an analysis of 533 cases of TSH-omas it has been shown that the median TSH at diagnosis was 6.75 (4.02–11.90) mU/L in the case series and 5.16 (3.20–7.43) mU/L in the case reports, whereas FT4 averaged 35.7 ± 8.5 and 41.5 ± 15.3 pmol/L, respectively (61). Interestingly, normal levels of total T4/T3 were recorded in several patients with TSH-omas despite the presence of clinical signs and symptoms of hyperthyroidism. This observation indicates that the measurement of circulating free thyroid hormones (FT4 and FT3) is mandatory. In fact, these measurements show the highest sensitivity for the correct diagnosis of central

hyperthyroidism and prevent misclassification in the case of excess circulating levels of thyroxine-binding globulin (26). Many different physiological or clinical conditions, such as pregnancy or RTHβ, may present with hyperthyroxinemia and unsuppressed serum TSH levels, and should be distinguished from TSH-omas. Most of these conditions may be recognized on the basis of either a patient's clinical history or by measuring the concentrations of FT4 and FT3 with direct "two-step" methods, i.e. the methods able to avoid possible interference due to the contact between serum factors and tracer at the time of the assay (e.g. equilibrium dialysis + RIA, adsorption chromatography + RIA, and back-titration) (163,164). In fact, some factors may interfere with the measurement of either thyroid hormones or TSH. The presence of anti-iodothyronine autoantibodies (anti-T4 and/or anti-T3) or abnormal albumin/transthyretin forms, such as those circulating in familial dysalbuminemic hyperthyroxinemia, may cause FT4 and/or FT3 to be overestimated, particularly when "one-step" analog methods are employed (165,166). The more common factors interfering in TSH measurement and giving spuriously high levels of TSH are the circulating heterophilic antibodies, i.e. antibodies directed against mouse gamma-globulins (36, 166).

About 30% of TSH-oma patients with an intact thyroid gland showed TSH levels within the normal reference range (1,2). In this context, it is important to emphasize that the “reflex TSH strategy” (i.e., measurement of FT4 test only in the presence of an abnormal TSH result) fails to recognize both central hypo- and hyperthyroidism and thus misses the diagnosis of TSH deficiency or a TSH-oma (167,168). Quite surprisingly, the diurnal rhythm is preserved in TSH-omas and TSH secretion shares many characteristics (cross-approximate entropy, cross-correlation and cosinor regression) of other pituitary hormone-secreting adenomas (169). Interestingly, a case of TSH-oma with cyclic fluctuations in serum TSH levels has recently been reported (170).

Interestingly, despite the TSH-dependent origin of hyperthyroidism, there is no direct correlation between free thyroid hormone and immunoreactive TSH levels (Figure 2). An increased biological activity of secreted TSH molecules likely accounts for the finding of a normal TSH in the presence of high levels of FT4 and FT3 (139). TSH molecules secreted by pituitary tumors are heterogeneous and may have either a normal, reduced, or increased ratio between their biological and immunological activities, probably due to modification of glycosylation processes secondary to alterations of the post-translational processing of the hormone within the tumor cell (171,172). Remarkably, TSH levels in patients previously treated with partial thyroid ablation were 6-fold higher than in untreated patients, though free thyroid hormone levels were still in the hyperthyroid range (140). Moreover, tumoral thyrotrophs may undergo more active cellular proliferation in response to even small reductions in circulating thyroid hormone levels, as documented by the higher number of invasive macroadenomas found in previously treated patients (Figure 1), beyond the increase of TSH secretion.

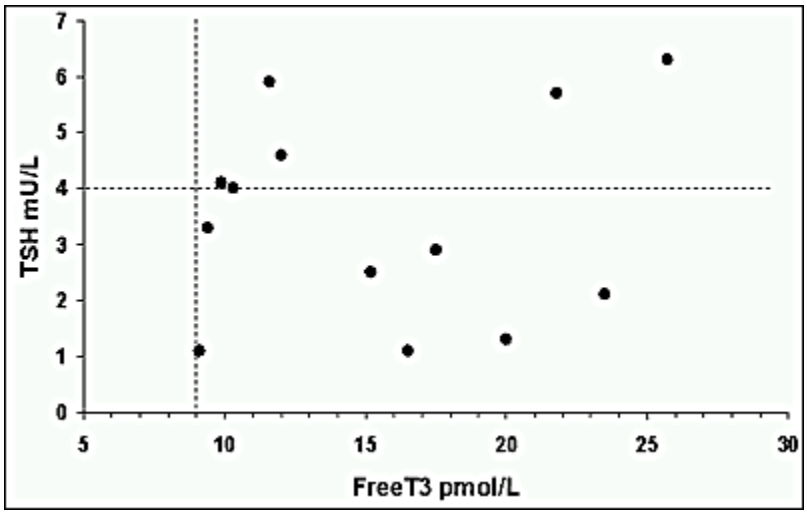


**Figure 2. Absent correlation between immunoreactive concentrations of circulating TSH and FT3 in 14 patients with TSH-secreting adenomas. Dotted lines indicate the upper limits of normal ranges for both parameters.**

Independently of previous thyroid ablation, circulating free alpha-GSU levels and alpha-GSU/TSH molar ratios were clearly elevated in most patients with TSH-omas, either due to unbalanced secretion of the subunit or to the presence of a mixed TSH/alpha-GSU adenoma (89). The calculation of the alpha-GSU/TSH molar ratio increases the diagnostic sensitivity of hormone measurements, and an alpha-GSU/TSH molar ratio above 1.0 was associated with the presence of a TSH-secreting pituitary adenoma (2, 8). However, data from our group show that the individual values must be compared with those of control groups matched for TSH and gonadotropin levels before drawing any diagnostic conclusions. Controls with normal levels of TSH and gonadotropins may have alpha-GSU/TSH molar ratios as high as 5.7, and values as high as 29.1 can be found in euthyroid postmenopausal women (173). Indeed, hypersecretion of alpha-GSU is not unique to TSH-omas, being present in the majority of true gonadotropinomas, in a subset of non-functioning pituitary adenomas, and in a number of GH- or PRL-secreting tumors. Moreover, high alpha-GSU levels may be observed in conditions other than pituitary adenomas, such as in patients with inflammatory bowel disease (e.g., ulcerative colitis, Crohn disease) or with other neuroendocrine tumors (e.g., carcinoids) (173).

## PARAMETERS OF THYROID HORMONE ACTION

Patients with central hyperthyroidism present with manifestations of thyroid hormone overproduction. Therefore, the measurements of several parameters of peripheral thyroid hormone action have been proposed to quantify the degree of tissue hyperthyroidism (2, 5-8, 98). Some of them are measured *in vivo* (basal metabolic rate, cardiac systolic time intervals, "Achilles" reflex time) and others *in vitro* (sex hormone-binding globulin: SHBG, cholesterol, angiotensin converting enzyme, soluble interleukin-2 receptor, osteocalcin, carboxyterminal cross-linked telopeptide of type I collagen (ICTP or CTX)). Liver (SHBG) and bone parameters have been successfully used to differentiate hyperthyroid patients with TSH-omas from those with RTHβ (Figure 3). In fact, as seen in the common forms of hyperthyroidism, patients with TSH-omas have high SHBG and ICTP levels, while they are in the normal range in patients with RTHβ (174,175).

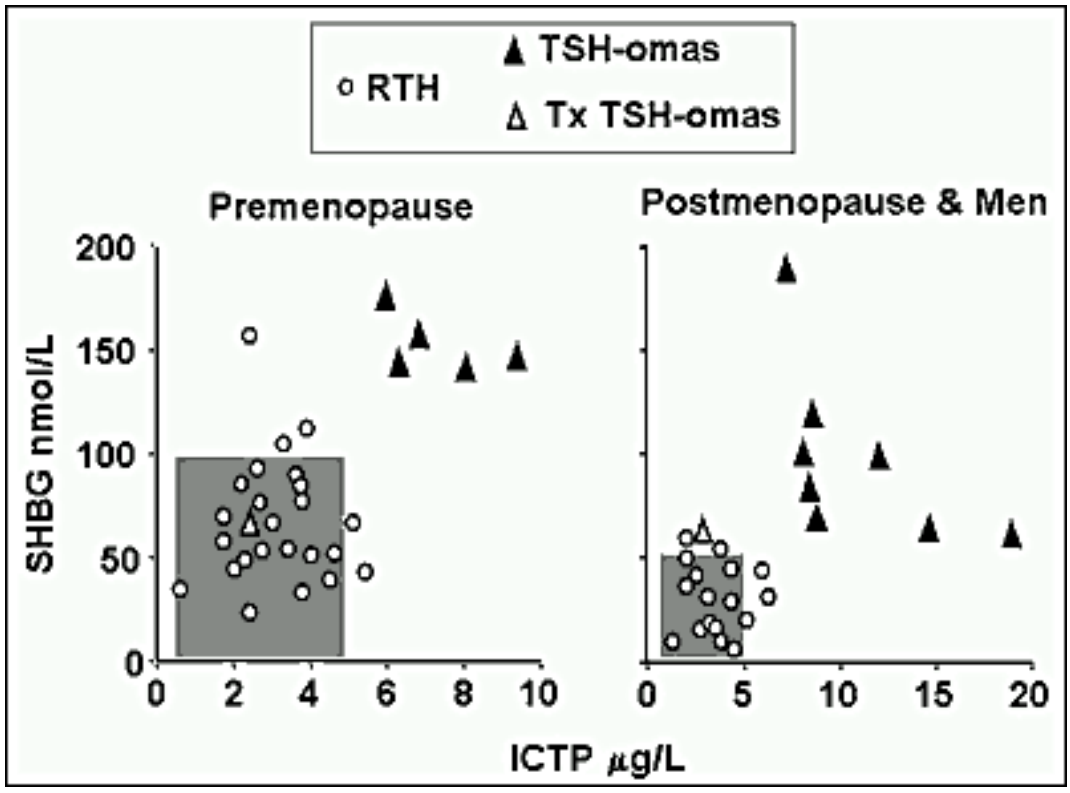


**Figure 3. Values of sex hormone-binding globulin (SHBG) and carboxyterminal cross-linked telopeptide of type 1 collagen (ICTP or CTX) in patients with RTHβ or TSH-omas. Shaded areas represent the normal ranges either in premenopausal women or in postmenopausal women and men. The combined measurement of parameters from different tissues may be useful for the differential diagnosis and by-pass possible interference by different factors (age, liver or bone diseases, combined alteration of pituitary functions, treatments, etc.). Tx TSH-omas, treated TSH-omas.**

## DYNAMIC TESTING

Although both stimulatory and inhibitory tests had been proposed for the diagnosis of TSH-omas, none of them is of clear-cut diagnostic value. Classically, the T3 suppression test has been used to assess the presence of a TSH-oma. A complete inhibition of TSH secretion after T3 suppression test (80-100 mcg/day for 8-10 days) has never been recorded in patients with TSH-omas. The T3 suppression test can be combined with TRH testing, where normal subjects and TSH-oma patients do not show a TSH response to TRH, while RTHβ patients maintain a brisk elevation (1, 152). In patients with previous thyroid ablation, T3 suppression is the most sensitive and specific test in assessing the presence of a TSH-oma (2, 8, 117,152). However, this test is strictly contraindicated in elderly patients or in those with heart disease.

TRH testing has been widely used to investigate the presence of a TSH-oma. In the vast majority of patients, TSH and alpha-GSU levels exhibit a blunted response after TRH injection (1,152). In patients with hyperthyroidism, discrepancies between TSH and alpha-GSU responses to TRH (i.e., higher alpha-GSU than TSH response) are pathognomonic of TSH-omas cosecreting other pituitary hormones. Such a discrepancy is also found in an opposite clinical condition, i.e., the congenital hypothyroidism due to a TSH beta gene mutation (176).

The majority of TSH-omas maintain sensitivity to native somatostatin and its analogues. Indeed,

administration of the native neuropeptide or its analogues (e.g., octreotide or lanreotide) induces a reduction of TSH levels in the majority of cases, and these tests may be predictive of the efficacy of long-term treatment (30, 119, 122, 123, 152). Recently, it has been confirmed that a positive somatostatin test result is suggestive for a TSH-oma even before positive findings become apparent on pituitary imaging (123, 152).

As suggested by the 2013 guidelines by the European Thyroid Association, we recommend the use of both T3 suppression and TRH tests whenever possible, because the combination of their results increases the specificity and sensitivity of the diagnostic work-up (152).

## IMAGING STUDIES AND LOCALIZATION OF THE TUMOR

As for other tumors of the region of the sella turcica, nuclear magnetic resonance imaging (MRI) is nowadays the preferred tool for the visualization of a TSH-oma. High-resolution computed tomography (CT) is the alternative investigation in the case of contraindications. Most TSH-omas have been diagnosed in the past at the stage of macroadenomas, and various degrees of suprasellar extension or sphenoidal sinus invasion are seen in two thirds of cases.

Microadenomas are now reported with increasing frequency in several clinical and surgical series. Pituitary scintigraphy with radiolabeled octreotide (*Octreoscan*) has been shown to successfully localize TSH-omas that express somatostatin receptors (8, 177,178). However, the specificity of the *Octreoscan* is low, since positive scans can be seen in the case of a pituitary mass of different types, either secreting or non-secreting. The risk of assigning a wrong diagnosis of TSH-oma when a pituitary lesion is found associated with the biochemical features of central hyperthyroidism should always be considered before sending the patient to neurosurgery. Confirmatory testing is therefore recommended to exclude the possible association of RTHβ with a non-functioning pituitary lesion (152).

Finally, ectopic localization of a TSH-oma has been reported by different groups who found a nasopharyngeal mass in 16 patients (2.1% of total cases, Table 1) with clinical and biochemical features of central hyperthyroidism (21, 32, 83, 84,179-185). Histological and immunohistochemical studies of both specimens collected during the operation showed unequivocally that the tumor was a TSH-oma, and the resection of the mass restored TSH and alpha-GSU levels to normal. Interestingly, in these cases either the Octreoscan or a Gallium 68 DOTATATE Positron Emission Tomography/Computed Tomography might be helpful in identifying an ectopic lesion (185).

## DIFFERENTIAL DIAGNOSIS

If FT4 and FT3 concentrations are elevated in the presence of measurable TSH levels, it is important to exclude methodological interferences due to the presence of circulating autoantibodies (e.g., against T3 and T4) or heterophilic antibodies (e.g., for TSH). A recent publication by Campi and others indicated assay interference as the main source of error due to the widespread use of high-throughput platforms based on one-step assays that increased the frequency of assay artifacts, due to interference from biotin, circulating heterophilic antibodies or abnormal binding proteins (152). In an asymptomatic patient with elevated FT4/FT3 and a normal TSH level, it is particularly important to consider Familial Dysalbuminemic Hyperthyroxinemia (FDH) in the differential diagnosis. FDH is a familial autosomal dominant condition caused by an abnormal albumin molecule with an increased affinity for serum thyroxine thus leading to an increase in total T4 and, with many immunometric assays, a false increase of FT4 and FT3 (165, 186). The diagnosis of FDH can now be easily confirmed or excluded by mutational analysis of the *albumin (ALB)* gene. In a patient with signs and symptoms of hyperthyroidism, the confirmed presence

of elevated FT4/FT3 and detectable TSH levels rules out Graves' disease or other forms of primary hyperthyroidism. In patients receiving levothyroxine replacement therapy or suppressive therapy, the detection of measurable/high TSH levels with concomitantly high FT4/FT3 levels may be suggestive of an underlying TSH-oma. However, noncompliance (high TSH) or intake just prior to blood collection should be ruled out (187).

When the existence of central hyperthyroidism is confirmed, several diagnostic steps should be carried out to differentiate a TSH-oma from RTHβ and avoid inappropriate treatments (Table 2) (1, 5-8, 30, 119, 122, 123, 152, 158, 188). The presence of neurological signs and symptoms (visual defects, headache) of an expanding intra-cranial mass or clinical feature of concomitant hypersecretion of other pituitary hormones (acromegaly, galactorrhoea/amenorrhea) points to the presence of a TSH-oma. The presence of alterations of the pituitary content on MRI or CT scanning strongly supports the diagnosis of a TSH-oma. Nevertheless, the differential diagnosis may be difficult when the pituitary adenoma is small, or in the case of confusing lesions, such as an empty sella. Moreover, the possibility of pituitary incidentalomas should always be considered, due to their high prevalence. In our series, about 20% of RTHβ patients have a pituitary lesion on MRI.

No significant differences in age, sex, previous thyroid ablation, TSH levels or free thyroid hormone concentrations were seen between patients with TSH-oma and those with RTHβ. However, in contrast to RTHβ patients, familial cases of TSH-oma have never been documented. Therefore, one of the most specific tools to uncover RTHβ is the search of the biochemical signature of central hyperthyroidism in the first-degree relatives of the proband case, as the biochemical signature co-segregates with the inheritance of the dominant negative mutation in the *THRB* gene (6). Serum TSH levels within the normal range are more frequently found in RTHβ, while elevated alpha-GSU concentrations and/or a high alpha-GSU/TSH molar ratio are typically present in patients with TSH-omas. Moreover, a blunted TSH response to TRH stimulation and/or to T3 suppression tests favors the presence of a TSH-oma. We have shown that chronic administration of long-acting somatostatin analogues in patients with central hyperthyroidism caused a marked decrease of FT3 and FT4 levels in all patients but one with TSH-oma, while patients with RTHβ do not respond at all (30). Thus, administration of long-acting somatostatin analogues for 2 months (Octreotide LAR 30 mg injection at days 0 and 28, with TSH, FT4, FT3 determination at baseline and after 28 and 56 days) can be very useful in establishing the etiology of central hyperthyroidism (30, 152) (Table 2). Very recently, a Chinese group suggested the potential utility of a short octreotide test for the confirmation of the diagnosis of TSH-oma (75); however, this new finding requires confirmation on additional cases.

Indicators of thyroid hormone action at the tissue level (such as SHBG or ICTP/CTX levels) are in the hyperthyroid range in most patients with TSH-omas, while they are generally normal/low in RTHβ (Figure 3). Exceptions are the findings of normal SHBG levels in patients with mixed GH/TSH adenomas, due to the inhibitory action of GH on SHBG synthesis and secretion, and of high SHBG in RTHβ patients treated with estrogens or affected by profound hypogonadism. Genetic analyses of the *THRB* gene are useful in the differenital diagnosis since germline mutations are found in about 90% of patients with a RTHβ phenotype (Table 2).

**Table 2. Differential Diagnosis Between TSH-Secreting Adenomas (TSH-omas) and Resistance to Thyroid Hormone beta (RTHβ).**

| Parameter | TSH-omas | RTHβ | P |
|---|---|---|---|
| Female/Male ratio | 1.3 | 1.4 | NS |
| Familial cases | 0 % | 85 % | <0.0001 |
| TSH mU/L | 3.0 ±0.4 | 2.3 ±0.3 | NS |
| FT4 pmol/L | 38.8 ±3.9 | 29.9 ±2.3 | NS |
| FT3 pmol/L | 14.0 ±1.2 | 11.3 ±0.8 | NS |
| Lesions on CT or MRI | 99 % | 23 % | <0.0001 |
| Germline THRB mutation | 0% | 84% | <0.0001 |
| High biological activity of circulating serum TSH | 38% | 90% | NS |
| High alpha-GSU levels | 69 % | 3 % | <0.0001 |
| High alpha-GSU/TSH molar ratio | 81 % | 2 % | <0.0001 |
| Elevated SHBG and/or ICTP/CTX | 90% | 8% | <0.0001 |
| Blunted TSH response to TRH test (delta TSH cutoff <3 mU/L in males and <5 mU/L in females) | 87 % | 2 % | <0.0001 |
| Abnormal TSH response to T3 suppression[a] | 100 % | 100 % [b] | NS |
| FT4/FT3 reduction/normalization during long-acting somatostatin analogue | 92% | 0% | <0.0001 |

[a] Werner's test (80-100 µg T3 for 8-10 days). Quantitatively normal responses to T3, i.e. complete inhibition of both basal and TRH-stimulated TSH levels, have never been recorded in either group of patients.

[b] Although abnormal in quantitative terms, TSH response to T3 suppression test was qualitatively normal in 45/47 RTHβ patients.

[c] Two or more injections of somatostatin analogues (e.g., Octreotide-LAR 30 mg every month or Lanreotide Autogel 120 mg every 6-8 weeks).

Only patients with intact thyroid were taken into account. Data are obtained from patients followed at our Department and are expressed as mean ± SE.

## TREATMENT AND OUTCOMES

As stated in the 2013 guideline by European Thyroid Association (188), surgical resection is the recommended therapy for TSH-secreting pituitary tumors, with the aim of removing neoplastic tissue and restoring normal pituitary/thyroid function. However, radical removal of large tumors can be particularly difficult because of the marked fibrosis of these tumors and the local invasion involving the cavernous sinus, internal carotid artery, and/or the optic chiasm. Considering the propensity toward high invasiveness, surgical removal or debulking of the tumor by transsphenoidal or subfrontal adenomectomy, depending on the tumor volume and its suprasellar extension, should be undertaken as soon as possible (189). According to the review of 535 cases of TSH-omas by De Herdt and others, surgical resection of the adenoma was performed in 87.7% of patients of which 33.5% had residual adenomatous tissue (61). Particular attention has to be paid to the presurgical preparation of the patient, particularly in the

preanesthetic period (190): antithyroid drugs or octreotide along with propranolol should be used, aiming at restoration euthyroidism. In patients with very severe hyperthyroidism, the administration of iopanoic acid has been successfully employed (25). Though the preoperative treatment with long-acting somatostatin analogues may be useful to reduce hyperthyroid signs and symptoms in a significant number of patients, as well as the adenoma size (190-193), no correlations between FT4/FT3 normalization and a higher rate of remission has been demonstrated (70). However, a recent multicenter, single-arm, phase 3 study in Japan confirmed that preoperative lanreotide autogel treatment was effective in normalizing thyroid function in 10/13 patients with TSH-omas, and to induce a -23.8% median percent change in pituitary tumor size from baseline at final assessment (194). Finally, a single report on the efficacy of pasireotide in the pre-operative treatment of a TSH-omas has been published (195). The adjuvant treatment with long-acting somatostatin analogues is nowadays more frequently prescribed in TSH-secreting macroadenomas prior to neurosurgery.

It is worth noting that somatostatin analogues may lead to a condition of TSH deficiency. In the series published by Illouz and others, TSH deficiency appeared in 15% of 46 treated TSH-omas after a median time of 4 weeks, the TSH deficiency occurring after one to three injections of long-acting somatostatin analogues (196). These data suggest that thyrotropic function should be reassessed after the first three injections of somatostatin analogues in order to diagnose TSH deficiency and to reduce the frequency or the dose of injections when control of thyrotoxicosis is the aim of the treatment.

After surgery, partial or complete hypopituitarism may result (197,198). However, a case of thyroid storm after pituitary surgery was documented (199). Evaluation of pituitary function, particularly ACTH secretion, should be carefully undertaken soon after surgery and hormone replacement therapy must be initiated, if indicated. In case of failure of pituitary surgery such as incomplete resection or tumor regrowth, and in the presence of life-threatening hyperthyroidism, total thyroidectomy or thyroid ablation with radioiodine is indicated (200).

According to the largest published series, pituitary surgery is effective in restoring euthyroidism in 75% to 83% of patients with TSH-omas (63, 75, 88, 201), and a metanalysis by Cossu and others showed that the pooled rate of postoperative biochemical remission was 69.7% and a gross total resection was observed in 54% of patients (70). As expected, the extent of resection was significantly increased in microadenomas and cavernous sinus invasion was predictive of lower gross total resection (70).

If pituitary surgery is contraindicated or declined, as well as in the case of surgical failure, pituitary radiotherapy and/or medical treatment with somatostatin analogues (octreotide or lanretotide) are valid alternatives (152, 188). In the case of radiotherapy, the recommended dose is no less than 45 Gy fractionated at 2 Gy per day, or 10-25 Gy in a single dose if a stereotactic gamma knife is available (188, 202,203). Radiotherapy and radiosurgery are effective in normalizing thyroid function in 37% of patients within 2 years (97). The successful experience of an invasive TSH-oma associated with an unruptured aneurysm treated by two-stage operation and gamma knife has been reported (204). Although earlier diagnosis has improved the surgical cure rate of TSH-omas, several patients have required medical therapy in order to control the hyperthyroidism. Dopamine agonists, and particularly cabergoline, have been employed in some TSH-omas with variable results, positive effects being mainly observed in some patients with mixed PRL/TSH adenomas (146, 205, 206). Today, the medical treatment of TSH-omas relies on long-acting somatostatin analogues, such as octreotide or lanreotide (12, 13, 119, 188, 207-210). Indeed, many studies suggest the use of somatostatin analogues as first-line therapy for patients with TSH-omas, particularly for invasive macroadenomas (207, 211-213). Treatment with these analogues lead to a reduction of TSH and alpha-GSU secretion in almost

all cases, with restoration of the euthyroid state in the majority of them, and it is safe even during pregnancy (18, 24, 215, 216). During somatostatin analogue therapy, tumor shrinkage occurs in about 50% of patients and vision improvement is seen in 75% (63, 97, 217). Very rapid shrinkage of the tumor has also been described (34). Resistance to octreotide treatment has been documented in a few cases. Patients on somatostatin analogues have to be carefully monitored, as untoward side effects, such as cholelithiasis and carbohydrate intolerance, may become manifest. The dose administered should be tailored for each patient, depending on the therapeutic response. Tolerance is usually very good, as gastrointestinal side effects are transient with long-acting analogues (12, 13, 57, 217). As a whole, post-operative treatment with a somatostatin analogue induces a biochemical remission (70) or lesds to stable disease in the vast majority of patients with residual tumors (61).

## CRITERIA OF CURE AND FOLLOW-UP

Due to the rarity of the disease and the great heterogeneity of the methods used, the criteria of cure of patients operated or irradiated for TSH-omas has not been clearly established. Previous thyroid ablation makes some of these criteria inapplicable (Table 3).

**Table 3. Criteria for the Evaluation of the Outcome of Treatment**

| Criteria | Comments |
|---|---|
| Remission of hyperthyroid manifestations (clinical and biochemical) | Clinical improvement may be transient<br>No predictive value |
| Disappearance of neurological manifestations (adenoma imaging, visual field defects, headache) | May be transient<br>Poor predictive value |
| Normalization of free thyroid hormone levels | Biochemical remission may be transient<br>Poor predictive value |
| Normalization of circulating TSH levels | Not applicable to patients with TSH in the reference range<br>Poor predictive value |
| Undetectable TSH one week after neurosurgery | Applicable to hyperthyroid patients that stopped treatments at least 10 days before surgery<br>Good prognostic value |
| Normalization of alpha-GSU levels and alpha-GSU/TSH molar ratio | Not applicable to patients with normal values before neurosurgery<br>Lack of sensitivity |
| Positive T3-suppression test with undetectable TSH and no response to TRH (or central hypothyroidism) | Not applicable to elderly patients or in those with cardiac diseases<br>Optimal sensitivity/specificity and predictive value |

In previously hyperthyroid patients achieving euthyroidism through therapy, it is reasonable to assume that they are in remission. However, the findings of normal free thyroid hormone concentrations or indices of peripheral thyroid hormone action (SHBG, ICTP/CTX, etc.) are not

synonymous of complete removal or destruction of tumoral cells, since transient clinical remission with relapse at a later time point is possible (63, 64, 70, 117, 140). Disappearance of neurological signs and symptoms is also a good prognostic event. The resolution of specific neuroradiological abnormalities is not always conclusive, since pituitary imaging performed soon after surgery is often difficult to interpret. The criteria of normalization of circulating TSH is not applicable to previously thyroidectomized patients and to the 26% of patients with normal basal values of TSH. In our experience, undetectable TSH levels one week after surgery are likely to indicate complete adenomectomy, provided that adjuvant treatments to control hyperthyroidism have been stopped before surgery (140). A recent publication from a Korean group analyzing the outcomes of adenomectomy in a series of 31 TSH-omas found that immediate postoperative TSH level at 12 hours after surgery, with a cutoff at 0.62 µIU/mL, was the strongest predictor of cure (165a). Normalization of alpha-GSU and/or the alpha-GSU/TSH molar ratio is in general a good index for the evaluation of the succes of therapy (8, 140). However, both parameters can be normal in about 25% of patients with TSH-omas prior to surgery. The most sensitive and specific test to document the complete removal of the adenoma remains the T3 suppression test (140). In fact, only patients in whom T3 administration completely inhibits basal and TRH-stimulated TSH secretion, appear to be truly cured.

Few data on the recurrence rates of TSH-omas in patients judged cured after surgery or radiotherapy have been reported. However, recurrences of the adenoma do not appear to be frequent, at least in the first years after successful surgery (64, 140). In general, the patient should be evaluated clinically and biochemically 2 or 3 times during the first year after surgery, and then every year. Pituitary imaging should be performed every two or three years but should be promptly done whenever an increase in TSH and thyroid hormone levels, or clinical symptoms of hyperthyroidism occur. In the case of a persistent macroadenoma, close visual field follow-up is required, as visual function could be threatened. Emergency surgical decompression is not always able to reverse even a recent visual deficit.

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