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Thyrotropin-secreting pituitary adenomas: a systematic review and meta-analysis of postoperative outcomes and management

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Abstract

Purpose TSH-secreting pituitary adenomas are rare pituitary tumors. An efficient treatment is essential to limit the mortality and morbidity in untreated patients. The aim of this study is to summarize the evidence about the postoperative outcomes and management of this rare pathology.

Methods A systematic search and meta-analysis of surgical series was performed.

Results Our analysis included 23 articles (536 patients). No sex difference was observed and mean age at diagnosis was 45 years. Hyperthyroidism was reportedly clinical in 67% and biochemical in 90% of patients. Co-secretion of other pituitary hormones was present in 42% of cases. Macroadenomas were found in 79% of patients, showing in 44% and 30% of cases respectively extrasellar extension and cavernous sinus invasion. The pooled rate of postoperative biochemical remission was 69.7% and a gross total resection (GTR) was observed in 54% of patients. The extent of resection was significantly increased in microadenomas ($p < 0.001$) and cavernous sinus invasion was predictive of lower GTR rate ($p < 0.001$). A biochemical remission was achieved in 66% of patients after adjuvant radiation therapy and in 76% after adjuvant medical treatment. The combination of both allowed remission in 67% of cases. At final follow-up the overall biochemical remission rate was significantly improved (85.8%) when compared to the postoperative biochemical remission ($p < 0.001$).

Conclusion When compared to the early postoperative period, at last follow-up biochemical remission was significantly greater ($p < 0.001$). GTR was achieved in half of patients; the size of tumor and cavernous sinus invasion determined the extent of resection.

Keywords Endoscopy · Pituitary adenoma · SITSH · Thyrotropin secreting adenoma · Transsphenoidal · TSH-secreting adenoma

Introduction

TSH-secreting pituitary adenomas (TSH-omas) are rare entities and represent 0.5–3% of pituitary adenomas in surgical series [1, 2]. Their pathogenesis is still unknown: TSH-omas are monoclonal and the fact that TSH-producing cells account for < 5% of pituitary cells might explain the rarity of these tumors [2, 3]. To date, no specific mutations in oncogenes or anti-oncogenes have been characterized [4, 5]. Functioning adenomas present a combination of transcription factors similar to those observed in physiological conditions [6] and Pit-1 and GATA-2 might play a key role in the development of TSH-omas. Some papers advance a possible role of mutations of the thyroid hormone receptor, responsible for refractoriness to the inhibitor effect of thyroid hormone. This might favor

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TSH-omas development [7–9]. The correct diagnosis and an early treatment are imperative because of the higher risk of mortality and morbidity in patients with untreated hyperthyroidism [10]. The surgical treatment is considered the mainstay of treatment and the transsphenoidal approach is considered the gold standard [11].

TSH-omas are generally diagnosed as macroadenoma and usually present an extrasellar extension. According to literature data, a gross total resection (GTR) may be achieved in a variable percentage of cases (14–84%) [12–15] and the factors limiting the extent of resection are the important intralesional fibrosis and the suprasellar extension or cavernous sinus invasion of the tumor at diagnosis [16–18]. The biochemical remission is also highly different among studies and may vary from 30 to 96% [19, 20].

The 2013 European Guidelines [21] on the subject clearly state that the criteria of cure for patients with TSHomas operated and/or irradiated have not been clearly established. The clinical remission of hyperthyroidism, resolution of neurological symptoms and of radiological abnormalities and biological normalization of thyroid hormones and TSH are the factors commonly considered. However none seems to be useful in predicting cure and long-term remission.

Adjuvant treatments such as radiotherapy and medical therapy, most frequently somatostatin receptor ligands (SRL) and dopamine agonists (DA), may be considered in cases of persistent disease after surgery [11, 12, 15, 16]. Some authors recently suggest that SRL may play a role in the treatment of these adenomas as primary therapy [15, 22–27].

In this context we aimed to review all the surgical series treating TSH-secreting adenomas to summarize the literature evidence and obtain objective data on epidemiology, postoperative outcomes in terms of GTR and biochemical remission and establish the role of adjuvant treatments to update the knowledge on this field.

Materials and methods

Search strategy

A literature search was performed using PubMed platform and including articles published from January 1990 till March 2018. The search was performed using the MeSH terms: “Thyrotropin” AND “Pituitary Neoplasms”.

The “related articles” function was used to find additional pertinent studies and a screening of the bibliography of included studies was performed manually to identify any relevant report. No unpublished data or congress presentations were included.

Study selection

Two authors (GC and MM) reviewed independently all the titles and abstracts to assess eligibility. Included study fulfilled the following requirements:

1. include patients with TSH-secreting pituitary adenomas;
2. patients should be treated through a surgical procedure alone or combined with any other neoadjuvant or adjuvant treatment
3. the postoperative outcome should be reported, in terms of clinical and biochemical remission and radiological extent of resection.

Reviews, case reports and small case series reporting ≤ than 5 patients were not included. Also larger series with no surgical treatment or where the postoperative outcomes were not specified were excluded.

Only studies in English, French, Italian, German and Spanish were considered.

Data abstraction

Two authors (GC and MM) independently abstracted epidemiological and clinical data as well as radiological features. Adenomas were classified as microadenomas when the size was < 10 mm and macroadenoma when the diameter was ≥ 10 mm. The cavernous sinus invasion was defined as present or absent and the Knosp classification was reported when specified.

Authors also analyzed the treatments performed in terms of surgical procedures, neoadjuvant and adjuvant treatments as well as the clinical and biological outcomes in the early postoperative period and at follow-up. The criteria used to define remission were also reported for each article included.

Statistical analysis

We used meta-analytic techniques to calculate a pooled estimate of the postoperative outcomes in terms of biochemical remission and extent of resection (weighted summary rates were obtained through meta-analysis models) and we stratified the results according to the tumor size (macro versus microadenoma) and to the cavernous sinus invasion.

The pooled postoperative biochemical remission was defined as the normalization or detection of low levels of thyroid hormones and TSH and it was recorded in the immediate postoperative period, after adjuvant treatments

and at last follow-up. The extent of resection was defined as GTR or subtotal resection on the basis of the postoperative imaging.

Tests for heterogeneity were performed for each meta-analysis and if the heterogeneity was significant, a binary random effects model (DerSimonian-Laird method) was used. The random effects model incorporates the variance of treatment effect and gives the magnitude of heterogeneity of treatment effect.

The OpenMetaAnalyst platform from AHRQ was used to perform these analyses.

If a 100% or a 0% success rate were reported, the variance was estimated as the pooled variances obtained from the other studies. Fisher exact test was performed to check the independence of categorical variables recorded in the population of study. Values of $p < 0.05$ were considered statistically significant.

Results

The literature search identified a total of 651 articles. After exclusion of 628 articles, 23 full-text articles were included for further analysis [2, 11–17, 19, 20, 28–40] for a total of 536 patients (Fig. 1 flow chart).

Seventeen studies were monocentric [12–14, 17, 19, 20, 28–30, 32–35, 37–40] and 6 multicentric [2, 11, 14–16, 31, 36]. All the included studies were retrospective analysis except one, which was prospective [40].

The remission criteria varied among studies and in one study they were not directly defined in the text [19]. They are reported in details in Table 1.

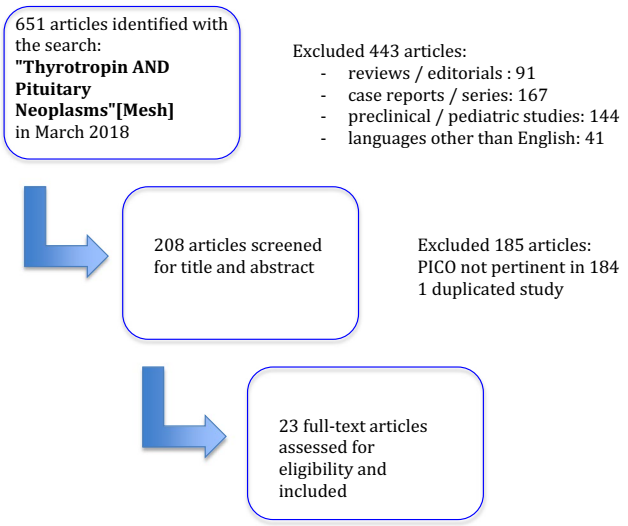

Fig. 1 Flow chart illustrating the procedure of article selection

Cohort description

A total of 536 patients were described in surgical series of TSH-secreting adenomas. There were no differences in sex ratio (260 males, 48%) and the mean age at diagnosis was 45 years. 67% of patients presented a clinical hyperthyroidism (241/358), while 90% presented a biochemical hyperthyroidism (410/455).

Patients without clinical symptoms of hyperthyroidism (23%) were diagnosed during headaches investigations or secondarily to the presence of visual symptoms. In most of cases a blood test confirmed the TSH-dependent hyperthyroidism and only in a minority of cases (10%) there was no biochemical hypersecretion. In these cases the diagnosis of TSH-secreting adenoma was possible thank to the immunohistochemical analysis, which was positive for TSH.

A biological cosecretion was described in 42% of patients (147/350), most frequently GH and PRL (in 53% and 40% of cases respectively) (Fig. 2).

Macrodenomas were reported in 79.6% of patients (395/499). The percentage of microadenomas diagnosed in surgical series significantly increased in papers published after 2000 (22% versus 11% before 2000, Fisher exact test $p = 0.04$).

The presence of an "extrasellar extension" was specified in 15 studies [11, 14–17, 19, 28, 31–36, 38, 40] and it was present in 44.5% of cases (146/328).

The invasion of the cavernous sinus is a well-recognized factor predictive of biological aggressiveness [41]. It was specified only in 12 studies [12–17, 19, 28, 30–32, 37] and it was present in 30% of cases (95/315). Only one study [12] used the Knosp classification [42].

Immunohistochemical analysis other than TSH was specified in 14 articles [13, 14, 16, 17, 28–32, 35–39] and the staining for other pituitary hormones was variable between 20 and 100%. Most frequently tumor tissue stained for GH and PRL.

Post-operative outcomes

The postoperative follow-up was available in 92.5% of patients (496/536).

Biochemical remission

The biochemical remission in the postoperative period was specified in 21 studies [2, 11–17, 19, 20, 29–34, 36–40] and it was achieved in 69.7% of cases (95% CI 61.1–78.4%). A binary random-effects estimate analysis was used because of evidence of heterogeneity ($I^2 = 83\%$; $p < 0.001$), (Fig. 3).

Table 1 The characteristics of each study and the remission criteria used are specified for every study included in our analysis

Article	No. of pts	Type of study				Remission criteria				
		Monocentric	Multicentric	Retrospective	Prospective	TH and TSH normalization	TH and TSH normalization at stimulation tests	Normalization of cosecretion	No residue at postop MRI	Long-term FU (> 12mo)*
Rotermund 2017 [20]	15	x		x		x				x
Astaf'eva 2016 [28]	21	x		x		x			x	
Azzalin 2016 [13]	20	X		x		x			x	
Gatto 2015 [31]	13		x	x		x			x	x
Kirkman 2014 [32]	32	x		x		x			x	x
Malchiodi 2014 [11]	70		x	x		x	x	x	x	x
Van Varsseveld 2014 [15]	18		x	x		x			x	x
Yamada 2014 [12]	90	X		x		x		x	x	x
Onnestam 2013 [2]	28		X	x		x			x	x
Zhao 2012 [40]	8	X			x	x			x	x
Elston 2010 [19]	6	x		x		x	x		x	x
Macchia 2009 [34]	26	X		X		x			x	x
Marucci 2009 [14]	10	X		x		x			x	x
Clarke 2008 [30]	21	X		x		x			x	x
Ness-Abramof 2007 [36]	11		X	x		x			x	x
Socin 2003 [16]	43		x	x		x			x	x
Wu 2003 [38]	7	X		X		x	X		x	
Sanno 2000 [37]	16	x		x		x	x		x	x
Brucker-Davis 1999 [17]	25	X		x		x	x		x	x
Losa 1999 [33]	24	X		X		x			X	
Mindermann and Wilson 1993 [35]	19	X		X		x				x
Wynne 1992 [39]	6	X		X		x			x	x
Beckers 1990 [29]	7	x		x		x				

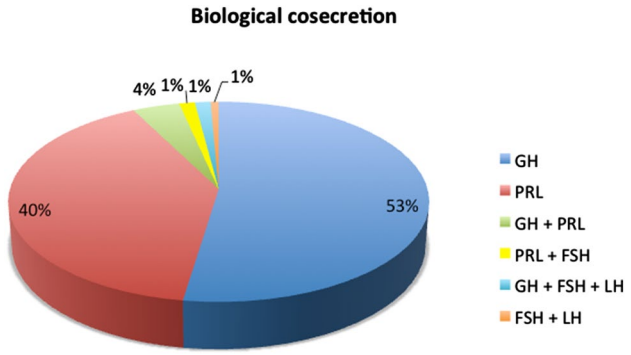

Fig. 2 Graphical representation of the distribution of the co-secretion of TSH with other pituitary hormones. Most of patients presented as associated secretion of TSH and GH or TSH and PRL

Extent of resection

The extent of resection was specified in 19 studies [11–17, 19, 28, 30–34, 36–40] and GTR was obtained in 54.1% of cases (95% CI 41.2–66.9%; test for heterogeneity $I^2 = 89.2\%$, $p < 0.001$) (Fig. 4).

When the adenomas were stratified according to the size, GTR was obtained in 49% of cases of macroadenomas (95% CI 32–66%; test for heterogeneity $I^2 = 90.6\%$, $p < 0.001$) and in 87% of microadenomas (95% CI 76.6–96.7%; test for heterogeneity $I^2 = 47.6\%$, $p = 0.05$) (Fig. 5).

A statistically significant difference was found between the two groups ($p < 0.001$).

GTR in cases of cavernous sinus invasion was specified only in 6 studies [12, 14, 17, 19, 28, 30] and it was obtained only in 15.6% of cases (10/49) presenting a cavernous sinus involvement at diagnosis (95% CI 2.2–29.3%; test for heterogeneity $I^2 = 50.1\%$, $p = 0.075$). The invasion of the cavernous sinus predicted an inferior rate of GTR ($p < 0.001$) (Fig. 5).

Only three studies [11, 17, 37] used a stimulation or suppression test in the early postoperative period (within 3 months from surgery) to verify the biological remission and only 39% of patients with a postoperative biological remission (26/66) presented a normal response to TRH stimulation or T3 suppression tests. It was not specified in these studies if these patients had a longer remission period than patients with abnormal provocative tests.

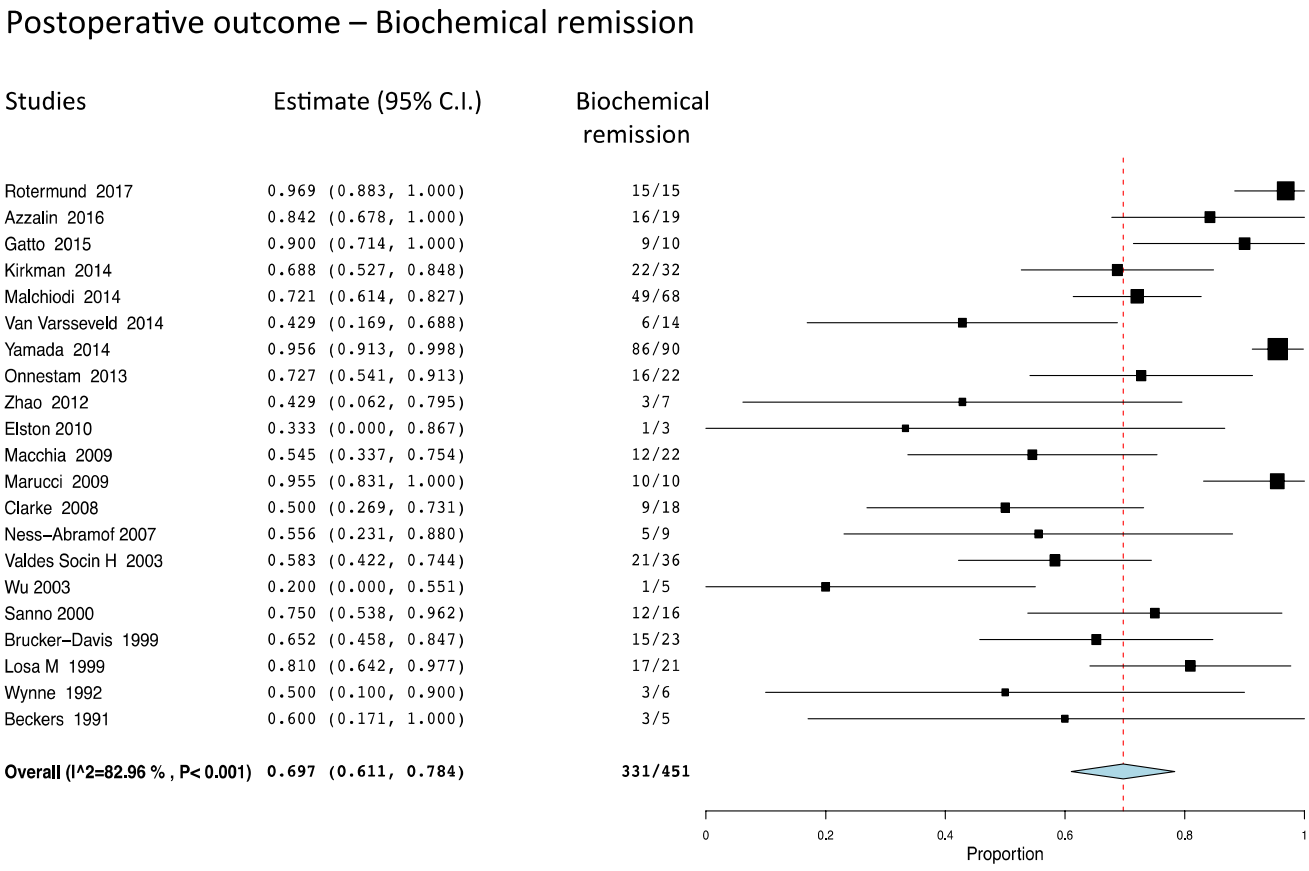

Fig. 3 The postoperative outcome in terms of biochemical remission with normalization or low levels of TSH and thyroid hormones is reported for every study included. It was achieved in about 70% of patients

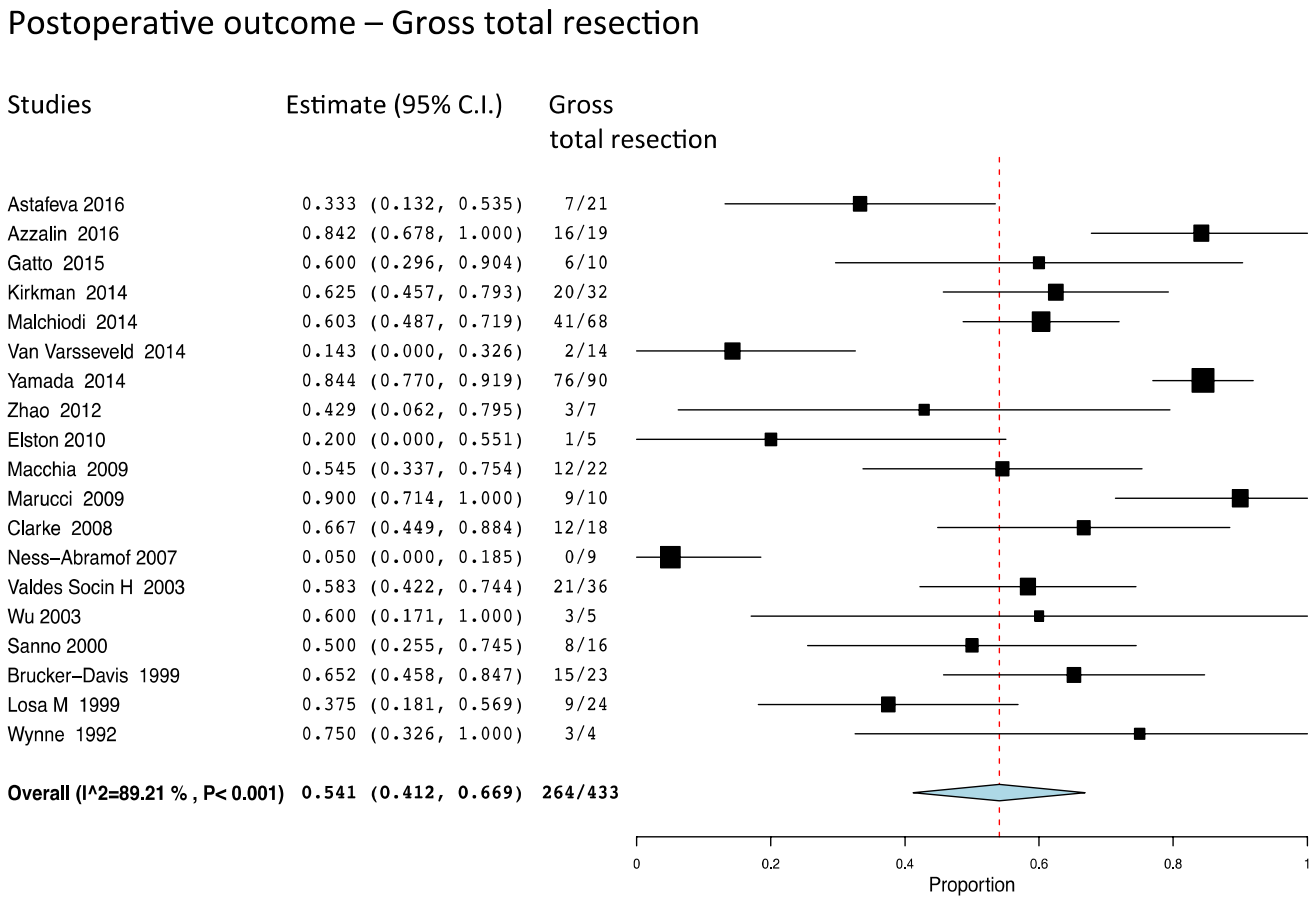

Fig. 4 The gross total resection rate, evaluated trough the analysis of postoperative MRI or CT scan, is specified for every study. The mean estimate was 54%

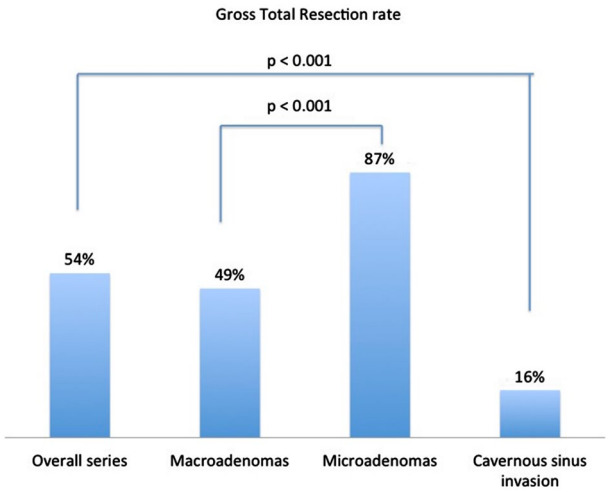

Fig. 5 Rates of gross total resection are stratified according to the size of the adenoma (macro versus micro-adenomas) and according to the invasion of the cavernous sinus. A statistically significant lower rate of gross total resection was noted in patients with macroadenomas (versus micro-adenomas, $p < 0.001$) and in patients with cavernous sinus invasion ($p < 0.001$)

Neo-adjuvant treatments

The percentage of misdiagnosed patients treated with chemical and surgical thyroid ablation is variable among studies, with a mean of 33.8%. Only 6 studies had no initial misdiagnosis [11, 13, 14, 31, 32, 36]. The rate of misdiagnosed patients significantly decreased in studies published after 2000 (17% versus 56% till 2000; $p < 0.001$).

A neo-adjuvant treatment was used in 34.5% of patients (167/484): SRL in 88% of cases and DA in 10% of cases, while a combination of both treatments was used in 2% of cases. Authors reported no differences in terms of postoperative outcomes when a neo-adjuvant treatment was administered [11, 13, 34] but a pooled data analysis was not possible.

Adjuvant treatments

Patients not in remission after surgery were treated with adjuvant treatments that included radiation therapy and medical therapy.

Adjuvant radiotherapy was administered using different protocols of treatment: 9 studies used stereotactic forms of radiotherapy as gamma knife radiosurgery or cyberknife [11, 12, 16, 17, 19, 30, 33, 34, 40] and 6 studies used fractionated pituitary irradiation [11, 12, 16, 17, 19, 30]. The dose administered for the stereotactic irradiation was specified in only one case [11] and it was between 15 and 25 Gy. The fractionated conventional radiotherapy was between 46 and 54 Gy with fractions of 2 Gy according to Malchiodi [11], 42–45 Gy in 28 treatments according to Socin [16] and 50 Gy according to Sanno [37].

Fifteen studies specified the biological outcome after adjuvant radiotherapy [2, 11–13, 16, 17, 19, 30–34, 37, 39, 40] and the use of radiation therapy allowed achieving a biochemical remission in 65,9% of patients (34/50; 95% CI 48–83,8%; test for heterogeneity $I^2 = 72.95\%$, $p < 0.001$) (Fig. 6). Radiation therapy favors reaching euthyroidism (OR 3.71, 95% CI 0.85–16.33).

The adjuvant medical treatment employed the use of SRL or DA. The choice was taken according to the presence of hormonal cosecretion and/or from the immunohistochemical analysis of the tissue if performed. Two studies also reported the use of antithyroid drugs as adjuvant treatment to achieve euthyroidism [33, 34]. Fifteen studies [12, 14–17, 19, 20, 29, 31–34, 36–38] specified patients' outcome after adjuvant medical therapies. Three studies used DA [20, 33, 37], while 3 others used SRL [17, 32, 36]. In 3 studies [12, 15, 38] a combination of both drugs was used. With the use of a medical adjuvant treatment, 76% of patients (36/44) reached a biochemical remission (95% CI 63.1–88.4%; test for heterogeneity $I^2 = 41\%$, $p = 0.048$) (Fig. 6). The use of a medical adjuvant treatment significantly favored the achievement of biochemical remission (OR 6.1, 95% CI 1.65–22.96).

No differences in terms of statistical significance were observed in terms of biochemical remission between radiation therapy and medical therapy ($p = 0.16$).

A combined adjuvant treatment, including radiation therapy associated with a medical treatment was used in patients not responsive to a single treatment to achieve a biochemical remission. The outcome was reported in 12 studies [2, 11–13, 15–17, 19, 32, 33, 36, 38] and a biochemical remission was reached in 28 out of 38 patients (67%, 95% CI 50.4–83.6%; test for heterogeneity $I^2 = 50.5\%$, $p = 0.023$); (OR 4.19, 95% CI 0.99–17.66) (Fig. 6).

A long-term follow-up was defined as a follow-up period longer than 24 months and it was reported in 17 articles (474 patients) [2, 11, 12, 14–17, 19, 30–32, 34–37, 39, 40]. When all the treatments were summarized, a biochemical remission was obtained in 85.8% (95% CI 80.7–90.8%) and a statistically significant difference was reported when compared with the postoperative biochemical remission ($p < 0.001$) (Fig. 6).

Unfortunately it was not possible to stratify the biochemical remission according to the size of the adenoma, as this was specified only in one study [34]. Intuitively we could suppose that the biochemical rate is better with microadenomas but no definitive conclusions on the subject are possible through the analysis of our data.

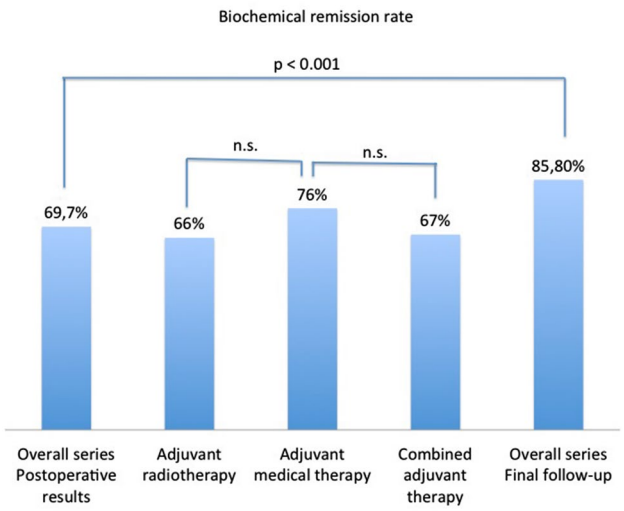

Fig. 6 The biochemical remission rate is stratified according to the treatment performed. A statistically significant difference was reported between the early postoperative remission and the remission recorded at last follow-up, when all the adjuvant treatment are summarized ($p < 0.001$)

Discussion

The number of patients diagnosed with TSHomas has tripled in the last decade [2, 43] and our knowledge about this rare pathology is improving thanks to an increase in the number of publications dealing with this subject. Through an extensive systematic review of the literature published on this subject since 1990, we want to summarize the existing knowledge on the state of the art of the surgical and adjuvant management of this rare variety of pituitary adenoma.

TSHomas present the same prevalence in both sexes. According to our meta-analysis, less than 70% of patients have clinical manifestations of hyperthyroidism and a biological profile of secondary hyperthyroidism was documented in 90% of cases. This means that about one-third of patients have no signs or symptoms of hyperthyroidism whilst 10% of patient may have no modification of the thyroid profile and are diagnosed essentially by immunohistochemistry, as clinical and radiological features are not specific.

Azzalin et al. [13] reported a series of 20 beta TSH-positive adenomas of which only 6 provoked a hyperthyroidism,

while 14 presented with headaches, mass effect or other hypersecretory syndromes. Silent TSHomas may thus be defined as tumors with TSH immunopositivity and no evidence of preoperative hypersecretion or mild hypersecretion and no clinical features. They seems to have a similar outcome than secreting adenomas [13, 32] but in our analysis it was not possible to stratify the postoperative outcomes according to the secretory status as patients were analyzed together in all study but two [13, 32].

Plurihormonal pituitary adenomas with biological co-secretion are considered rare but in the case of TSHomas a biological co-secretion was documented in 42% of cases and in some cases the primary clinical manifestation was acromegaly or galactorrhea rather than manifestations of hyperthyroidism. The prevalent co-secretion of GH and PRL is secondary to the fact that GH-PRL-and TSH-producing cells share the same cell lineage (Pit-1 lineage) [44].

According to our review, the immunohistochemistry stained positive for pituitary hormones other than TSH in a percentage of cases variable between 20 and 100%, thus superior than general series where plurihormonal pituitary adenomas represent 10–15% of all pituitary lesions [45].

When all the surgical series are considered together, in 80% of cases a macroadenoma is described. However a trend towards a greater prevalence of microadenomas is evident in more recent articles if the studies are stratified according to the year of publication. An earlier diagnosis is probably responsible for the higher rate of microadenomas described in the series published after 2000 ($p = 0.04$).

Thanks to the greater attention of clinicians, the number of misdiagnosed patients decreased over the years with an important drop after 2000 ($p < 0.001$). Improper thyroid ablation and administration of anti-thyroid agents or radioiodine neutralize the physiologic negative feedback loop of thyroid hormones and it is associated with the development of pituitary hyperplasia in patients with no previous pituitary disease [46, 47]. This has also a deleterious impact in patients with a known pituitary adenoma, as it is associated with an increase in size and aggressiveness of the tumor [1], like in Nelson's syndrome for Cushing's disease [48]. However, the real role of this absent negative feedback in TSH-oma pathogenesis is still matter of debate.

Tumor size was predictive of GTR, as a complete resection was achieved in 49% of macroadenomas versus 87% of microadenomas ($p < 0.001$). The invasion of the cavernous sinus was reported in 30% of cases, thus higher than other general series reporting an invasion in 6–10% of cases [49, 50]. In published series the rate of cure falls from 78 to 92 to 20–52% in cases of adenomas with parasellar extension [51]. Our analysis also confirms that TSH-omas follow a pattern similar to other secreting tumors, where cavernous sinus invasion is a factor predicting the extent of resection, as GTR declines from 54% for all the patients to 16% in cases presenting with cavernous sinus invasion ($p < 0.001$). According to our data, studies presenting a cavernous sinus invasion in less than 20% of cases report a GTR rate of 60–90% [13, 14, 31, 32], against 14–50% of GTR when the cavernous sinus invasion was reported in more than 50% of patients [15, 28, 37] ($p = 0.06$).

Other probable factors predicting GTR described in literature, such as tumor consistency and co-secretion of GH [12], were not analyzed. The Ki-67 was rarely specified and it didn't differ from other adenoma histotypes [32].

Since 2000 the endoscope was progressively introduced to perform trans-sphenoidal approaches [52–54], initially as an adjunct to microscopic techniques and then as primary tool to perform the procedure. However, even with these technological advances and higher prevalence of microadenomas, the GTR rate did not improve in series published before and after 2000 ($p = 0.13$).

The different studies are heterogeneous in their definition of remission criteria and the standardization of the term "cured" remains difficult with these rare tumors.

Surgical cure may be defined by the presence of a biochemical and clinical euthyroidism, associated with normalization of other pituitary hormones in cases of co-secretion [12] and absence of residual tumor on postoperative imaging [16, 17, 21, 30, 31, 55]. Nevertheless all these criteria are insufficient to predict a long-term remission, as recurrences were observed after GTR and complete biochemical remission in one-third of cases [15, 32].

Biochemical remission was observed in about 70% of cases and results seems to be better than those recorded using the 2010 remission criteria with GH-secreting adenomas [56] but similar to the results obtained using the 2000 remission criteria for GH secreting adenomas [56] and to those recently described in a cohort with Cushing's disease [57]. As in other secreting adenomas, a postoperative biochemical remission is not predictive of the extent of resection [12, 13, 37]. The residual tumor may in fact secrete hormones inefficiently and thus determine biochemical normalization, as described for GH adenoma [58, 59].

Nevertheless, unlike GH-adenomas, the cut-off of TSH value to define the surgical cure is not mentioned in literature. Losa et al. [18, 33] tried to define patients with long-term remission while measuring the TSH in the first postoperative week: no recurrence was observed during a mean follow-up of 44 months if the early postoperative TSH was undetectable. Also measurements of alpha subunit and TSH molar ratio as well as the TRH stimulation and T3 suppression tests were used to predict which patient would obtain a long-term remission. However, no conclusive results were obtained to support the widespread use of these measurements [16–18, 21, 33, 37].

The use of neoadjuvant treatments was not associated with improved postoperative outcomes [11, 13, 34] and the

presence of a preoperative euthyroid status was not associated with a higher rate of remission [13].

On the other hand, the use of adjuvant treatment like radiation therapy and SRL or DA therapy in cases of persistent disease after surgery, was determinant in improving the long-term remission rate ($p < 0.001$).

A long-term clinico-radiological and biochemical follow-up is necessary to detect delayed recurrence.

Conclusion

TSH-omas form a rare subgroup of secreting pituitary adenomas and can represent a challenge in their diagnosis and treatment. The trans-sphenoidal surgery forms the mainstay of treatment. Overall GTR was observed in 54% of patients and the size of the tumor as well as cavernous sinus invasion were the principal factors determining the extent of resection. This meta-analysis showed that postoperative biochemical remission was observed in 70% of patients. When adjuvant treatments like radiotherapy, SRL/DA therapy or a combination of both were used, a pooled overall biochemical remission was observed in 86% of patients at last follow-up. Neoadjuvant therapy, when used, had no effect on the surgical outcome in our analysis.

Larger surgical series and longer follow-up periods should prove useful to determine the factors predicting a long-term remission.

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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