Endocrine (2018) 61:407–421
https://doi.org/10.1007/s12020-018-1645-x

ENDOCRINE SURGERY

Giant pituitary adenoma: histological types, clinical features and therapeutic approaches

Pedro Iglesias[1] · Víctor Rodríguez Berrocal[2] · Juan José Díez[1]

Received: 21 April 2018 / Accepted: 29 May 2018 / Published online: 16 June 2018

Abstract

Giant pituitary adenomas comprise about 6–10% of all pituitary tumors. They are mostly clinically non-functioning adenomas and occur predominantly in males. The presenting symptoms are usually secondary to compression of neighboring structures, but also due to partial or total hypopituitarism. Functioning adenomas give rise to specific symptoms of hormonal hypersecretion. The use of dopamine agonists is considered a first-line treatment in patients with giant macroprolactinomas. Somatostatin analogs can also be used as primary treatment in cases of growth hormone and thyrotropin producing giant adenomas, although remission of the disease is not achieved in the vast majority of these patients. Neurosurgical treatment, either through transsphenoidal or transcranial surgery, continues to be the treatment of choice in the majority of patients with giant pituitary adenomas. The intrinsic complexity of these tumors requires the use of different therapies in a combined or sequential way. A multimodal approach and a therapeutic strategy involving a multidisciplinary team of expert professionals form the basis of the therapeutic success in these patients.

Keywords Giant pituitary adenoma · Clinically non-functioning pituitary adenoma · Acromegaly · Prolactinoma · Neurosurgery · Radiotherapy · Medical therapy

Introduction

Although not very common, giant pituitary adenomas remain a therapeutic challenge because of their size, invasiveness, and commonly found extrasellar extensions. Most giant adenomas are slow-growing and histologically benign tumors despite giant in size and troublesome to manage [1, 2].

Transsphenoidal surgery is the standard treatment in the majority of these pituitary adenomas [3–6]. However, they may become intractable even in the best neurosurgical centers. Radical removal of giant adenomas has been achieved in fewer than one half of the cases reported in the literature [7]. Giant adenomas are not only difficult to resect but also have a greater risk of complications.

We herein review the epidemiological, pathological, clinical, features of this kind of rare tumors, as well as the different therapeutic approaches available in the management of patients harboring these challenging pituitary tumors.

Definition

The definition of giant pituitary adenoma varies according to different authors. The first report of unusually large suprasellar extension of pituitary adenomas was that of Jefferson [8]. Later, Symon et al. [9] used the term "giant pituitary adenoma" for those pituitary tumors with an extension of more than 40 mm from the midline of the jugum sphenoidale in any direction or within 6 mm of the foramina. Other authors have considered the diagnosis of a giant pituitary adenoma when the tumor presents a vertical diameter > 30 mm above the tuberculum sellae, or a superior margin of > 20 mm above the jugum sphenoidale regardless of its volume. Today, the most commonly used criterion for the diagnosis of giant pituitary adenoma is the presence of the largest diameter of the tumor ≥ 4 cm [10].

✉ Pedro Iglesias
piglo65@gmail.com

[1] Department of Endocrinology. Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain

[2] Department of Neurosurgery. Hospital Ramón y Cajal, Madrid, Spain

Epidemiology

The prevalence of giant pituitary adenoma is around 6–10% of all pituitary adenomas [11, 12]. In a series of 800 surgically treated pituitary adenomas, 77 (9.6%) were giant tumors, defined as suprasellar tumor extensions of more than 20 mm above the diaphragma sellae [11]. The type of pituitary tumor most commonly reported (68.8%) was clinically non-functioning pituitary adenoma (CNFPA), that were more than double than functioning pituitary adenomas (31.2%). Giant pituitary tumors were more frequently seen in patients with CNFPA, being present in 31.5% and in 3.8% of the non-functioning and functioning pituitary adenomas, respectively. They were also more commonly reported in males than in females (58.4% vs. 41.5%), with a male:female ratio of 1.2 and 2.0, in non-functioning and functioning pituitary adenomas, respectively. The most frequently reported functioning giant pituitary adenoma was prolactinoma (54.2%), followed by somatotropinoma (29.2%), gonadotropinoma (8.3%), corticotropinoma (4.2%), and thyrotropinoma (4.2%). Mean age at diagnosis was slightly lower in men than in women (47.8 years vs. 53.8 years) in CNFPA and the contrary occurred in functioning tumors (40.3 years vs. 28.2 years, men vs. women). Giant pituitary adenomas are rare below the age of 20 years, mainly occurring in teenage women [13]. These last tumors are usually aggressive prolactinomas, and less frequently somatotropic adenomas, often resistant to medical treatment or other therapies [14].

Clinical symptoms

The clinical symptoms associated with giant pituitary adenoma can be secondary to the compression of surrounding brain structures, pituitary hormone deficiency or hypopituitarism, and sometimes, tumor hormonal hypersecretion.

Tumor mass effect

Visual impairment and visual field defects are the most common (72%) preoperative symptoms followed by headache (13%) in non-secreting giant pituitary adenoma [15] (Table 1). Similarly, visual field defect is the most common complaint as initial symptom at diagnosis (51%) and the main symptom (71%), followed by headache (59%) in giant prolactinomas [10, 16, 17]. Although very infrequent, compression of the ventricular system at the level of the third ventricle may cause an accumulation of cerebrospinal fluid in the lateral ventricles resulting in hydrocephalus. As a consequence of this increased intracranial pressure, several symptoms such as headache, nausea, vomiting, papilledema, blurry vision, loss of bladder control, memory loss, difficulty walking, poor coordination or balance, irritability, change in personality, problems with attention, sleepiness or coma can develop [16, 18–21]. Invasion of frontal lobes by the giant pituitary adenoma can be associated to generalized seizures or even dementia [22, 23].

Rarely, the lateral extension of the tumor into the cavernous sinus may be associated with cranial nerve palsy. The III cranial nerve is the most frequently affected, followed by VI and IV cranial nerves [24]. Main symptoms are mydriasis, diplopia, limitation of gaze, and ptosis. Cranial nerve palsy is an exceptional event in secreting giant pituitary adenomas [16]. Lastly, invasion of medial temporal lobes by the giant pituitary adenoma can be accompanied by temporal epilepsy [25]. The invasion of the nasopharynx may lead to nasal obstruction, headaches, recurrent nose bleeds, and/or rhinorrhea [26]. The invasion of the orbit may cause vision loss and proptosis [17, 27, 28].

The erosion of the occipital condyles may cause craniocervical joint instability [29]. The posterior extension of the tumor can be accompanied by erosion of the clivus and compression of brainstem and cerebellar structures [30, 31].

Table 1 Tumor mass effects in giant pituitary adenomas

Extension	Compression/invasion	Symptoms
Suprasellar extension	Chiasm or optic nerves Ventricular system Frontal lobes	Visual field defects Intracranial hypertension symptoms Epilepsy / dementia
Lateral extension	Sinus cavernous Medial temporal lobes	Cranial nerve palsy (III, VI, and IV) Temporal epilepsy
Anterior extension	Nasopharinx Orbit	Nasal obstruction, headaches, recurrent nose bleeds, and/or rhinorrhea Vision loss and proptosis
Inferior extension	Occipital condyles	Cranio-cervical joint instability
Posterior extension	Brainstem Cerebellar structures	Brainstem compression syndrome Cerebellar syndrome

Pituitary hormone deficiency

Partial hypopituitarism is present in the majority of patients with giant adenomas [11, 16]. Corticotropin (ACTH) insufficiency has been reported in up to 40% of patients with giant CNFPA [11]. Panhypopituitarism has been described in 17–33% of patients with giant prolactinomas [10, 16]. Although this prevalence may seem low due to the large size of the adenoma, a recent series of 47 patients with giant prolactinoma showed a similar prevalence of hypopituitarism to that found in 152 macroprolactinomas (17% vs. 10%, ns). Central hypogonadism, as a consequence of hyperprolactinemia and/or effect mass, is the most common pituitary deficiency (87%), followed by central hypothyroidism (55%), Growth hormone (GH) deficiency (28%), and secondary adrenal deficiency (17%) [16]. Central hypothyroidism has been reported to be significantly more frequent in giant prolactinoma than in macroprolactinomas (55% vs. 34%; $p = 0.007$); however, no significant differences were found in central hypogonadism, central hypocortisolism, and GH deficiency between giant prolactinomas and macroprolactinomas [16].

Tumor hormonal hypersecretion

A recent review of the major series of giant prolactinomas revealed a median prolactin at diagnosis of 6420 ng/ml associated with a mean tumor diameter of 52 ± 14 mm [10]. Amenorrea is virtually present in all women with giant prolactinomas, being primary in 22.5% [17]. Galactorrhea has been reported in approximately 8.5–33% of women younger than 50 years [10, 16, 17]. Erectile dysfunction and decrease of libido in men with giant prolactinomas are present in 50% and 55%, respectively, showing a similar prevalence to that of non-giant macroprolactinomas [16].

GHtumor excess by GH-secreting adenoma cause the development of acromegaly, a clinical syndrome characterized by acral overgrowth, soft-tissue swelling, arthralgias, jaw prognathism, mild hyperglycemia, menstrual disturbances, erectile dysfunction, hyperhidrosis, headache, sleep apnea, severe hypertension, and cardiac failure [32]. Because of the insidious onset and slow progression, approximately 60–75% of patients have macroadenomas at the time of presentation [33].

Thyrotropin (TSH)-secreting adenomas present with thyroid hyperfunction that is characterized by the increased serum free thyroid hormone levels accompanied by non-suppressed TSH levels, which contrasts with the suppressed TSH levels observed in the usual forms of hyperthyroidism. In addition to TSH, these tumors usually secrete the alpha-subunit, a common subunit of the glycoprotein pituitary hormones. In some cases, TSH secretion may be accompanied by other pituitary hormones such as GH and prolactin [34–38].

Giant clinically non-functioning pituitary adenoma

CNFPA is the most common (~70%) histological type of giant pituitary adenoma [11, 15]. This high prevalence could be related to the absence of a clinical syndrome associated with tumor hormonal hypersecretion, which would delay the diagnosis.

CNFPA are also named “silent adenomas” due to lack of endocrine symptoms despite the immunohistochemical expression in the tumor cells of anterior pituitary hormones in the majority of tumors. According to the recent WHO 2017 morphofunctional classification of pituitary adenomas, focused on pituitary-cell lineage and transcription factors, CNFPA are divided into eight subtypes: gonadotropoh, corticotroph, somatotroph, thyrotroph, lactotroph, plurihormonal Pit-1, null-cell adenoma, and double/triple adenoma [39, 40].

In 2004, Goel et al. [41] proposed a classification of giant pituitary adenoma which related the anatomical tumor extension and the surgical probability of complete tumor resection, the need for adjuvant treatment and the long-term outcome (Table 2). Grade I tumors can be resected radically and completely and the long-term is good. Radical surgery by a transsphenoidal route would be indicated in Grade II–III with clinical observation of the residual tumor in the cavernous sinus in Grade II tumors and radiotherapy adjuvant in Grade III tumors. Although Grade IV tumors could be resected radically, such a resection can be accompanied by serious surgical complications and could be life-threatening. For this reason, partial tumor resection followed by radiotherapy could be suitable for Grade IV pituitary tumors [41, 42].

Surgery

Surgery is considered the initial treatment for most giant pituitary tumors, except for prolactinomas. Its main objective is the maximum possible safe resection, preserving the neurological function. The most used approach routes have been the microscopic transsphenoidal surgery (MTS), and transcranial (TC) approaches, reserved for giant pituitary tumors with important supra- and parasellar extension. However, the development of endonasal endoscopic transsphenoidal surgery (EETS) since the late 1990s [43–45] has expanded the limits of transnasal approaches to these tumors and the whole skull base.

Today, in most reference centers, EETS is adopted as the first surgical option for the vast majority of giant pituitary

Table 2 Main classifications of pituitary adenomas

Anatomical (radiographic and operative) classification Wilson-Hardy et al. [136]	
Extension	
Suprasellar extension	
0	None
A	Expanding into suprasellar cistern
B	Anterior recesses of 3rd ventricle obliterated
C	Floor of 3rd ventricle grossly displaced
Parasellar extension	
D	Intracranial (intradural): specify (1) anterior (2) middle, or (3) posterior fossa
E	Into or beneath cavernous sinus (extradural)
Invasion / spread	
Floor of sella intact	
I	Sella normal or focally expanded; tumor ≤ 10 mm
II	Sella enlarged; tumor ≥ 10 mm
Sphenoid extension	
III	Localized perforation of sellar floor
IV	Diffuse destruction of sellar floor
Distant spread	
V	Spread via CSF or blood-borne

Classification according to invasion of the cavernous sinus space Knosp et al. [137]	
Grade 0	The adenoma does not pass the tangent of the medial aspects of the supra and intracavernous internal carotid artery
Grade 1	Tumor extension that does not pass a line between the cross sectional centers of the carotid arteries
Grade 2	Tumor extending beyond the intercarotid line, but not extending beyond or tangent to the lateral aspects of the intra and supracavernous internal carotid artery
Grade 3	Tumor extending lateral to the lateral tangent of the intra and supracavernous internal carotid artery
Grade 4	Total encasement of the intracavernous carotid artery

Classification of giant pituitary adenomas Goel et al. [41]	
Grade I	Tumors located within the confines of the sellar dura and under the diaphragma sellae without cavernous sinus invasion
Grade II	Tumors with cavernous sinus invasion
Grade III	Tumors accompanied by an elevation of the dura of the superior wall of the cavernous sinus and extension of this elevation into various compartments of brain
Grade IV	Pituitary adenomas with supradiaphragmatic-subarachnoid extension

adenomas (Fig. 1), remaining TC approaches as a complementary route in case of important post-surgical tumor remnants. In fact, in the series by Koutourousiu et al. [46] and Gondim et al. [47], no patient required a subsequent TC approach. In cases with contraindicatioin for EETS the TC route would be the first surgical option [48].

In 2012 Komotar et al. [49] conducted a systematic review (1995–2010) to compare EETS with MTS, and open TC resection in giant pituitary adenomas. The EETS cohort had higher rates of gross total resection (47.2%) compared with the MTS (30.9%) and open TC (9.6%) cohorts. The EES cohort also showed an improved visual outcome (91.1%) compared with MT surgery (34.8%) and open TC (45.7%) cohorts, with a lower morbidity and mortality.

Given the size and extension of these tumors, the rate of complete resections is low regardeless of the approach (Table 3). However, if we take into account the near total resection (>90%), the rate rises to 56%–84.6% [46, 50–52] (Table 3).

Of the multiple existing classifications, Knosp's is the most used today to predict the resecability of the tumors (Table 2). The endoscopic approach provides a better visualization than the conventional microsurgical approach beyond the confines of the sella turcica, being precisely in

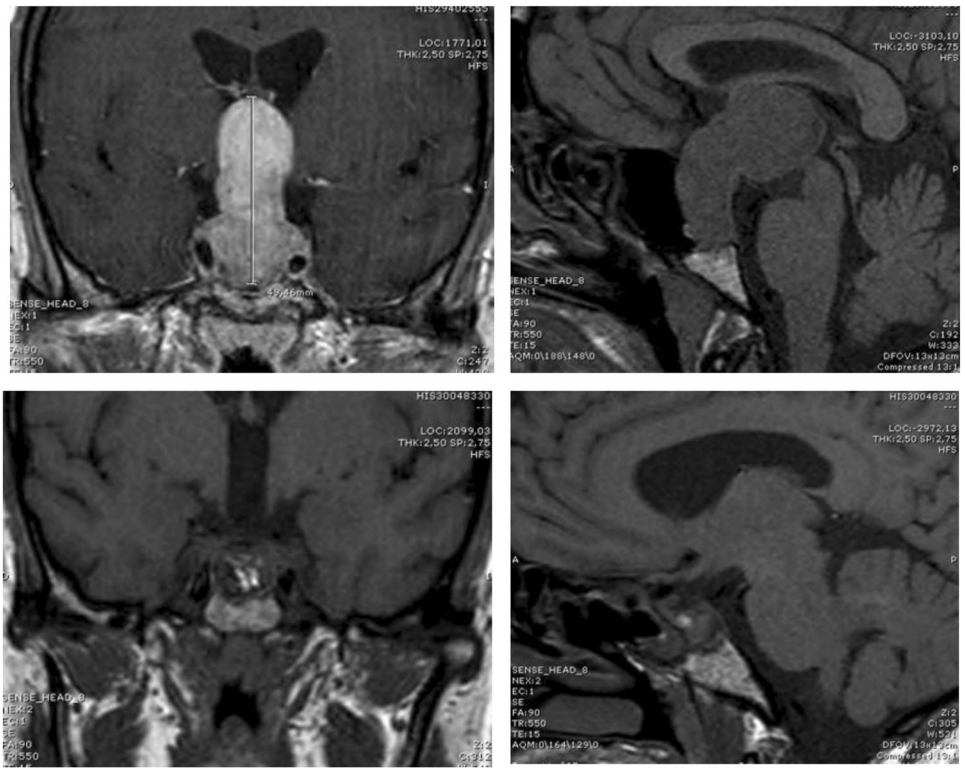

Fig. 1 Coronal and sagittal planes from pituitary MRI of a giant non-functioning pituitary adenoma in a 49-year-old man at diagnosis (top) and after endonasal endoscopic transsphenoidal resection (bottom)

this type of patients with giant adenomas or invasion of the cavernous sinus (Knosp grades 3 and 4) where greater differences are achieved in the resection rate between both groups (21% MTS vs. 47% EETS) [46, 52–56]. Other factors that have been related to subtotal resection are multilobulated tumors, hard-fibrous tumors and those previously treated (operated or irradiated tumors) [46, 51].

The visual prognosis after EETS is usually excellent with a significant improvement in the majority (62–80%) of patients [46, 47, 51, 52], showing a worsening after surgery in only a small percentage (<5%) [46, 51]. In addition, among the different approaches, EETS has proven to be much more effective than MTS or TC approach to improve visual prognosis [46]. One of the factors that determine the reversibility of visual damage is the time and severity of compression that manifests by the thickness of the retina nerve fiber layer that can be visualized through an optical coherence tomography [57].

Hipopituitarism remains unmodified in most patients (78.6%) after surgery, worsening in 17.8%, and improving in 3.6% [46]. The complication rate in this type of surgeries are not negligible, being the most frequent ones CSF fistula, new pharyngeal deficits, transient cranial nerve palsies, permanent DI, carotid rupture, and nasosinusal complications [44, 46, 47, 51, 52, 58].

Endocrine evaluation for pituitary dysfunction after surgery is recommended for all CNFPA patients. It has been suggest to evaluate all pituitary axes at 6 weeks after pituitary surgery and then periodically to monitor the development or resolution of pituitary deficiencies [59]. Postoperative evaluation of adrenal function on postoperative day 2, 6 weeks, and then 12 months has also been recommended in these patients [60]. All CNFPA patients with abnormal pituitary function undergoing surgical resection need an indefinite endocrinologic follow-up [60].

Radiation therapy

Radiotherapy of CNFPA as first-line treatment has not been shown to be superior or equivalent to surgery. However, its efficacy as adjuvant treatment in cases of tumor persistence or recurrence after surgery has been demonstrated [61, 62]. Radiotherapy is another therapeutic option in these patients achieving an excellent long-term local tumor control; being hypopituitarism the most commonly reported late complication (20–30% at 5 years after treatment).

Fractionated stereotactic radiotherapy (FSRT) has been shown to be an effective treatment for large or giant pituitary adenomas with low toxicity. FSRT has been evaluated for residual or recurrent large and invasive CNFPA in a group of 68 patients [63]. After a median of follow-up of 75 months, the 5- and 10-year actuarial local control were 97% and 91%, respectively, and overall survival 97% and 93%, respectively. Tumor reduction was reported in 72%, stable disease in 23.5%, and tumor progression in 4.4%. The relative tumor volume reduction was 47%. The incidence of new anterior pituitary deficits was 40% at 5 years

Table 3 Main surgical series of giant pituitary adenomas

Author et al. year [ref.]	Number of patients	Tumor size	Gross total resection (%)	Near total resection (>90%) (%)	Visual improvement (%)	Hormonal deterioration (%)	CSF leak (%)	Permanent DI (%)	Permanent neurological deficiency (%)	Postoperative mortality (%)	Surgical approach
Goel et al. 2004 [138]	118	>4	29	–	33.0	–	4.2	0	0.8	1–7	MT and TC
Mortini et al. 2007 [139]	95	>4	14.7	–	74.7	13.5	2.7	9.9	3.6	3.2	MT and TC
Sinha et al. 2010 [50]	250	>4	31	74	53	–	4.7	8	2.2	4.4	MT and TC
De Paiva Neto et al. 2010 [58]	51	>4	41.2	61	81.6	14.6	1.9	10.4	0	0	MT and endoscopic assisted
Koutourousiou et al. 2013 [46]	54	>4	20.4	67	80	16.7	16	9.6	0	0	EETS
Gondim 2014 [47]	50	>4	38	56	76	36	8	10	0	0	EETS
Juraschka et al. 2014 [51]	73	>3	24.2	77	61.8	7.4	9.6	0	0	0	EETS
Chabot et al. 2015 [52]	39	>3	56.4	85	79	12.8	10.3	7.7	0	0	EETS

CSF cerebrospinal fluid, *DI* diabetes insipidus, *MT* microscopic transsphenoidal, *TC* transcraneal, *EETS* endoscopic endonasal surgery

and 72% at 10 years without other radiation-induced complications.

Fractionated gamma knife surgery (FGKS) has also been used in giant pituitary adenomas. FGKS was evaluated as adjuvant therapy to surgery in 5 patients with non-functioning giant pituitary adenomas. At their last visit, all patients presented tumor stabilization or regression and none of them experienced tumor growth with a median duration to tumor regression of 6.5 months [64].

Medical therapy

There is little consistent evidence to support the efficacy of medical treatment in CNFPA. Dopamine agonists (DA) and somatostatin analogs (SSA), alone or in combination, have been used. The reported response rates have been 12–40%, 0–60%, and 12–40% for SSA, DA, and combination therapy, respectively [61]. Recent data suggest that DA have a positive effect on tumor remnant stabilization after surgery achieving an overall tumor control in over 85% of these patients, with a significant reduction in the need for repeat surgery or radiation therapy [65]. It seems reasonable to reserve medical therapy with DA and/or SSA for those patients who have not shown an adequate response to other conventional therapeutic measures [66]. More recently it has been suggested that DA treatment should be routinely considered for the management of CNFA patients with incompletely resected tumors [67].

Temozolomide (TMZ) has shown its efficacy in aggressive pituitary tumors and pituitary carcinomas [68]. TMZ could be considered as a therapeutic option in aggressive CNFPA after failure of standard (surgery and radiotherapy) therapies [14].

Giant prolactinoma

Giant prolactinomas are rare tumors accounting for 2–16% of all prolactinomas [16, 69, 70]. Due to the good therapeutic response to medical treatment of prolactinoma and, therefore, the absence of histological confirmation of the tumor in most cases, the diagnostic criteria for giant prolactinoma refers not only to its dimensions, but also to circulating serum prolactin concentration. Most studies consider a serum prolactin > 1000 ng/ml as a diagnostic criterion for giant prolactinoma [16, 17, 69, 71–73]. Therefore, so far, the concept of giant prolactinoma is a prolactin-secreting adenoma whose largest diameter is > 4 cm in association with serum prolactin levels > 1000 ng/ml after excluding a cosecretion of GH or ACTH by the tumor [10].

Giant prolactinomas have a male preponderance (male/female, ratio 8–9/1) [16, 17] and they have been reported in

approximately one-quarter of men with prolactinomas [74]. Some studies suggest that prolactinomas in males show a greater proliferative activity and aggressiveness than in females, indicating gender specific differences in their biological behavior [75–77].

The median age at diagnosis of giant prolactinoma is significantly lower (~10 years) in males compared to females (35 vs. 44 years, respectively, $p < 0.05$) [17].

The difference in sex distribution is even more striking in children, where the vast majority (~95%) of cases are males, being an exceptional event in girls [78]. The mean age at diagnosis in children is approximately 11 years and the mean tumor diameter is around 65 mm [10].

Medical therapy

Treatment with dopamine agonists (DA) has become the treatment of choice for giant prolactinoma compared with EEST, craniotomy, and/or radiation therapy [10, 16, 70, 79–81].

DA therapy has shown to reduce or normalize serum PRL levels, improve visual filed defects, restore menstruation in women and libido and erectile dysfunction in men, eliminate galactorrhea, and achieve significant tumor shrinkage in the majority of the patients [10, 16, 17, 73, 74, 82] (Fig. 2). These beneficial effects have been demonstrated even in giant prolactinomas larger than 60 mm in size [73]. Different DA have been shown to be effective in the treatment of giant prolactinoma, including bromocriptine [79, 82–84], pergolide [85], and cabergoline [16, 70, 80, 86–88].

According to the review of Maiter [10] normal serum PRL concentrations (<15ng/ml) is achieved in 60%, and hormonal resistance (absence of normoprolactinemia after bromocriptine ≥ 15 mg/day or cabergoline ≥ 2.0 mg/week) was present in 24% [10]. A significant reduction in tumor size (≥30%) is reached in 83% of patients. Although there are no comparative studies between bromocriptine and cabergoline in the management of giant prolactinoma, the demonstrated efficacy of cabergoline, as well as its tolerability and convenience of the treatment schedule, convert it in the election first-line therapy [10, 70, 87]. An infrequent complication associated with DA is spontaneous cerebrospinal fluid (CSF) leak, and even pituitary apoplexy, caused by rapid tumor shrinkage. This complication may occur early, within the first 1–3 months of treatment. Because many tumors are highly sensitive to DAs it is advisable to initiate treatment with the lowest effective dose (0.5–1.0 mg/week) and increase it progressively as needed [70, 87].

TMZ has been considered as an adjuvant therapy to surgery in patients with aggressive/invasive giant prolactinomas resistant to all conventional therapy [10, 81, 89, 90]. Recently, TMZ has been recommended as first-line

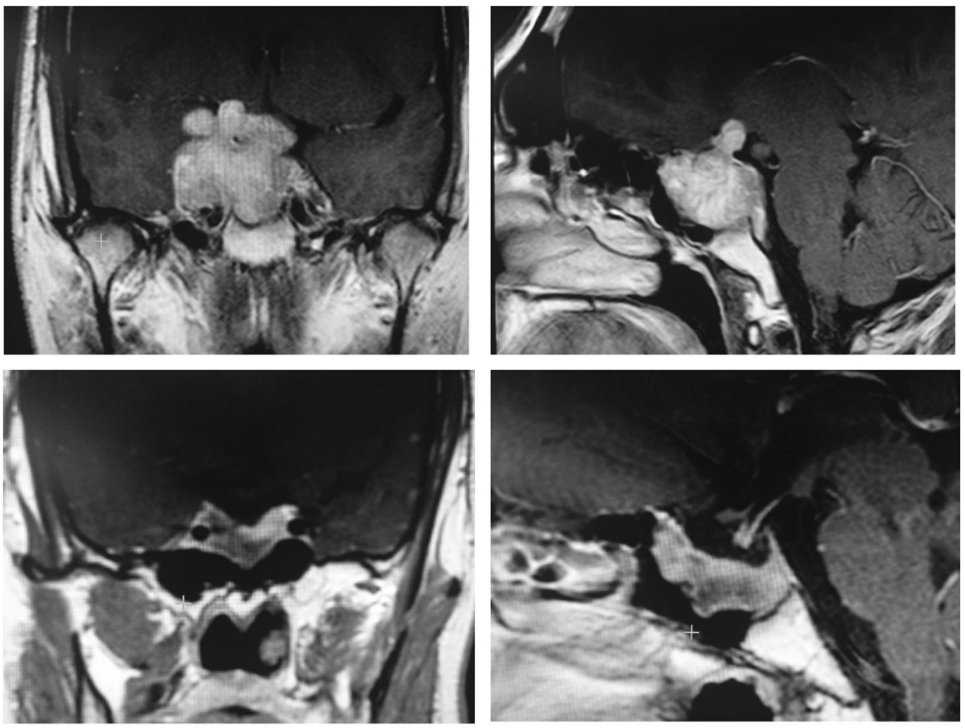

Fig. 2 Coronal and sagittal planes from pituitary MRI of a giant prolactinoma in a 24-year-old man at diagnosis (top) and 2 and a half years after starting medical therapy with cabergoline (bottom)

chemotherapy for aggressive pituitary tumors and pituitary carcinomas after failure of standard therapies, following documented tumor growth [14].

Surgery

Surgery is a second-line therapy for giant prolactinomas, and is usually reserved for patients with acute compressive symptoms or with resistance or intolerance to medical treatment (Fig. 3). The main surgical indications in giant prolactinoma are shown in Table 4.

DA-induced CSF leak has been reported in 12–17% of patients with giant prolactinomas [17, 73]. CSF rhinorrhea usually develops between 1 week and 4 months after starting DA treatment. It should be corrected surgically as soon as is feasible because of the high risk of secondary meningitis. In those cases in which the patient is not a candidate for surgery, the dose of DA could be reduced or withdrawn temporarily in order to achieve tumor re-expansion and tamponade of the fistula [91]. However, in some occasions, CSF rhinorrhea may restart when treatment is resumed.

Table 4 Main surgical indications in giant prolactinoma

First-line therapy	Second-line therapy
Pituitary tumor apoplexy	Drug-induced pituitary tumor apoplexy or CSF leak
Acute and progressive visual deterioration	DA intolerance
Spontaneous CSF leak	DA resistance
Cranial hypertension	Brain and optic chiasmal herniations into the sella
Debulking surgery	Tumor progression
Patient preference	Pneumoencephalus after DA therapy

CSF cerebrospinal fluid, *DA* dopamine agonist

In most studies, giant prolactinoma surgery is usually accompanied by persistent hyperprolactinemia and residual tumoral disease, and the number and grade of surgical complications are usually greater than that found in macroprolactinomas [83, 88]. Therefore, in almost all cases where surgery is used as the first-line therapy, post-surgical treatment with DA drugs is usually necessary [73, 83, 88].

Combined therapy with long-term therapy with high dose of cabergoline together with pituitary surgery has shown to be an effective therapeutic strategy in some patients with giant prolactinomas larger than 60 mm in size, achieving a clinical and biochemical remission [73].

In a recent series of 18 giant prolactinomas ≥ 60 mm in size [73], 9 (50%) patients underwent surgery (TS surgery $n = 7$; TC surgery $n = 2$). All patients were under DA therapy. Four patients were early operated after the diagnosis in order to perform debulking surgery due to the large tumor size together with intracranial hypertension. The other five patients underwent surgery later, after starting

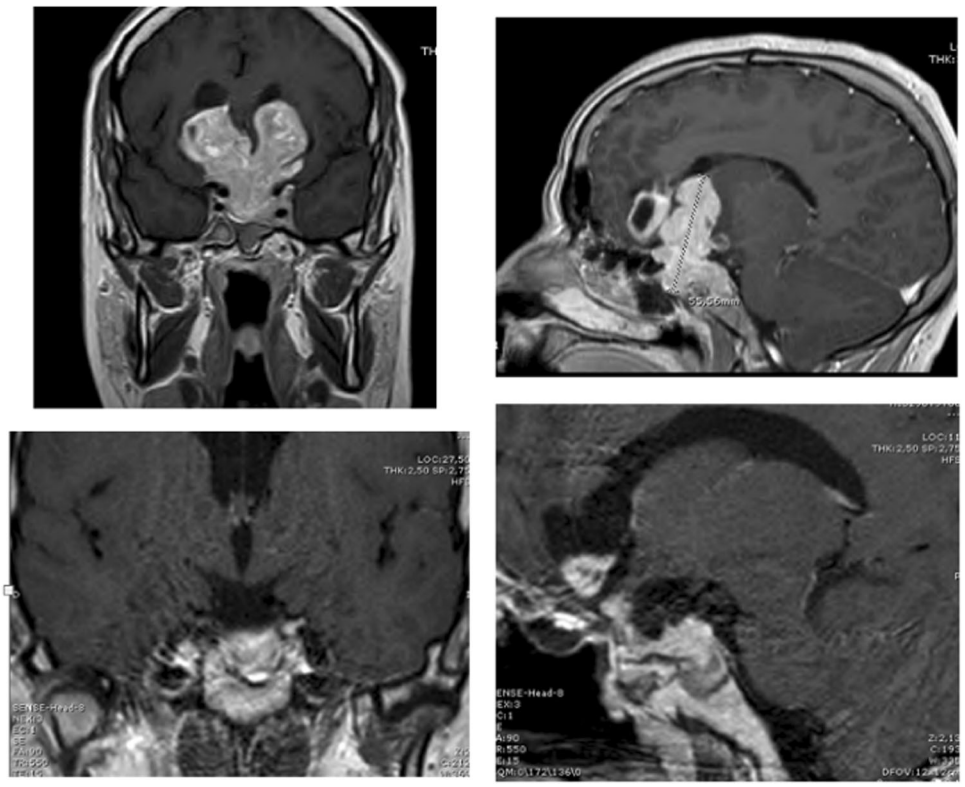

Fig. 3 Coronal and sagittal planes from pituitary MRI of a giant prolactinoma in a 29-year-old man at diagnosis (top) and 1 year after endonasal endoscopic transsphenoidal resection plus cabergoline therapy (bottom)

DA, due to cranial hypertension, DA resistance, pituitary apoplexy, and CSF leak. Four patients achieved normoprolactinemia after prolonged DA therapy, and seven patients showed a significant tumor shrinkage (four patients ≥ 90%; and two patients > 30%).

The major surgical complications in giant prolactinoma surgery are CSF leak, ophtalmoplegia, hypopituitarism, and diabetes insipidus [73].

Radiotherapy

Radiotherapy in giant prolactinomas may be used in those aggressive giant prolactinomas that are not controlled by conventional medical therapy and are not candidates for surgery or as adjuvant treatment to surgery and DA therapy after no tumor volume control [81]. Radiotherapy in giant prolactinoma has been used in small series of patients showing a decrease in PRL levels, tumor volume shrinkage but an elevated percentage of hormonal pituitary deficiencies [88, 92, 93].

Other

Although prolactinomas can express somatostatin receptors (SSTR2, SSRT3, and SSRT5), treatment with SSA is usually ineffective. The effectiveness of peptide receptor radionuclide therapy (PRRT) with 111In-DTPA-octreotide in a giant prolactinoma was reported in a 58 year-old woman with severe neurological symptoms, relapsing after surgery and resistant to DA and SSA therapy [94].

Giant somatotropin-secreting adenoma

GH-secreting pituitary adenomas represent approximately 11% of pituitary adenomas. [33, 95–100]. Data from the literature suggest that the prevalence of giant adenomas among acromegalic patients in general is <5%, however, during childhood and in young adulthood this percentage can reach up to 12% [101].

Giant GH-secreting pituitary adenomas usually present as invasive tumors and may include atypical adenomas, but most of them have histological features similar to usual GH-secreting adenomas. Sparsely granulated GH-secreting adenomas tend to be larger and more aggressive compared with densely granulated adenomas [102, 103]. Although benign, these large tumors may have an aggressive behavior and, in rare cases, fulfilling characteristics of pituitary carcinoma [104].

A recent published series analyzed clinical characteristics of 34 patients with giant adenomas form a cohort of 762 acromegalic subjects [105]. Results of these authors showed that mean age at diagnosis was 35 years and mean adenoma size was 49 mm. Thirty adenomas showed cavernous sinus invasion and 32 had suprasellar extension. Twenty-nine (85%) patient had visual field defects. Mean baseline IGF-1 was 3.4 times the upper limit of normality (ULN).

Surgery

Transsphenoidal surgery by an expert neurosurgeon is the preferred first-line treatment for patients with acromegaly [14]. High remission rate is obtained in patients with microadenomas or intrasellar macroadenomas. [106, 107]. However, giant GH-secreting pituitary adenomas are usually unsuitable for compete removal [33]. In particular, in the series of 34 patients reported by Shimon et al. [105] no patient achieved hormonal remission following first surgery. Nevertheless, patients with giant adenomas can benefit from surgical debulking that relieves chiasmal compression and can improve the subsequent response to medical treatment with SSA. Surgery may also decrease the radiation exposure to the optic pathways if radiation is planned.

Medical therapy

After unsuccessful pituitary surgery, first-generation SSA, drugs with affinity for somatostatin receptor SSTR2, are considered the first-line medical therapy for acromegalic patients [108–110]. Biochemical normalization is obtained in about 50-60% of patients. However, in the case of giant adenomas the remission rate is lesser. In the study by Shimon et al. [105] only 6 out of 32 patients (19%) treated with octreotide LAR or lanreotide autogel achieved normalization of the GH-IGF-1 axis, whereas nine others were partially controlled. The response rate to somatostatin analogs may be improved somehow with de addition of cabergoline [111].

Pasireotide LAR is a second generation multireceptor-targeted SSA that binds with affinity to 4 of the 5 somatostatin receptor subtypes, mainly SSTR2 and SSTR5. A recently reported large multicentre, randomized, 12-month, head-to-head superiority study investigated the efficacy and safety of pasireotide LAR compared with octreotide LAR in patients with de novo acromegaly and in those who had undergone unsuccessful surgery [112]. In this study, 31.3% of patients treated with pasireotide LAR, but only 19.2% of those treated with octreotide LAR, achieved levels of GH < 2.5 µg/l and age-normalized levels of IGF-1. Pasireotide LAR achieved hormonal remission in one of the six patients with giant GH-secreting pituitary adenoma [105]. Partial responses were obtained in two additional patients. Although mutations in the aryl hydrocarbon receptor interacting protein (*AIP*) gene are rare in sporadic acromegaly they have been reported in a higher frequency in some populations, such as familial isolated pituitary adenoma

(FIPA), pituitary gigantism, and patients with macroadenomas diagnosed under 30 years [113]. These patients usually respond poorly to SSA [114].

Pegvisomant, a GH receptor antagonist, is an effective therapeutic agent in patients with acromegaly who are not in remission after undergoing pituitary surgery. Shimon et al. [105] treated nine patients with giant-secreting GH-pituitary adenomas with pegvisomant, either alone ($n = 4$) or in combination with SSA ($n = 5$); biochemical remission (normal IGF-1) was achieved in five subjects (combination treatment in four), and partial control (IGF-1 < 1.5 ULN) was noticed in additional two patients.

TMZ may be used in combination with other drugs, like pasireotide or capecitabine. It has been suggested, although not proven, that these combinations could lead to improved responses rates [115]. Moreover, TMZ might have synergistic effects with radiotherapy, possibly having radiosensitizing properties [116].

Radiotherapy

Radiotherapy was used in 12 patients of the series of Shimon et al. [105], including radiosurgery in two subjects. This procedure was always used after surgical and/or medical treatment failure. Only one patient achieved control of GH and IGF 1-1 year following radiosurgery in this series [105]. Adjuvant radiotherapy should be considered in the setting of invasive tumor remnant with pathological markers strongly indicating aggressive behavior [14].

Giant thyrotropin-secreting adenoma

Thyrotropin-secreting pituitary adenomas (thyrotropinomas) are a rare cause of thyrotoxicosis and represent one of the less prevalent pituitary tumors, with reported frequencies of 0.5 to 3% of all pituitary adenomas [35, 36, 38, 117–120]. A Swedish study showed that the annual incidence of thyrotropinomas increased from 0.05 cases per million in 1990–1994 to 1 case per million in 2005–2009 [35]. These adenomas are often large and invasive lesions and in approximately 80% of cases are macroadenomas [34, 121–123]. Extrasellar extension, as well as cavernous sinus invasion are common [124, 125].

The frequency of giant adenomas is difficult to determine since many series do not report the size of the adenomas in detail [37]. In the cohort of 34 patients with macroadenomas reported by Socin et al. [34], three were giant (9%). In the large series of Yamada et al. [124], including 90 patients with TSH-secreting pituitary adenomas median maximum diameter was 16 mm, with interquartile range of 10–25 mm. Eighteen percent of these patients exhibited Knosp grade 3 or 4 tumors [124, 125]. Interestingly, in this series there were 14 patients that do not reach remission after surgery. Four out of these 14 patients (29%) exhibited giant adenomas. In the series of 18 patients reported by van Varsseveld et al. [38] tumor size reached a maximum of 80 mm in one patient.

The clinical diagnosis is established by the triad of high-serum free thyroxine with unsuppressed TSH levels and a pituitary mass. Clinical symptoms of thyrotoxicosis may be unapparent, mild, or severe. The presence of a diffuse goiter is common, but exophthalmos is not a clinical feature of patients with thyrotropinomas. Clinically silent thyrotropinomas or tumors with active hormonal production have similar prognosis and outcome [126]. Symptoms of local compression are the reason of detection in 29–38% of cases [35, 121].

Surgery

Neurosurgery is still considered the first-line therapy for thyrotropinomas [36, 127]. Complete tumor removal is achieved in most microadenomas, but only 30–60% of patients with macroadenomas are cured. This may be due, at least in part, to the frequent occurrence of local invasion and to the fact that these tumors frequently are hard and fibrous.

Approximately 30–80% of patients had postoperative tumor residual [34, 121, 126, 128]. Biochemical euthyroidism after surgery is achieved in 35–84% of the cases [34, 121, 124, 126]. Silent thyrotropinomas are positive for beta-TSH in immunohistochemical investigations without clinical or biochemical evidence of central hyperthyroidism. These tumors have similar size and postoperative outcomes as active thyrotropinomas [126].

Yamada et al. [124] adopted a more aggressive approach for tumors that had invaded the cavernous sinus, which involved extended transsphenoidal surgery or combined suprasellar and infrasellar approaches for giant adenomas. These authors suggest that the use of a tumor removal technique similar to that used for meningiomas might change the approach of neurosurgeons to treat fibrotic adenomas.

Pituitary hormone deficiencies have been reported to be up to 50–60% postoperatively [121, 126]. This percentage is notably higher than that found in other hormone-secreting pituitary adenomas [127, 129]. The time necessary for recovery of normal thyrotropes is variable and permanent hyposecretion may occur because of damage to the normal thyrotropes by tumor or surgery [130]. This high rate of postoperative hypopituitarism raises the question of the right management of thyrotropinomas and the role of SSA in their management.

Medical therapy

Thyrotropinomas express SSTR2 and SSTR5. Hence, medical therapy with SSA is nowadays increasingly used as

first-line or second-line therapy and is highly effective in reducing TSH secretion [127, 131]. Preoperative treatment with SSA has not been shown to significantly improve surgical results [132], although it reduces the risk of severe thyrotoxicosis perioperatively. An isolated case of a patient with a thyrotropinoma was reported to be cured completely by primary SSA therapy for 4 years [133].

Persistent disease after surgery is an indication for SSA as these drugs improve biochemical parameters and reduce tumor volume [38, 127, 131]. Restoration of normal thyroid hormone levels is achieved in 70–80% of patients [127, 134], and reduction in tumor volume has been reported in 20–70% of cases [34, 124, 127, 130]. DA have been used with variable results in patients with thyrotropinoma, in particular in those secreting TSH and prolactin.

Radiotherapy

Radiotherapy, including fractioned conventional radiation therapy or radiosurgery, has been used when surgery is inadvisable or as postoperative therapy in patients with residual or recurrent thyrotropinomas. Biochemical remission after radiation therapy has been variable, ranging from 36 to100% of cases in the long term [34, 35, 121, 124, 132, 135].

Conclusion

Giant pituitary adenomas, although not very common, represent a challenge in clinical endocrinology. In spite of complete tumor disappearance and correction of endocrine abnormalities are not achievable in the majority of cases the cautious combination of medical, surgical, and radiation therapies allows, nowadays, the control of the disease in a non-negligible number of patients. The multidisciplinary approach is mandatory in the planning of all the diagnostic and therapeutic arrangements that involve the management of these patients throughout the usually prolonged natural history of the disease.

Despite everything commented in this article, patients with pituitary giant adenomas stand for a good example of complex diseases with uncertain prognosis. It is in this field of human disease that precision medicine, in the near future, will have to establish a revolutionary twist in the coming decades. Every patient with giant adenoma is unique and the clinician facing his or her management should know that he or she is not dealing with a complex disease but with a particular subject who is ill. Nowadays, we are in a position to demand, from medical science, more and better methods of molecular characterization, personalized studies of greater precision (genomics, proteomics, metabolomics, etc.) and, above all, a better integration of all knowledge using a rapid exchange of communication and an increasing use of informatics, big data, robotics, and even artificial intelligence. Thereby, we will stop making medicine based on probability to move to medicine based on personal objective data of each patient. The challenge is already present, but the clinical benefit is out of doubt.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. A.F. Krisht, Giant invasive pituitary adenomas: management plan. Contemp. Neurosurg. **21**, 1–6 (1999)
2. H.H. Oruckaptan, O. Senmevsim, O.E. Ozcan, T. Ozgen, Pituitary adenomas: results of 684 surgically treated patients and review of the literature. Surg. Neurol. **53**, 211–219 (2000)
3. A.R. Dehdashti, A. Ganna, K. Karabatsou, F. Gentili, Pure endoscopic endonasal approach for pituitary adenomas: early surgical results in 200 patients and comparison with previous microsurgical series. Neurosurgery **62**, 1006–1015 (2008)
4. E. Magro, T. Graillon, J. Lassave, F. Castinetti, S. Boissonneau, E. Tabouret, S. Fuentes, L. Velly, R. Gras, H. Dufour, Complications related to the endoscopic endonasal transsphenoidal approach for nonfunctioning pituitary macroadenomas in 300 consecutive patients. World Neurosurg. **89**, 442–453 (2016)
5. A.N. Mamelak, J. Carmichael, V.H. Bonert, O. Cooper, S. Melmed, Single-surgeon fully endoscopic endonasal transsphenoidal surgery: outcomes in three-hundred consecutive cases. Pituitary **16**, 393–401 (2013)
6. M. Powell, Microscope transsphenoidal surgery. Acta Neurochir. (Wien.). **154**, 913–917 (2012)
7. H. Nishioka, T. Hara, Y. Nagata, N. Fukuhara, M. Yamaguchi-Okada, S. Yamada, Inherent tumor characteristics that limit effective and safe resection of giant nonfunctioning pituitary adenomas. World Neurosurg. **106**, 645–652 (2017)
8. G. Jefferson, Extrasellar extensions of pituitary adenomas: (section of neurology). Proc. R. Soc. Med. **33**, 433–458 (1940)
9. L. Symon, J. Jakubowski, B. Kendall, Surgical treatment of giant pituitary adenomas. J. Neurol. Neurosurg. Psychiatry **42**, 973–982 (1979)
10. D. Maiter, E. Delgrange, Therapy of endocrine disease: the challenges in managing giant prolactinomas. Eur. J. Endocrinol. **170**, R213–R227 (2014)
11. G. Mohr, J. Hardy, R. Comtois, H. Beauregard, Surgical management of giant pituitary adenomas. Can. J. Neurol. Sci. **17**, 62–66 (1990)
12. J. Trouillas, P. Roy, N. Sturm, E. Dantony, C. Cortet-Rudelli, G. Viennet, J.F. Bonneville, R. Assaker, C. Auger, T. Brue, A. Cornelius, H. Dufour, E. Jouanneau, P. Francois, F. Galland, F. Mougel, F. Chapuis, L. Villeneuve, C.A. Maurage, D. Figarella-Branger, G. Raverot; members of HYPOPRONOS, A. Barlier, M. Bernier, F. Bonnet, F. Borson-Chazot, G. Brassier, S. Caulet-Maugendre, O. Chabre, P. Chanson, J.F. Cottier, B. Delemer, E. Delgrange, L.Di Tommaso, S. Eimer, S. Gaillard, M. Jan, J.J. Girard, V. Lapras, H. Loiseau, J.G. Passagia, M. Patey, A. Penfornis, J.Y. Poirier, G. Perrin, A. Tabarin, A new prognostic clinicopathological classification of pituitary adenomas: a multicentric case-control study of 410 patients with 8 years post-operative follow-up. Acta Neuropathol. **126**, 123–135 (2013)

13. S. Salenave, D. Ancelle, T. Bahougne, G. Raverot, P. Kamenicky, J. Bouligand, A. Guiochon-Mantel, A. Linglart, P.F. Souchon, M. Nicolino, J. Young, F. Borson-Chazot, B. Delemer, P. Chanson, Macroprolactinomas in children and adolescents: factors associated with the response to treatment in 77 patients. J. Clin. Endocrinol. Metab. **100**, 1177–1186 (2015)
14. G. Raverot, P. Burman, A.I. McCormack, A.P. Heaney, S. Petersenn, V. Popovic, J. Trouillas, O. Dekkers, European Society of Endocrinology clinical practice guidelines for the management of aggressive pituitary tumours and carcinomas. Eur J Endocrinol. **178**, G1–G24 (2018).
15. J. Matsuyama, T. Kawase, K. Yoshida, M. Hasegawa, Y. Hirose, S. Nagahisa, S. Watanabe, H. Sano, Management of large and giant pituitary adenomas with suprasellar extensions. Asian J. Neurosurg. **5**, 48–53 (2010)
16. E. Espinosa, E. Sosa, V. Mendoza, C. Ramirez, V. Melgar, M. Mercado, Giant prolactinomas: are they really different from ordinary macroprolactinomas? Endocrine **52**, 652–659 (2016)
17. E. Delgrange, G. Raverot, M. Bex, P. Burman, B. Decoudier, F. Devuyst, U. Feldt-Rasmussen, M. Andersen, D. Maiter, Giant prolactinomas in women. Eur. J. Endocrinol. **170**, 31–38 (2013)
18. P. Iglesias, L.P. Macho, J.J. Diez, Resolution of macroprolactinoma-induced symptomatic hydrocephalus following cabergoline therapy. Age Ageing **33**, 410–412 (2004)
19. P. Scarone, M. Losa, P. Mortini, M. Giovanelli, Obstructive hydrocephalus and intracranial hypertension caused by a giant macroprolactinoma. Prompt Response Med. Treat. J. Neurooncol. **76**, 51–54 (2006)
20. S.M. Joshi, I.S. Chopra, M. Powell, Hydrocephalus caused by giant pituitary tumors: case series and guidelines for management. Br. J. Neurosurg. **23**, 30–32 (2009)
21. E. Koktekir, H. Karabagli, K. Ozturk, Simultaneous transsphenoidal and transventricular endoscopic approaches for giant pituitary adenoma with hydrocephalus. J. Craniofac. Surg. **26**, e39–e42 (2015)
22. F. Chentli, L. Akkache, K. Daffeur, S. Azzoug, General seizures revealing macro-adenomas secreting prolactin or prolactin and growth hormone in men. Indian. J. Endocrinol. Metab. **18**, 361–363 (2014)
23. M.H. Brisman, M.R. Fetell, K.D. Post, Reversible dementia due to macroprolactinoma. J. Neurosurg. **79**, 135–137 (1993)
24. S.H. Kim, K.C. Lee, S.H. Kim, Cranial nerve palsies accompanying pituitary tumour. J. Clin. Neurosci. **14**, 1158–1162 (2007)
25. D. Deepak, C. Daousi, M. Javadpour, I.A. MacFarlane, Macroprolactinomas and epilepsy. Clin. Endocrinol. (Oxf.). **66**, 503–507 (2007)
26. M.D. Hyrcza, S. Ezzat, O. Mete, S.L. Asa, Pituitary adenomas presenting as sinonasal or nasopharyngeal masses: A case series illustrating potential diagnostic pitfalls. Am. J. Surg. Pathol. **41**, 525–534 (2017)
27. J. Berwaerts, J. Verhelst, R. Abs, B. Appel, C. Mahler, A giant prolactinoma presenting with unilateral exophthalmos: effect of cabergoline and review of the literature. J. Endocrinol. Invest. **23**, 393–398 (2000)
28. P. Cackett, G. Eunson, L. Bath, A. Mulvihill, Proptosis as the presenting sign of giant prolactinoma in a prepubertal boy: successful resolution of hydrocephalus by use of medical therapy. Future Oncol. **8**, 1621–1626 (2012)
29. M.J. Zaben, S.E. Harrisson, N.V. Mathad, Giant prolactinoma causing cranio-cervical junction instability: a case report. Br. J. Neurosurg. **25**, 754–756 (2011)
30. N. Margari, J. Pollock, N. Stojanovic, A novel surgical approach for the management of giant invasive prolactinoma compressing the brainstem. Endocrinol. Diabetes Metab. Case Rep. **2016**, 150103–15-0103 (2016). Epub 2 Dec 2015
31. F. Chentli, M. Kasraoi, F. Belhimer, S. Azzoug, S. Abdelhak, N. Masmoudi, Pituitary tumors and pyramidal syndrome. Ann. d'Endocrinologie **75**, 427 (2014)
32. L. Vilar, C.F. Vilar, R. Lyra, R. Lyra, L.A. Naves, Acromegaly: clinical features at diagnosis. Pituitary **20**, 22–32 (2017)
33. P. Nomikos, M. Buchfelder, R. Fahlbusch, The outcome of surgery in 668 patients with acromegaly using current criteria of biochemical 'cure'. Eur. J. Endocrinol. **152**, 379–387 (2005)
34. H.V. Socin, P. Chanson, B. Delemer, A. Tabarin, V. Rohmer, J. Mockel, A. Stevenaert, A. Beckers, The changing spectrum of TSH-secreting pituitary adenomas: diagnosis and management in 43 patients. Eur. J. Endocrinol. **148**, 433–442 (2003)
35. L. Onnestam, K. Berinder, P. Burman, P. Dahlqvist, B.E. Engstrom, J. Wahlberg, H.F. Nystrom, National incidence and prevalence of TSH-secreting pituitary adenomas in Sweden. J. Clin. Endocrinol. Metab. **98**, 626–635 (2013)
36. A. Azzalin, C.L. Appin, M.J. Schniederjan, T. Constantin, J.C. Ritchie, E. Veledar, N.M. Oyesiku, A.G. Ioachimescu, Comprehensive evaluation of thyrotropinomas: single-center 20-year experience. Pituitary **19**, 183–193 (2016)
37. D.M. Nazato, J.Abucham,Diagnosis and treatment of TSH-secreting adenomas: review of a longtime experience in a reference center. J Endocrinol Invest **41**(4), 447–454 (2018).
38. N.C. van Varsseveld, P.H. Bisschop, N.R. Biermasz, A.M. Pereira, E. Fliers, M.L. Drent, A long-term follow-up study of eighteen patients with thyrotrophin-secreting pituitary adenomas. Clin. Endocrinol. (Oxf.). **80**, 395–402 (2014)
39. R.Y. Osamura, A. Grossman, M. Korbonits, K. Kovacs, M.B.S. Lopes, A. Matsuno, J. Trouillas, in *WHO Calssification of Tumours of Endocrine Organs*, ed. by R.V. Lloyd, R.Y. Osamura, G. Klöppel, J. Rosai, International Agency for Research on Cancer (IARC): Lyon, France (2017), pp. 14–18
40. E. Manojlovic-Gacic, B.E. Engstrom, O. Casar-Borota, Histopathological classification of non-functioning pituitary neuroendocrine tumors. Pituitary **21**, 119–129 (2018)
41. A. Goel, T. Nadkarni, D. Muzumdar, K. Desai, U. Phalke, P. Sharma, Giant pituitary tumors: a study based on surgical treatment of 118 cases. Surg. Neurol. **61**, 436–445 (2004). discussion 445-6
42. A. Goel, Challenge of giant pituitary tumors. World Neurosurg. **82**, e121–e124 (2014)
43. H.D. Jho, R.L. Carrau, Endoscopic endonasal transsphenoidal surgery: experience with 50 patients. J. Neurosurg. **87**, 44–51 (1997)
44. P. Cappabianca, A. Alfieri, E. de Divitiis, Endoscopic endonasal transsphenoidal approach to the sella: towards functional endoscopic pituitary surgery (FEPS). Minim. Invasive Neurosurg. **41**, 66–73 (1998)
45. D.L. Penn, W.T. Burke, E.R. Laws, Management of non-functioning pituitary adenomas: surgery. Pituitary **21**, 145–153 (2018)
46. M. Koutourousiou, P.A. Gardner, J.C. Fernandez-Miranda, A. Paluzzi, E.W. Wang, C.H. Snyderman, Endoscopic endonasal surgery for giant pituitary adenomas: advantages and limitations. J. Neurosurg. **118**, 621–631 (2013)
47. J.A. Gondim, J.P. Almeida, L.A. Albuquerque, E.F. Gomes, M. Schops, Giant pituitary adenomas: surgical outcomes of 50 cases operated on by the endonasal endoscopic approach. World Neurosurg. **82**, e281–e290 (2014)
48. A.S. Youssef, S. Agazzi, H.R. van Loveren, Transcranial surgery for pituitary adenomas. Neurosurgery **57**, 168–175 (2005). discussion 168-75
49. R.J. Komotar, R.M. Starke, D.M. Raper, V.K. Anand, T.H. Schwartz, Endoscopic endonasal compared with microscopic transsphenoidal and open transcranial resection of giant pituitary adenomas. Pituitary **15**, 150–159 (2012)

50. S. Sinha, B.S. Sharma, Giant pituitary adenomas--an enigma revisited. Microsurgical treatment strategies and outcome in a series of 250 patients. Br. J. Neurosurg. **24**, 31–39 (2010)
51. K. Juraschka, O.H. Khan, B.L. Godoy, E. Monsalves, A. Kilian, B. Krischek, A. Ghare, A. Vescan, F. Gentili, G. Zadeh, Endoscopic endonasal transsphenoidal approach to large and giant pituitary adenomas: institutional experience and predictors of extent of resection. J. Neurosurg. **121**, 75–83 (2014)
52. J.D. Chabot, S. Chakraborty, G. Imbarrato, A.R. Dehdashti, Evaluation of outcomes after endoscopic endonasal surgery for large and giant pituitary macroadenoma: A retrospective review of 39 consecutive patients. World Neurosurg. **84**, 978–988 (2015)
53. S. Dhandapani, H. Singh, H.M. Negm, S. Cohen, V.K. Anand, T.H. Schwartz, Cavernous sinus invasion in pituitary adenomas: Systematic review and pooled data meta-analysis of radiologic criteria and comparison of endoscopic and microscopic surgery. World Neurosurg. **96**, 36–46 (2016)
54. M. Messerer, J.C. De Battista, G. Raverot, S. Kassis, J. Dubourg, V. Lapras, J. Trouillas, G. Perrin, E. Jouanneau, Evidence of improved surgical outcome following endoscopy for non-functioning pituitary adenoma removal. Neurosurg. Focus. **30**, E11 (2011)
55. M.R. Schaberg, V.K. Anand, T.H. Schwartz, W. Cobb, Microscopic versus endoscopic transnasal pituitary surgery. Curr. Opin. Otolaryngol. Head. Neck Surg. **18**, 8–14 (2010)
56. J. Strychowsky, S. Nayan, K. Reddy, F. Farrokhyar, D. Sommer, Purely endoscopic transsphenoidal surgery versus traditional microsurgery for resection of pituitary adenomas: systematic review. J. Otolaryngol. Head. Neck. Surg. **40**, 175–185 (2011)
57. H.V. Danesh-Meyer, A. Wong, T. Papchenko, K. Matheos, S. Stylli, A. Nichols, C. Frampton, M. Daniell, P.J. Savino, A.H. Kaye, Optical coherence tomography predicts visual outcome for pituitary tumors. J. Clin. Neurosci. **22**, 1098–1104 (2015)
58. M.A. de Paiva Neto, A. Vandergrift, N. Fatemi, A.A. Gorgulho, A.A. Desalles, P. Cohan, C. Wang, R. Swerdloff, D.F. Kelly, Endonasal transsphenoidal surgery and multimodality treatment for giant pituitary adenomas. Clin. Endocrinol. (Oxf.). **72**, 512–519 (2010)
59. M. Fleseriu, I.A. Hashim, N. Karavitaki, S. Melmed, M.H. Murad, R. Salvatori, M.H. Samuels, Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. J. Clin. Endocrinol. Metab. **101**, 3888–3921 (2016)
60. M. Ziu, I.F. Dunn, C. Hess, M. Fleseriu, M.E. Bodach, L.M. Tumialan, N.M. Oyesiku, K.S. Patel, R. Wang, B.S. Carter, J.Y. Chen, C.C. Chen, C.G. Patil, Z. Litvack, G. Zada, M.K. Aghi, Congress of neurological surgeons systematic review and evidence-based guideline on posttreatment follow-up evaluation of patients with nonfunctioning pituitary adenomas. Neurosurgery **79**, E541–E543 (2016)
61. J.W. Lucas, M.E. Bodach, L.M. Tumialan, N.M. Oyesiku, C.G. Patil, Z. Litvack, M.K. Aghi, G. Zada, Congress of neurological surgeons systematic review and evidence-based guideline on primary management of patients with nonfunctioning pituitary adenomas. Neurosurgery **79**, E533–E535 (2016)
62. G. Minniti, J. Flickinger, B. Tolu, S. Paolini, Management of nonfunctioning pituitary tumors: radiotherapy. Pituitary **21**, 154–161 (2018)
63. G. Minniti, C. Scaringi, M. Poggi, M.L. Jaffrain Rea, G. Trillo, V. Esposito, A. Bozzao, M.M. Enrici, V. Toscano, R.M. Enrici, Fractionated stereotactic radiotherapy for large and invasive non-functioning pituitary adenomas: long-term clinical outcomes and volumetric MRI assessment of tumor response. Eur. J. Endocrinol. **172**, 433–441 (2015)
64. K. Zhao, X. Liu, D. Liu, Y. Li, Z. Zhang, Y. Lin, Y. Zhang, D. Xu, Fractionated Gamma Knife surgery for giant pituitary adenomas. Clin. Neurol. Neurosurg. **150**, 139–142 (2016)
65. Y. Greenman, O. Cooper, I. Yaish, E. Robenshtok, N. Sagiv, T. Jonas-Kimchi, X. Yuan, A. Gertych, I. Shimon, Z. Ram, S. Melmed, N. Stern, Treatment of clinically nonfunctioning pituitary adenomas with dopamine agonists. Eur. J. Endocrinol. **175**, 63–72 (2016)
66. A. Agrawal, R. Cincu, A. Goel, Current concepts and controversies in the management of non-functioning giant pituitary macroadenomas. Clin. Neurol. Neurosurg. **109**, 645–650 (2007)
67. N. Even-Zohar, Y. Greenman, Management of NFAs: medical treatment. Pituitary **21**, 168–175 (2018)
68. H. Lasolle, C. Cortet, F. Castinetti, L. Cloix, P. Caron, B. Delemer, R. Desailloud, C. Jublanc, C. Lebrun-Frenay, J.L. Sadoul, L. Taillandier, M. Batisse-Lignier, F. Bonnet, N. Bourcigaux, D. Bresson, O. Chabre, P. Chanson, C. Garcia, M. Haissaguerre, Y. Reznik, S. Borot, C. Villa, A. Vasiljevic, S. Gaillard, E. Jouanneau, G. Assie, G. Raverot, Temozolomide treatment can improve overall survival in aggressive pituitary tumors and pituitary carcinomas. Eur. J. Endocrinol. **176**, 769–777 (2017)
69. R.K. Shrivastava, M.S. Arginteanu, W.A. King, K.D. Post, Giant prolactinomas: clinical management and long-term follow up. J. Neurosurg. **97**, 299–306 (2002)
70. S.M. Corsello, G. Ubertini, M. Altomare, R.M. Lovicu, M.G. Migneco, C.A. Rota, C. Colosimo, Giant prolactinomas in men: efficacy of cabergoline treatment. Clin. Endocrinol. (Oxf.). **58**, 662–670 (2003)
71. P.O. Lundberg, P.O. Osterman, L. Wide, Serum prolactin in patients with hypothalamus and pituitary disorders. J. Neurosurg. **55**, 194–199 (1981)
72. M.P. Gillam, M.E. Molitch, G. Lombardi, A. Colao, Advances in the treatment of prolactinomas. Endocr. Rev. **27**, 485–534 (2006)
73. I. Shimon, E. Sosa, V. Mendoza, Y. Greenman, A. Tirosh, E. Espinosa, V. Popovic, A. Glezer, M.D. Bronstein, M. Mercado, Giant prolactinomas larger than 60 mm in size: a cohort of massive and aggressive prolactin-secreting pituitary adenomas. Pituitary **19**, 429–436 (2016)
74. P. Iglesias, C. Bernal, C. Villabona, J.C. Castro, F. Arrieta, J.J. Diez, Prolactinomas in men: a multicentre and retrospective analysis of treatment outcome. Clin. Endocrinol. (Oxf.). **77**, 281–287 (2012)
75. E. Delgrange, J. Trouillas, D. Maiter, J. Donckier, J. Tourniaire, Sex-related difference in the growth of prolactinomas: a clinical and proliferation marker study. J. Clin. Endocrinol. Metab. **82**, 2102–2107 (1997)
76. R.D. Calle-Rodrigue, C. Giannini, B.W. Scheithauer, R.V. Lloyd, P.C. Wollan, K.T. Kovacs, L. Stefaneanu, A.B. Ebright, C.F. Abboud, D.H. Davis, Prolactinomas in male and female patients: a comparative clinicopathologic study. Mayo Clin. Proc. **73**, 1046–1052 (1998)
77. E. Delgrange, A. Vasiljevic, A. Wierinckx, P. Francois, E. Jouanneau, G. Raverot, J. Trouillas, Expression of estrogen receptor alpha is associated with prolactin pituitary tumor prognosis and supports the sex-related difference in tumor growth. Eur. J. Endocrinol. **172**, 791–801 (2015)
78. R.M. Scott, E.T. Hedley-Whyte, Case record of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 35-2002. A nine-year-old girl with cold intolerance, visual-field defects, and a suprasellar tumor. N. Engl. J. Med. **347**, 1604–1611 (2002)
79. C. Yu, Z. Wu, J. Gong, Combined treatment of invasive giant prolactinomas. Pituitary **8**, 61–65 (2005)
80. E.H. Cho, S.A. Lee, J.Y. Chung, E.H. Koh, Y.H. Cho, J.H. Kim, C.J. Kim, M.S. Kim, Efficacy and safety of cabergoline as first

line treatment for invasive giant prolactinoma. J. Korean Med. Sci. **24**, 874–878 (2009)
81. A.B. Moraes, C.M. Silva, L. Vieira Neto, M.R. Gadelha, Giant prolactinomas: the therapeutic approach. Clin. Endocrinol. (Oxf.). **79**, 447–456 (2013)
82. A. Chattopadhyay, A. Bhansali, S.R. Masoodi, Long-term efficacy of bromocriptine in macroprolactinomas and giant prolactinomas in men. Pituitary **8**, 147–154 (2005)
83. J.R. Davis, M.C. Sheppard, D.A. Heath, Giant invasive prolactinoma: a case report and review of nine further cases. Q. J. Med. **74**, 227–238 (1990)
84. N. Saeki, M. Nakamura, K. Sunami, A. Yamaura, Surgical indication after bromocriptine therapy on giant prolactinomas: effects and limitations of the medical treatment. Endocr. J. **45**, 529–537 (1998)
85. P.U. Freda, C.I. Andreadis, A.G. Khandji, M. Khoury, J.N. Bruce, T.P. Jacobs, S.L. Wardlaw, Long-term treatment of prolactin-secreting macroadenomas with pergolide. J. Clin. Endocrinol. Metab. **85**, 8–13 (2000)
86. I. Shimon, C. Benbassat, M. Hadani, Effectiveness of long-term cabergoline treatment for giant prolactinoma: study of 12 men. Eur. J. Endocrinol. **156**, 225–231 (2007)
87. S.V. Acharya, R.A. Gopal, P.S. Menon, T.R. Bandgar, N.S. Shah, Giant prolactinoma and effectiveness of medical management. Endocr. Pract. **16**, 42–46 (2010)
88. P. Andujar-Plata, R. Villar-Taibo, M.D. Ballesteros-Pomar, A. Vidal-Casariego, B. Perez-Corral, J.M. Cabezas-Agricola, P. Alvarez-Vazquez, R. Serramito, I. Bernabeu, Long-term outcome of multimodal therapy for giant prolactinomas. Endocrine **55**, 231–238 (2017)
89. B.C. Whitelaw, D. Dworakowska, N.W. Thomas, S. Barazi, P. Riordan-Eva, A.P. King, T. Hampton, D.B. Landau, D. Lipscomb, C.R. Buchanan, J.A. Gilbert, S.J. Aylwin, Temozolomide in the management of dopamine agonist-resistant prolactinomas. Clin. Endocrinol. (Oxf.). **76**, 877–886 (2012)
90. G. Raverot, F. Castinetti, E. Jouanneau, I. Morange, D. Figarella-Branger, H. Dufour, J. Trouillas, T. Brue, Pituitary carcinomas and aggressive pituitary tumours: merits and pitfalls of temozolomide treatment. Clin. Endocrinol. (Oxf.). **76**, 769–775 (2012)
91. K.S. Leong, P.M. Foy, A.C. Swift, S.L. Atkin, D.R. Hadden, I.A. MacFarlane, CSF rhinorrhoea following treatment with dopamine agonists for massive invasive prolactinomas. Clin. Endocrinol. (Oxf.). **52**, 43–49 (2000)
92. S.K. Grebe, J.W. Delahunt, C.M. Feek, Treat. extensively Invasive (giant) Prolactino. bromocriptine. N. Z. Med. J. **105**, 129–131 (1992).
93. Z.B. Wu, C.J. Yu, Z.P. Su, Q.C. Zhuge, J.S. Wu, W.M. Zheng, Bromocriptine treatment of invasive giant prolactinomas involving the cavernous sinus: results of a long-term follow up. J. Neurosurg. **104**, 54–61 (2006)
94. S. Baldari, F. Ferrau, C. Alafaci, A. Herberg, F. Granata, V. Militano, F.M. Salpietro, F. Trimarchi, S. Cannavo, First demonstration of the effectiveness of peptide receptor radionuclide therapy (PRRT) with 111In-DTPA-octreotide in a giant PRL-secreting pituitary adenoma resistant to conventional treatment. Pituitary **15**, S57–S60 (2012). **Suppl 1**
95. T.P. Ip, F.L. Chan, A.W. Kung, K.S. Lam, Giant growth-hormone secreting pituitary tumour with extracranial extension. Australas. Radiol. **40**, 88–90 (1996)
96. S. Konar, B.I. Devi, T.C. Yasha, D.P. Shukla, Clival tumor presenting with acromegaly. Neurol. India **61**, 186–187 (2013)
97. M. Ravikiran, A. Bhansali, P. Dutta, P. Singh, K.K. Mukherjee, R. Walia, Giant somatotropinoma. BMJ Case Rep. https://doi.org/10.1136/bcr.01.2009.1483 (2009)
98. O.F. Tropinskaia, L.V. Shishkina, A.N. Shkarubo, L.I. Astaf'eva, V.N. Shimanskii, [Rare observation of giant pituitary adenoma spreading into posterior cranial fossa]. Zh. Vopr. Neirokhir. Im. N. N. Burdenko. **4**, 54–5 (2009)
99. A. Sidhaye, P. Burger, D. Rigamonti, R. Salvatori, Giant somatotrophinoma without acromegalic features: more "quiet" than "silent": case report. Neurosurgery **56**, E1154 (2005). discussion E1154
100. R. Cahyanur, W. Setyawan, D.G. Sudrajat, S. Setyowati, D. Purnamasari, P. Soewondo, Diagnosis and management of acromegaly: giant invasive adenoma. Acta Med. Indones. **43**, 122–128 (2011)
101. Y. Nagata, N. Inoshita, N. Fukuhara, M. Yamaguchi-Okada, H. Nishioka, T. Iwata, K. Yoshimoto, S. Yamada, Growth hormone-producing pituitary adenomas in childhood and young adulthood: clinical features and outcomes. Pituitary. **21**, 1–9 (2018).
102. J. Brzana, C.G. Yedinak, S.H. Gultekin, J.B. Delashaw, M. Fleseriu, Growth hormone granulation pattern and somatostatin receptor subtype 2A correlate with postoperative somatostatin receptor ligand response in acromegaly: a large single center experience. Pituitary **16**, 490–498 (2013)
103. L.V. Syro, F. Rotondo, C.A. Serna, L.D. Ortiz, K. Kovacs, Pathology of GH-producing pituitary adenomas and GH cell hyperplasia of the pituitary. Pituitary **20**, 84–92 (2017)
104. T. Tanaka, N. Kato, K. Aoki, M. Watanabe, T. Arai, Y. Hasegawa, T. Abe, Long-term follow-up of growth hormone-producing pituitary carcinoma with multiple spinal metastases following multiple surgeries: case report. Neurol. Med. Chir. (Tokyo). **53**, 707–711 (2013)
105. I. Shimon, R.S. Jallad, M. Fleseriu, C.G. Yedinak, Y. Greenman, M.D. Bronstein, Giant GH-secreting pituitary adenomas: management of rare and aggressive pituitary tumors. Eur. J. Endocrinol. **172**, 707–713 (2015)
106. J.A. Jane Jr, R.M. Starke, M.A. Elzoghby, D.L. Reames, S.C. Payne, M.O. Thorner, J.C. Marshall, E.R. Laws Jr, M.L. Vance, Endoscopic transsphenoidal surgery for acromegaly: remission using modern criteria, complications, and predictors of outcome. J. Clin. Endocrinol. Metab. **96**, 2732–2740 (2011)
107. M. Shirvani, R. Motiei-Langroudi, Transsphenoidal surgery for growth hormone-secreting pituitary adenomas in 130 patients. World Neurosurg. **81**, 125–130 (2014)
108. A. Giustina, P. Chanson, D. Kleinberg, M.D. Bronstein, D.R. Clemmons, A. Klibanski, A.J. van der Lely, C.J. Strasburger, S. W. Lamberts, K.K. Ho, F.F. Casanueva, S. Melmed, Acromegaly Consensus Group, Expert consensus document: A consensus on the medical treatment of acromegaly. Nat. Rev. Endocrinol. **10**, 243–248 (2014)
109. L. Katznelson, E.R. Laws Jr, S. Melmed, M.E. Molitch, M.H. Murad, A. Utz, J.A. Wass, Endocrine Society, Acromegaly: an endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. **99**, 3933–3951 (2014)
110. F. Cordido, J.A. Garcia Arnes, M. Marazuela Aspiroz, E. Torres Vela, grupo de Neuroendocrinologia de la Sociedad Espanola de Endocrinologia y Nutricion, Practical guidelines for diagnosis and treatment of acromegaly. Grupo de Neuroendocrinologia de la Sociedad Espanola de Endocrinologia y Nutricion. Endocrinol. Nutr. **60**, 457.e1–457.e15 (2013)
111. R.S. Jallad, M.D. Bronstein, Optimizing medical therapy of acromegaly: beneficial effects of cabergoline in patients uncontrolled with long-acting release octreotide. Neuroendocrinology **90**, 82–92 (2009)
112. A. Colao, M.D. Bronstein, P. Freda, F. Gu, C.C. Shen, M. Gadelha, M. Fleseriu, A.J. van der Lely, A.J. Farrall, K. Hermosillo Resendiz, M. Ruffin, Y. Chen, M. Sheppard, Pasireotide C2305 study group, Pasireotide versus octreotide in acromegaly: a head-to-head superiority study. J. Clin. Endocrinol. Metab. **99**, 791–799 (2014)

113. L. Rostomyan, I. Potorac, P. Beckers, A.F. Daly, A. Beckers, AIP mutations and gigantism. Ann. Endocrinol. (Paris). **78**, 123–130 (2017)
114. M.R. Gadelha, L. Kasuki, M. Korbonits, Novel pathway for somatostatin analogs in patients with acromegaly. Trends Endocrinol. Metab. **24**, 238–246 (2013)
115. A. Di Ieva, F. Rotondo, L.V. Syro, M.D. Cusimano, K. Kovacs, Aggressive pituitary adenomas-diagnosis and emerging treatments. Nat. Rev. Endocrinol. **10**, 423–435 (2014)
116. C. Halevy, B.C. Whitelaw, How effective is temozolomide for treating pituitary tumours and when should it be used? Pituitary **20**, 261–266 (2017)
117. P. Beck-Peccoz, F. Brucker-Davis, L. Persani, R.C. Smallridge, B.D. Weintraub, Thyrotropin-secreting pituitary tumors. Endocr. Rev. **17**, 610–638 (1996)
118. A. Tjornstrand, K. Gunnarsson, M. Evert, E. Holmberg, O. Ragnarsson, T. Rosen, H. Filipsson Nystrom, The incidence rate of pituitary adenomas in western Sweden for the period 2001-2011. Eur. J. Endocrinol. **171**, 519–526 (2014)
119. M. Gruppetta, C. Mercieca, J. Vassallo, Prevalence and incidence of pituitary adenomas: a population based study in Malta. Pituitary **16**, 545–553 (2013)
120. A. Raappana, J. Koivukangas, T. Ebeling, T. Pirila, Incidence of pituitary adenomas in Northern Finland in 1992-2007. J. Clin. Endocrinol. Metab. **95**, 4268–4275 (2010)
121. F. Brucker-Davis, E.H. Oldfield, M.C. Skarulis, J.L. Doppman, B.D. Weintraub, Thyrotropin-secreting pituitary tumors: diagnostic criteria, thyroid hormone sensitivity, and treatment outcome in 25 patients followed at the National Institutes of Health. J. Clin. Endocrinol. Metab. **84**, 476–486 (1999)
122. M. Bertholon-Gregoire, J. Trouillas, M.P. Guigard, B. Loras, J. Tourniaire, Mono- and plurihormonal thyrotropic pituitary adenomas: pathological, hormonal and clinical studies in 12 patients. Eur. J. Endocrinol. **140**, 519–527 (1999)
123. N. Sanno, A. Teramoto, R.Y. Osamura, Thyrotropin-secreting pituitary adenomas. Clin. Biol. Heterog. Curr. Treat. J. Neurooncol. **54**, 179–186 (2001)
124. S. Yamada, N. Fukuhara, K. Horiguchi, M. Yamaguchi-Okada, H. Nishioka, A. Takeshita, Y. Takeuchi, J. Ito, N. Inoshita, Clinicopathological characteristics and therapeutic outcomes in thyrotropin-secreting pituitary adenomas: a single-center study of 90 cases. J. Neurosurg. **121**, 1462–1473 (2014)
125. A. Tjornstrand, H.F. Nystrom, Diagnosis of endocrine disease: Diagnostic approach to TSH-producing pituitary adenoma. Eur. J. Endocrinol. **177**, R183–R197 (2017)
126. M.A. Kirkman, Z. Jaunmuktane, S. Brandner, A.A. Khan, M. Powell, S.E. Baldeweg, Active and silent thyroid-stimulating hormone-expressing pituitary adenomas: presenting symptoms, treatment, outcomes, and recurrence. World Neurosurg. **82**, 1224–1231 (2014)
127. F. Gatto, L.F. Grasso, E. Nazzari, T. Cuny, P. Anania, C. Di Somma, A. Colao, G. Zona, G. Weryha, R. Pivonello, D. Ferone, Clinical outcome and evidence of high rate post-surgical anterior hypopituitarism in a cohort of TSH-secreting adenoma patients: Might somatostatin analogs have a role as first-line therapy? Pituitary **18**, 583–591 (2015)
128. M.S. Elston, J.V. Conaglen, Clinical and biochemical characteristics of patients with thyroid-stimulating hormone-secreting pituitary adenomas from one New Zealand centre. Intern. Med. J. **40**, 214–219 (2010)
129. J.A. Gondim, J.P. Almeida, L.A. Albuquerque, M. Schops, E. Gomes, T. Ferraz, W. Sobreira, M.T. Kretzmann, Endoscopic endonasal approach for pituitary adenoma: surgical complications in 301 patients. Pituitary **14**, 174–183 (2011)
130. F.G. Amlashi, N.A. Tritos, Thyrotropin-secreting pituitary adenomas: epidemiology, diagnosis, and management. Endocrine **52**, 427–440 (2016)
131. F. Rimareix, S. Grunenwald, D. Vezzosi, L.D. Riviere, A. Bennet, P. Caron, Primary medical treatment of thyrotropin-secreting pituitary adenomas by first-generation somatostatin analogs: a case study of seven patients. Thyroid **25**, 877–882 (2015)
132. E. Malchiodi, E. Profka, E. Ferrante, E. Sala, E. Verrua, I. Campi, A.G. Lania, M. Arosio, M. Locatelli, P. Mortini, M. Losa, E. Motti, P. Beck-Peccoz, A. Spada, G. Mantovani, Thyrotropin-secreting pituitary adenomas: outcome of pituitary surgery and irradiation. J. Clin. Endocrinol. Metab. **99**, 2069–2076 (2014)
133. E. Fliers, W.R. van Furth, P.H. Bisschop, Cure of a thyrotrophin (TSH)-secreting pituitary adenoma by medical therapy. Clin. Endocrinol. (Oxf.). **77**, 788–790 (2012)
134. P. Caron, S. Arlot, C. Bauters, P. Chanson, J.M. Kuhn, M. Pugeat, R. Marechaud, C. Teutsch, E. Vidal, P. Sassano, Efficacy of the long-acting octreotide formulation (octreotide-LAR) in patients with thyrotropin-secreting pituitary adenomas. J. Clin. Endocrinol. Metab. **86**, 2849–2853 (2001)
135. N. Sanno, A. Teramoto, R.Y. Osamura, Long-term surgical outcome in 16 patients with thyrotropin pituitary adenoma. J. Neurosurg. **93**, 194–200 (2000)
136. C.B. Wilson, A decade of pituitary microsurgery. The Herbert Olivecrona lecture. J. Neurosurg. **61**, 814–833 (1984)
137. E. Knosp, E. Steiner, K. Kitz, C. Matula, Pituitary adenomas with invasion of the cavernous sinus space: a magnetic resonance imaging classification compared with surgical findings. Neurosurgery **33**, 610–617 (1993)
138. A. Goel, T. Nadkarni, D. Muzumdar, K. Desai, U. Phalke, P. Sharma, Giant pituitary tumors: a study based on surgical treatment of 118 cases. Surg. Neurol. **61**, 436–445 (2004)
139. P. Mortini, R. Barzaghi, M. Losa, N. Boari, M. Giovanelli, Surgical treatment of giant pituitary adenomas: strategies and results in a series of 95 consecutive patients. Neurosurgery **60**, 993–1002 (2007)