Introduction

Acromegaly: a fascinating pituitary disorder

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Although acromegaly and gigantism are uncommon, since the clinical features originally reported by Johannes Wier in 1567 and Pierre Marie in 1886, there has been considerable interest in description of the condition, elucidating the etiology and pathophysiology as well as the development of treatments. There is a long-standing history of giants in the circus, skeletons of giants on display, and more recently, giants playing college and professional basketball.

Acromegaly (along with gigantism) is a systemic disease resulting from a growth hormone–secreting pituitary adenoma and, rarely, from an ectopic tumor (pancreatic or carcinoid tumor) producing growth hormone–releasing hormone. Although the clinical features, such as facial deformities including frontal bossing, prognathism, large hands and feet (and gigantism), are recognizable, the less commonly appreciated features are the risk of premature death and significant morbidity if the disease is not treated successfully.

Acromegaly is a systemic disease that affects the whole body including thickened skin, skin tags, hyperhidrosis, and cystic acne. Skeletal effects include frontal bossing, sinus enlargement (resonate voice), enlargement of the lower jaw ("alligator jaw") with dental malocclusion and increased spacing between the teeth, enlargement of the larynx (deepening of the voice), enlargement of the bones of the hands and feet, carpal tunnel syndrome, and enlargement of the rib cage ("barrel chest"). Bone density is usually normal but may be reduced by concomitant hypogonadism. As a result of bony overgrowth, the most common problem is osteoarthritis of the large joints, often requiring surgical procedures. Cardiovascular effects include hypertension, cardiomegaly, and heart failure; pulmonary consequences include obstructive sleep apnea (an effect of soft-tissue enlargement of the posterior pharynx and also central sleep apnea). Gastrointestinal tract effects include increased prevalence of colon polyps and potentially colon cancer. Metabolic effects of excessive growth hormone are insulin resistance and diabetes mellitus (in 25%–50% of patients). In women, infertility or loss of regular menses may occur. Men often have a subnormal testosterone level. There is also an increased prevalence of thyroid gland nodules and ovarian cysts. Another effect of excessive growth hormone production is reduction in fat mass and increase in muscle mass.

A continuing problem is the delay in diagnosis, often 10 years or more from the onset of symptoms. Patients are treated for the acromegaly-related consequences such as hypertension, heart disease, sleep apnea, diabetes mellitus, and osteoarthritis without recognition of the underlying etiology. The gradual change in physical features and the lack of recognition of the physical characteristics, which patients often attribute to aging, result in the delay in diagnosis.

Acromegaly includes 2 general features that are the focus of treatment: the tumor and the excess growth hormone and its consequences. This issue of *Neurosurgical Focus* describes the history of recognition of acromegaly, the pathogenesis of the disease, changes in cranial anatomy, the specific features of growth hormone–secreting tumors, types of treatment (surgery, radiation therapy, medical treatments), and the outcomes of these treatments. Because of the delay in diagnosis, many patients harbor a large, invasive, pituitary adenoma when the disease is finally recognized. Resection is the first treatment but patients often require additional therapies for a sustained remission with the goal of reducing morbidity and the risk of premature death. Patients with acromegaly and other types of pituitary adenomas exemplify the need for multimodality therapy to achieve optimal outcomes. *(DOI: 10.3171/2010.10.FOCUS.Intro)*

Neurosurg Focus 29 (4):E1, 2010

Early descriptions of acromegaly and gigantism and their historical evolution as clinical entities

Historical vignette

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Giants have been a subject of fascination throughout history. Whereas descriptions of giants have existed in the lay literature for millennia, the first attempt at a medical description was published by Johannes Wier in 1567. However, it was Pierre Marie, in 1886, who established the term "acromegaly" for the first time and established a distinct clinical diagnosis with clear clinical descriptions in 2 patients with the characteristic presentation. Multiple autopsy findings revealed a consistent correlation between acromegaly and pituitary enlargement. In 1909, Harvey Cushing postulated a "hormone of growth" as the underlying pathophysiological trigger involved in pituitary hypersecretion in patients with acromegaly. This theory was supported by his observations of clinical remission in patients with acromegaly in whom he had performed hypophysectomy. In this paper, the authors present some of the early accounts of acromegaly and gigantism, and describe its historical evolution as a medical and surgical entity.
(DOI: 10.3171/2010.7.FOCUS10160)

Key Words • **acromegaly** • **gigantism** • **historical vignette** • **pituitary tumor**

Acromegalic individuals and giants have been the subject of fascination for millennia. Whereas there have been a multitude of descriptions in the lay literature since the beginnings of the written word, the first scientific description was probably made by Dutch physician and occultist Johannes Wier. His medical description of a giantess was published in 1567 in the *Medicarum Observationum*.[48] Further descriptions surfaced in the late 18th and early 19th centuries by Noel (1779), Saucerotte (1801), Gall (1810), and Magendie (1839).[15,24,27,36] In 1835, French dermatologist Jean-Louis-Marc Alibert described "Geant scrofuleux" in his monograph on dermatological disorders.[1] In 1857, W. O. Chalk described a case of pathological dislocation of the jaw secondary to macroglossia in a patient with acromegaly.[9] In 1864, the Italian neurologist Andre Verga described "prosopectasia" (widening of the face), while in 1868, Lombroso described "macrosomia."[25,26,45] These were followed by case descriptions by Friedreich in 1868 and Henrot in 1877, the latter including an autopsy report in which a 45 × 30–mm tumor in the position of the pituitary body was described.[14,20,21] Brigidi, in 1877, described the case of the Italian actor Ghirlenzoni, stating:

> … unfortunately, he could not speak clearly, on account of the excessive size of his tongue … the rest of the face had more the appearance of an ape than a man. It was lengthened, with very marked prognathism, flattened and indented laterally, as if the cheeks had been elevated by a blow from the hatchet on each side.[7,8]

Taruffi described the skeletal deformities associated with acromegaly in 1877.[41,42] A series of descriptions were to follow during the late 19th century.[10,11,18,19,24,46] Even though multiple descriptions of this condition were reported by other physicians, the term "acromegaly" did not exist until 1886 when Pierre Marie defined the disease in his classic essay titled "Sur deux cas d'acromégalie; hypertrophie singulière non congénitale des extrémités supérieures, inférieures et céphalique."[29]

Pierre Marie: Establishment of Acromegaly as a Diagnosis

Despite early descriptions of acromegalic patients, there was no consensus on a unifying underlying diagnosis. Early in the 19th century, the concept of an endocrine system was not yet discovered. Therefore, most physicians at that time attributed the clinical findings of acromegaly to manifestations of other diseases such as Paget disease, myxedema, tuberculosis, syphilis, rheumatism, or gout. It was not until 1885 when Pierre Marie described 2 cases of an unusual noncongenital hypertrophy of the head and the upper and lower extremities, which were subsequently published in 1886.[29] It was in this manuscript that the term "acromegaly" was first coined, and where it was

Fig. 1. Photographs of Marie's acromegalic patients in the clinic of Professor Charcot.

deemed a distinct clinical disease (also known as "Marie's malady"). These 2 cases were observed in Professor Charcot's clinic at the Salpêtrière Hospital in Paris.

Marie's first case was that of a 37-year-old woman who had not sought medical attention before, but who had developed amenorrhea and headaches at the age of 24 years (Fig. 1). Describing his findings, he stated:

> It was at the age of twenty-four, at the time the menstruation suddenly ceased, that she noticed the sudden increase in her hands. Her face at this time also underwent changes, … so that when the patient returned home none of her relatives could recognize her…. The whole feet are large, including the toes. Though the latter are increased in size, they have preserved their form, there is no true deformity, their appearance is simply that of a very big person…. The tongue is enlarged. The patient is a little deaf, and the sight is also slightly defective…. The cranial vertex is of nearly the same size as the end of the chin. The lower jaw is well developed…[29]

In addition to a detailed description of this patient's acromegalic appearance, Marie also reported a finding consistent with diabetes insipidus: "The patient's thirst is intense, obliging her to beg tea of her friends in order to satisfy it. The quantity of urine is excessive...."[29]

The second case was that of a 54-year-old woman who developed amenorrhea at the age of 29 years. The year after that, the patient completely lost her vision and became permanently blind. This patient went on to notice incremental increases in the size of her head, hands, and feet. Marie described:

> The borders of the orbits are very thick, also the frontal eminences, making between them and the upper border of the malar bone a deep depression, something similar to the corresponding region of a cow. The nose is large. The lower jaw is very thick...[29]

In addition to coining the term "acromegaly," Marie's major contribution to the field was the establishment of a unique clinical entity, whose characteristics he vividly described with his detailed case reports. Although he did not postulate on the underlying pathophysiological mechanisms of acromegaly, he did state that he believed the disease was not attributed to previously implicated origins, such as myxedema or Paget disease. Marie's work was followed by a thesis on acromegaly by his intern, Souza-Leite, who further bolstered these arguments with more case reports (Fig. 2).[38] At this point in time, the cause of acromegaly was still not known. However, it is interesting to note that Marie frequently observed the occurrence of great hypertrophy of the pituitary body.[38]

Pituitary Tumors and Sellar Enlargement: an Observation in Patients With Acromegaly

The underlying pathophysiological mechanism of acromegaly and gigantism was an area of great debate since the time of Saucerotte in 1801.[36] Verga,[45] in 1864, reported sellar enlargement in a patient with acromegaly. After that, multiple reports emerged suggesting the connection between acromegaly and pituitary pathological entities. In 1887, Oscar Minkowski[33] of Germany published a series of autopsy studies that strengthened this association. He found pituitary enlargement in all patients with acromegaly, and was probably the first to realize the causal relationship between acromegaly and pituitary enlargement. Massalongo[30,31] attributed acromegaly to pituitary hyperfunction by demonstrating pituitary tumor cells that contained granular cytoplasm in a patient with acromegaly. In 1898, Woods Hutchinson[22] described the association between pituitary hyperfunction and clinical acromegaly. Despite the multiple observations of pituitary tumors in patients with acromegaly, the link between the two remained controversial for many years.

The relationship of acromegaly and gigantism was also an area of contention. Marie[28,29] and Souza-Leite[38] believed that these were distinct entities. As detailed in Bartels' account,[3] Fritsche and Klebs, on the other hand,

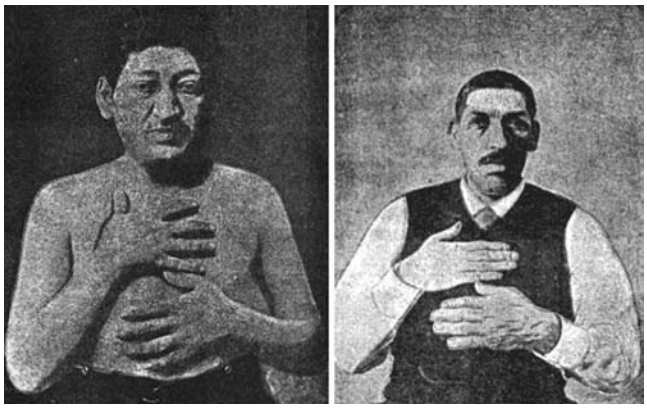

Fig. 2. Photographs of acromegalic patients, from Souza-Leite's thesis on acromegaly published in 1890.

Fig. 3. The French giantess, Lady Aama, as photographed by Frank Wendt, New York.

believed that acromegaly and gigantism were the same disorder, the former being acquired and the latter congenital. Evidence for a pituitary cause of gigantism was supported by Hutchinson's pathological descriptions of a French giantess known as Lady Aama (Fig. 3). She died at the age of 18 years and stood 6 feet, 7.75 in tall. Pathological examination of her skull revealed a very large pituitary fossa (31 × 37 mm) and a huge frontal sinus. Hutchinson[22] stated: "The pituitary body was found to be greatly enlarged…. It appeared to be about the size of a pigeon's egg…." It was eventually recognized that both acromegaly and gigantism had the same underlying pathogenesis, but differed in the patient's age at onset. Acromegaly occurred in adulthood (Fig. 4), whereas gigantism occurred in childhood prior to the closure of the growth plates in the long bones (Figs. 5 and 6).

Harvey Cushing: Postulation of Pituitary Hyperfunction

The debate about an underlying pituitary disorder in acromegaly continued in the early 1900s. Harvey Cushing, in his book *The Pituitary Body and Its Disorders: Clinical Status Produced by Disorders of the Hypophysis Cerebri*,[12] further tackled the debate by describing the 4 prevailing theories of the pituitary origin of acromegaly and gigantism. The first theory was postulated by Marie, who stated that the clinical manifestations were due to pituitary hyposecretion. The second theory, advocated by Massalongo,[30,31] Tamburini,[40] Benda,[5] Modena,[34] and Fisher,[13] proposed that pituitary hypersecretion was the cause. In the third theory,

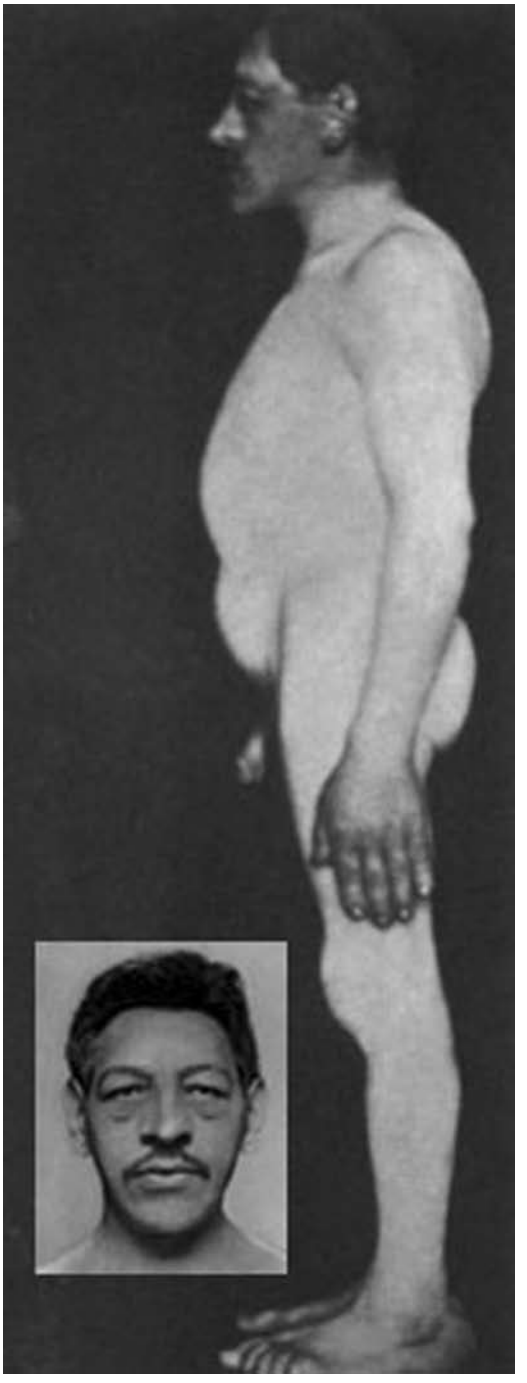

Fig. 4. Photographs of a 40-year-old tanner with acromegaly. Note "the enormous paw-like hand with outsized, clubbish thick fingers and the short broad nails, as well as the monstrous foot, in which is also noticeable the thickening of the toes, the significant volume of the wide rearward looming heel and the bulging thickness of the pedal margins" (from Heinrich Curschmann's *Klinische Abbildungen: Sammlung von Darstellungen der Veränderung der äusseren Körperform bei inneren Krankheiten*).

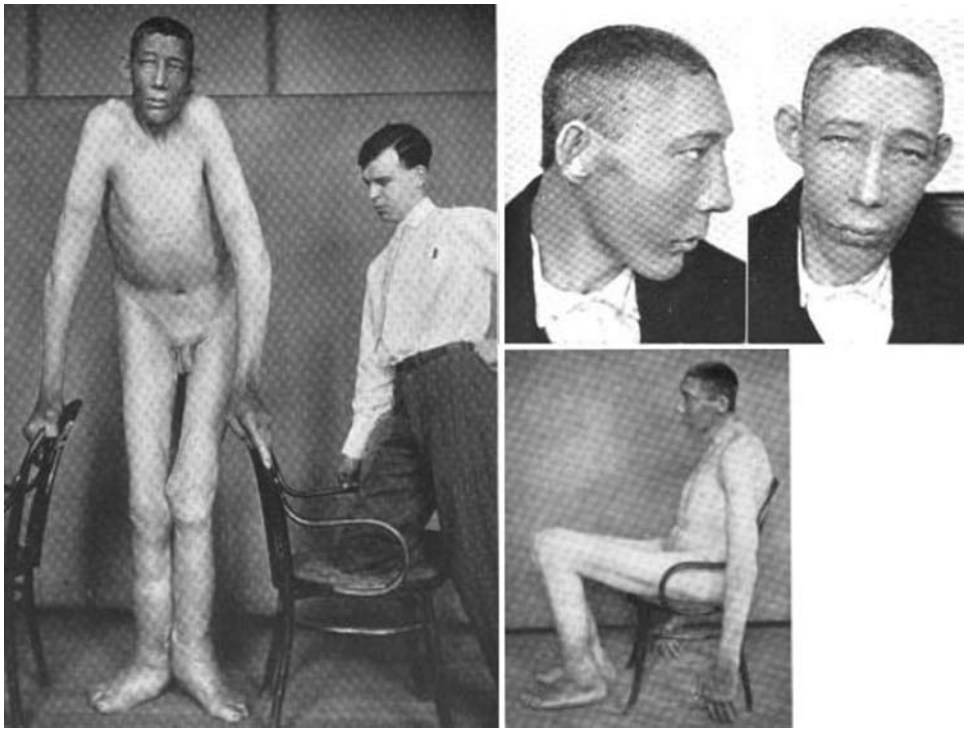

Fig. 5. Preadolescent hyperpituitarism with giant overgrowth in a patient who was referred to Dr. Cushing in 1910 (from Cushing's *The Pituitary Body and Its Disorders: Clinical Status Produced by Disorders of the Hypophysis Cerebri*).

clinical acromegalic features were attributed to a nutritional disorder, with the pituitary enlargement as a secondary manifestation. This theory was supported by Gauthier,[16] Strumpell,[39] Vassale,[44] and Guerrini.[17] The fourth theory, proposed by Silvestrini,[37] Arnold,[2] Warda,[47] and Petrén,[35] suggested that there was no causative relationship between clinical acromegaly and the pituitary gland.

Cushing[12] supported the theory of pituitary hypersecretion (Fig. 7) and stated:

> Certainly most of the circumstantial evidence in our possession points in the direction of an oversecretion, whether normal or pathological; and this is at least the most acceptable present working hypothesis.

Cushing was so certain of a pituitary source of acromegaly that in 1909 he obtained permission to open the skull of the Irish Giant, Charles Byrne (also known as O'Brien) of Littlebridge, Ireland (Fig. 8). Mr. Byrne, who was thought to be the tallest person with acromegaly of his time, stood 7 feet, 7 in tall, and died in 1783. His body was promptly acquired by Dr. John Hunter, who boiled all the flesh off of the bones and ultimately put the skeleton on display, without having performed any anatomical dissection. When Cushing opened the skull, he found an enlarged pituitary fossa measuring 21 × 24 × 11 mm, suggestive of glandular hypertrophy.[6,32] Cushing's theory of pituitary hypersecretion was also supported by his own observations of clinical remission in patients with acromegaly who underwent hypophysectomy. In 1909, he was among the first to postulate a "hormone of growth" in the pituitary gland, which laid the foundation for the hypothesis that hyperfunctioning of the anterior pituitary was responsible for the manifestations of acromegaly.

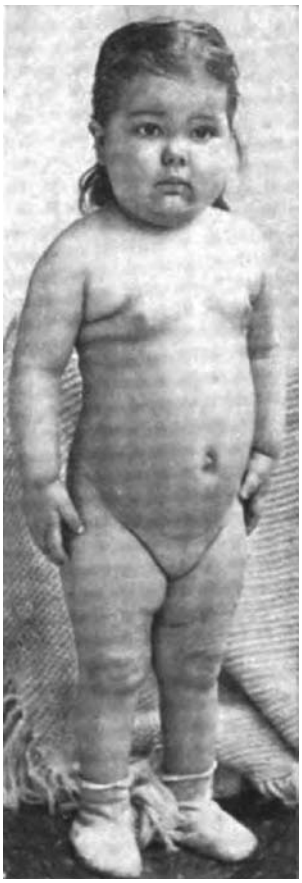

Fig. 6. Photograph of a 3-year-old patient with a hypophyseal tumor, exhibiting gigantism and adiposity (from Cushing's *The Pituitary Body and Its Disorders*).

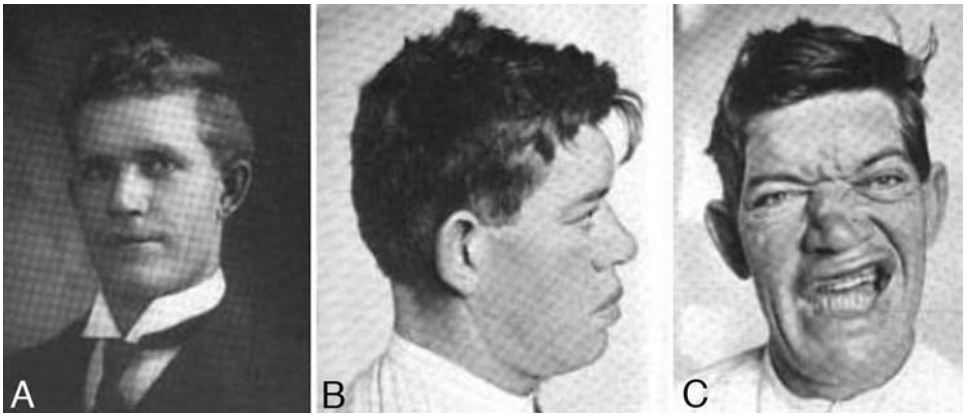

Fig. 7. A patient with a hypophyseal tumor who was referred to Dr. Cushing. At the age of 25 years **(A)**, the patient is free from acromegalic changes. At the age of 35 years **(B and C)**, the patient demonstrates acromegalic features (from Cushing's *The Pituitary Body and Its Disorders*).

The Establishment of a Hormone of Growth: Birth of Neuroendocrinology

The development of the recognition of acromegaly and gigantism as clinical entities cannot be concluded without an understanding of the endocrinology system as it relates to the pathogenesis. In 1902, following an elegant set of experiments on dog intestine, Bayliss and Starling[4] demonstrated that an extract of duodenal mucosa injected into the bloodstream resulted in stimulation of pancreatic secretion, and named this active material "secretin." They proposed a hormone system in which substances produced at one site had the ability to bring about physiological changes at a distant site without a direct neural stimulus. The term "hormone" (from the Greek meaning to excite) was introduced by Starling at the suggestion of William Hardy in 1905. Although Cushing was the first to postulate a pituitary "hormone of growth" in 1912, it was not until 1944 when growth hormone was finally isolated by Li and Evans, as detailed by Kaplan.[23] Furthermore, it was not until the 1950s that the insulin-like growth factors were discovered by Salmon and Daughaday, as described by Van den Brande.[43] The measurement of endocrine function would later be revolutionized by radioimmunoassays. The physiological mechanisms of the growth hormone and insulin-like growth factor system were eventually understood. Innovations in modern neuroimaging, pituitary surgery, radiotherapy, and medical therapy contributed to the advancements that set the stage for modern medical and surgical management of acromegaly and gigantism.

Fig. 8. A print of Charles Byrne (The Irish Giant) by John Kay, 1803 (from the Bridgeman Art Library, City of Westminster Archive Centre, London).

Conclusions

Although accounts have appeared in the lay literature for millennia, the recognition of acromegaly and gigantism as clinical pathological entities has evolved over the last 125 years. The cornerstone was laid by Marie, with his establishment of acromegaly as a distinct clinical phenomenon. Following this, a multitude of anatomical, pathological, and physiological studies have added to our clinical understanding, with pituitary hypersecretion of growth hormone being established as the underlying pathophysiological mechanism. As we establish new techniques for the management of this fascinating disease, the clinical evolution of acromegaly and gigantism continues to be of tremendous interest.

Disclosure

The authors report no conflict of interest with regard to the production of this manuscript.

Author contributions to the study and manuscript preparation

include the following. Conception and design: Liu, Eloy. Acquisition of data: Liu, Mammis. Analysis and interpretation of data: Liu, Mammis. Drafting the article: Liu, Mammis. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: Liu.

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Manuscript submitted June 15, 2010.
Accepted July 12, 2010.

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Neurosurg Focus 29 (4):E2, 2010

Growth hormone-secreting adenomas: pathology and cell biology

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The majority of patients with acromegaly harbor a functioning growth hormone (GH) pituitary adenoma. Growth hormone–secreting adenomas correspond to about 20% of all pituitary adenomas. From the histopathological point of view, a variety of adenomas may present with clinical signs and symptoms of GH hypersecretion including pure GH cell adenomas (densely and sparsely granulated GH adenomas), mixed GH and prolactin cell adenomas, and monomorphous adenomas with primitive cells able to secrete GH and prolactin including the acidophilic stem cell adenoma and the mammosomatotroph cell adenoma. In this article, the author reviews the main pathological features of the GH-secreting adenomas and some of the molecular genetics mechanisms involved in their pathogenesis. *(DOI: 10.3171/2010.7.FOCUS10169)*

Key Words • **pituitary neoplasm** • **acromegaly** • **molecular genetics** • **animal model**

The great majority of patients with acromegaly have a pituitary GH-secreting adenoma; ectopic GHRH or GH-secreting neuroendocrine tumors producing acromegaly represent less than 5% of the patient population.[10] Growth hormone–secreting adenomas are accompanied by high serum GH and IGF-I levels and signs and symptoms of acromegaly or gigantism.[10] Overall, these adenomas constitute about 20% of all pituitary adenomas.[27] Most patients with acromegaly have macroadenomas when first diagnosed, many of them with suprasellar expansion and parasellar invasion.[27] Consequently, symptoms due to an expanding tumor mass, including headaches and visual field defects, may also be present in patients with large tumors. In about 30%–50% of the patients, cosecretion of PRL with GH by the tumor results in signs and symptoms of hyperprolactinemia.[28,47]

Pathological Features of GH-Secreting Tumors

Growth Hormone–Secreting Adenomas

Pure GH-secreting adenomas are histologically classified into the following 2 variants: the DGGH cell adenoma and the SGGH cell adenoma, reflecting the variable amount of secretory granules present in the cellular cytoplasm (Fig. 1).

The DGGH cell adenomas are composed of large cells with eosinophilic cytoplasm showing considerable granularity, reflecting the great numbers of secretory granules seen at the ultrastructural level (Fig. 2). The nucleus tends to be central and oval with prominent nucleoli. Characteristically, immunohistochemical stains show strong GH positivity dispersed diffusely within the entire tumor. At the ultrastructural level, the DGGH adenomas are composed of cells that resemble the normal somatotrophs of the pituitary gland and are characterized by a well-developed rough endoplasmic reticulum network, prominent Golgi complexes, and numerous large (300–600 nm) secretory granules.[25]

The SGGH cell adenomas contain cells more chromophobic in appearance than DGGH cell adenomas, and they have eccentric nuclei. The most distinctive feature of these adenomas is the presence of paranuclear eosinophilic structures called fibrous bodies. Immunostaining for GH is distributed focally within the tumor, and in the cell it can be in a dotlike appearance, reflecting the small amount of secretory granules seen at ultrastructure. In addition, fibrous bodies are strongly positive for cytokeratin (Fig. 3).[37] Fibrous bodies are characterized at the ultrastructural level by an accumulation of intermediate filaments and tubular smooth-surfaced endoplasmic reticulum (Fig. 3).[25]

Abbreviations used in this paper: CNC = Carney complex; DGGH = densely granulated GH; FIPA = familial isolated pituitary adenoma; GH = growth hormone; GHRH = GH releasing hormone; IGF-I = insulin-like growth factor–I; LOH = loss of heterozygosity; MEN-1 = multiple endocrine neoplasia Type 1; PRL = prolactin; SGGH = sparsely granulated GH.

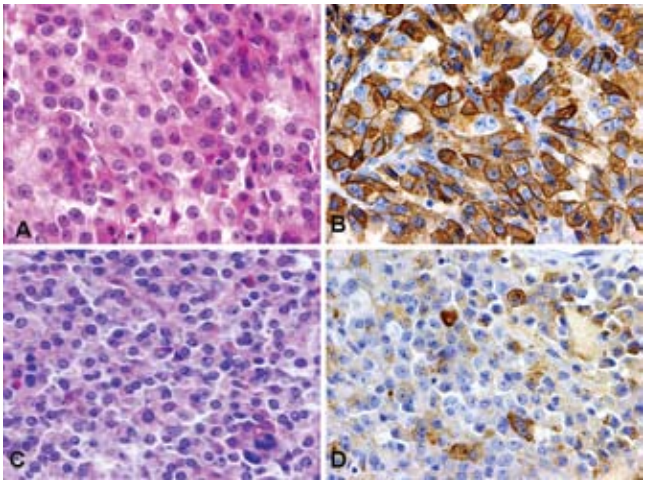

Fig. 1. Photomicrographs of a GH-secreting adenoma. **A:** A DGGH cell adenoma showing large cells with eosinophilic, granular cytoplasm, and a central nucleus with prominent nucleoli (H & E). **B:** The tumor shows intense and diffuse immunostaining for GH. **C:** An SGGH cell adenoma is characteristically more chromophobic with H & E staining. **D:** Immunohistochemistry for GH is heterogeneous and less prominent for SGGH cell adenomas than for DGGH cell adenomas. Original magnification × 200.

The distinction of these 2 subtypes of GH cell adenomas is important since these tumors appear to have different clinical behavior. The SGGH cell adenomas exhibit more aggressive biological behavior than the DGGH cell adenomas.[28,38,56] In a review of almost 90 patients with acromegaly who underwent follow-up at our institution, although no significant difference in cure rate and survival was present between these 2 subtypes of GH-secreting adenomas, SGGH cell adenomas were more likely to be locally invasive than DGGH cell tumors.[28] Obari et al.[38] have reported similar findings with a significantly higher incidence of suprasellar extension and cavernous sinus invasion in SGGH than DGGH cell adenomas (65% vs 38%, respectively; $p < 0.05$). Although no significant differences were seen in clinical presentation and GH or IGF-I levels, these authors reported a lower mean patient age at the diagnosis of an SGGH cell adenoma than that of a DGGH cell adenoma (43.6 ± 11.1 years vs 49.6 ± 13.8 years; $p < 0.05$).[38]

Additionally, the response of tumors to adjuvant medical treatment appears to differ according to the subtype of GH cell adenoma.[7] Tumor subtyping (DGGH) was the strongest predictor of IGF-I normalization in patients with acromegaly receiving postoperative somatostatin analog therapy.

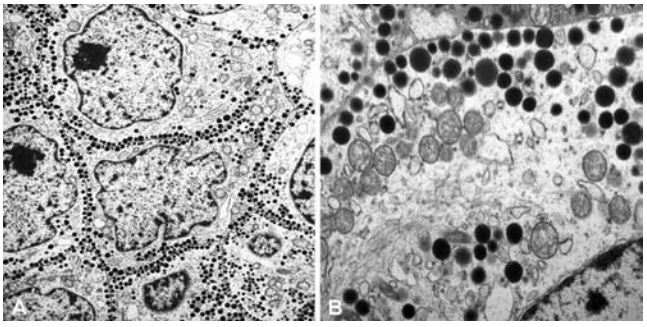

Fig. 2. A DGGH cell adenoma. The ultrastructure exhibits well-developed organelles and abundant large secretory granules. Original magnification × 2500 **(A)** and × 5000 **(B)**.

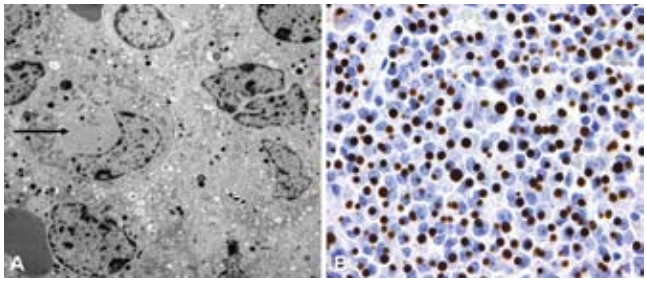

Fig. 3. An SGGH cell adenoma. **A:** The ultrastructure of SGGH cells display sparse neurosecretory granules and the typical fibrous bodies *(arrow)*. **B:** Cytokeratin immunostaining highlights fibrous bodies typically seen in these sparsely granulated tumors. Original magnification × 2500 **(A)** and × 200 **(B)**.

A number of GH-secreting adenomas display secondary immunoreactivity for other pituitary hormones that do not necessarily show clinical or biochemical evidence of hormonal hypersecretion.[28,46] Secondary immunoreactivity is mostly seen for PRL and for the glycoprotein hormone α-subunit; less frequently, immunoreactivity is seen for β–follicle-stimulating hormone, β–luteinizing hormone, and β–thyroid-stimulating hormone. Apart from the well-characterized mixed GH/PRL-secreting adenomas (see below), plurihormonal differentiation is not clinically symptomatic in the majority of cases.

Mixed GH/PRL-Secreting Adenomas

A large percentage of GH-secreting adenomas also secrete PRL. About half of the patients with surgically removed GH-secreting adenomas in our institution presented with signs and symptoms of acromegaly and hyperprolactinemia.[28]

Three morphological tumor types that cosecrete GH and PRL can be identified as follows: the mixed GH cell/PRL cell adenoma, the mammosomatotroph cell adenoma, and the acidophilic stem cell adenoma.[12,24,26,28,31] Mixed GH cell/PRL cell adenomas and mammosomatotroph cell adenomas present clinically with acromegaly and mild hyperprolactinemia; on the other hand, patients with acidophilic stem cell adenoma present with hyperprolactinemia and only rarely with acromegaly. In our experience, these mixed tumors behave more aggressively than any pure GH-secreting adenomas with a lower surgical cure rate.[28]

Mixed GH Cell/PRL Cell Adenoma. These adenomas morphologically resemble GH-secreting adenomas, but immunohistochemistry is demonstrated for both GH and PRL with varying degrees of staining and distribution. The 2 cell types may form small groups or they may be scattered. At the ultrastructural level, these adenomas are bimorphous tumors, consisting of 2 separate cell populations, DGGH or SGGH cells and PRL cells (Fig. 4).[12,31]

Mammosomatotroph Cell Adenoma. This rare GH/PRL-producing tumor accounts for less than 2% of all

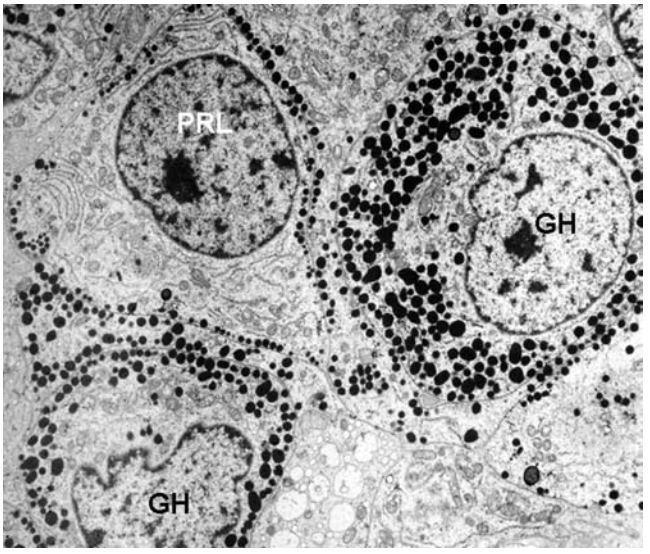

Fig. 4. Mixed GH/PRL cell adenoma. Ultrastructure of a mixed GH cell/PRL cell–secreting adenoma showing bimorphous cell population with densely granulated GH cells and PRL cells. Original magnification × 2500.

pituitary adenomas and about 8% of tumors associated with acromegaly.[24] Histologically, the adenomas are acidophilic on H & E staining, and immunohistochemical analysis demonstrates the presence of GH and PRL in the cytoplasm of the same tumor cells. These findings have been confirmed by double-labeling studies and by immunoelectron microscopy.[24] At the ultrastructural level, a monomorphous cell population contains features of GH and PRL cells.[25] The cells are mostly similar to DGGH cells, but with irregular secretory granules of variable sizes (200–2000 nm). Granular extrusions and extracellular deposits of secretory material, features consistent with PRL cell differentiation, are characteristically present.

Acidophilic Stem Cell Adenoma. This subtype of mixed adenoma is very rare and represents only the minority of GH/PRL-producing tumors.[28,44] Unlike the 2 subtypes previously discussed, most of the patients present with symptoms of hyperprolactinemia; acromegaly is uncommon.[26] The majority of the tumors are rapidly growing macroadenomas with invasive features, a distinct behavior pattern of ordinary prolactinomas; therefore, the diagnosis of such adenomas is of clinical relevance. Histologically, acidophilic stem cell adenomas are chromophobic with focal oncocytic changes of the cytoplasm. Immunoreactivity for PRL and, to a lesser extent, GH is present in the cytoplasm of the same tumor cells. Electron microscopy is necessary for precise identification of this adenoma.[25,26] They are composed of a single population of immature cells exhibiting features reminiscent of both SGGH cells and PRL cells. Oncocytic change with the presence giant mitochondria is characteristic of these adenomas.

Growth Hormone–Secreting Pituitary Carcinomas

Pituitary carcinomas are very rare, comprising less than 1% of all pituitary neoplasms.[32,41,45] By definition, pituitary carcinomas are characterized by the presence of either craniospinal dissemination or systemic metastases.[45]

The great majority of reported pituitary carcinomas are hormonally active tumors with endocrine manifestations indistinguishable from those of pituitary adenomas. The most common endocrine syndromes are adrenocorticotropic hormone–secreting tumors with Cushing disease (42%) and PRL-secreting tumors presenting with hyperprolactinemia (33%).[45] Carcinomas associated with acromegaly or gigantism represent only about 6% of the reported cases.[42]

The diagnosis of pituitary carcinoma is dependent on the demonstration of metastatic spread.[45] There are no morphological criteria to distinguish locally aggressive or even markedly atypical adenomas from carcinomas when the tumor is confined to the sella. However, all reported GH carcinomas have presented as highly invasive tumors at the initial presentation.[41]

Medical Treatment and GH-Secreting Adenomas

Medical therapy is part of the multistep treatment of acromegaly.[35] Three classes of drugs are mostly available for the treatment of acromegaly including dopamine agonists, somatostatin receptor ligands, and a GH receptor antagonist.[35] These drugs may change the morphology of GH-secreting adenomas. Unlike the dramatic effects of dopamine agonists seen in prolactinomas, significant reduction in cell size is uncommonly seen in the GH tumors treated with dopamine agonists and somatostatin receptor ligands. Most frequent changes are characterized by variable degree of perivascular and interstitial fibrosis.[21,50] An increase in size of the secretory granules and the presence of larger and heterogeneous lysosomes with takeup of secretory granules (crinophagy) are seen at the ultrastructural level and are believed to be due inhibition of hormone release.

Pathological effects of the GH receptor antagonist in GH-secreting adenomas are not very well known. This drug does not have a direct antitumor effect. One case report of a GH-secreting adenoma with comparison of pre- and posttreatment effects reported insignificant changes in morphological features.[16] However, these authors have shown that proliferative markers (Ki 67 and topoisomerase-α) were markedly greater in the pegvisomant-exposed tumor than in the earlier specimen. However, there has not been substantiated confirmation of these findings.

Molecular Genetics of GH-secreting Tumors

Pituitary adenomas appear to result from a multistep and multicausal process in which hereditary genetic disposition, endocrine factors, and specific somatic mutations may serve as contributing factors. Adenomas are mostly monoclonal expansions as demonstrated by X-chromosomal inactivation analysis.[11] The great majority of adenomas arise in a sporadic manner, and only a minority of adenomas are part of hereditary or familial syndromes.[14]

Familial syndromes in which GH-secreting adenomas arise include the following: 1) MEN-1, linked to somatic mutations of the tumor suppressor gene *MEN-1* located at the 11q13 locus;[8] 2) CNC, linked to mutations of the tumor suppressor gene *PRKAR1A* located at 17q22-24;[49] and less commonly 3) McCune-Albright syndrome,

linked to activating mutation of the *gsp* oncogene located at 20q13[55] (see below). Growth hormone–secreting adenomas linked to either MEN-1 or CNC are believed to correspond to about 3% of all GH-secreting tumors.[9]

In addition, a small number of familial pituitary GH-secreting adenomas have been described in the absence of either MEN-1 or CNC. The so-called isolated familial somatotropinoma or FIPA is defined as a clinical syndrome characterized by more than 2 cases of acromegaly or gigantism in a family in the absence of MEN-1 or CNC.[53] FIPAs are believed to correspond to about 1% of all GH-secreting adenomas.[9] In several groups of the FIPAs, an association with LOH at the 11q13 locus unrelated to the *MEN-1* gene has been demonstrated.[5] Recently, a germline mutation of the aryl hydrocarbon receptor–interacting protein *(AIP)* gene has been reported in a set of Finnish and Italian families with pituitary adenoma predisposition.[54] The *AIP* gene is located at 11q13, the same region as the *MEN1* gene. Tumor samples from affected individuals showed LOH at the *AIP* locus, suggesting that *AIP* acts as a tumor suppressor gene. In the remaining FIPAs there has not been yet characterization of a single genetic alteration. In the overall group, however, there is a description of mutations of the *AIP* gene in about 15% of families.[13] Thus far, 3 sites of mutations of the *AIP* gene have been identified in this group of familial somatotrofinomas.[39] Mutations of the *AIP* gene were also found in a small number of patients with sporadic pituitary adenomas, mostly GH-secreting tumors.[39]

The majority of GH-secreting adenomas are, however, sporadic tumors in which the primary genetic defect remains unknown. A number of oncogenes and tumor suppressor genes have been recognized as potential participants in tumorigenesis of pituitary adenomas including GH-secreting adenomas.[17] As previously discussed, in patients with MEN-1, LOH of 11q13 is present in pituitary adenomas and in other lesions commonly seen in the syndrome, including parathyroid hyperplasia and tumors of the endocrine pancreas.[8] However, the *MEN-1* gene has not been proven to be a major player in sporadic GH-secreting adenomas.[4]

The most commonly found genetic alteration in sporadic GH-secreting adenomas is the activating mutation of the *gsp* gene.[29,30,52] The *gsp* oncogene mutation corresponds to a point mutation of the α-subunit of the stimulatory G-protein (GNAS), a stimulatory protein of adenylyl cyclase at the membrane level.[29,30,33] The GNAS protein is coupled to the GHRH receptor, a G protein–coupled receptor located at the cell membrane of somatotrophs, that mediates GH transcription by inducing cyclic adenosine monophosphate via a cyclic adenosine monophosphate response element-binding protein (CREB). The mutated GNAS protein inhibits GTPase activity, maintaining the adenylyl cyclase system in a continuously turned-on state, therefore mimicking the effects of GHRH on hormone signaling. The *gsp* gene mutation has been identified in about 40% of GH-secreting adenomas in Caucasians and in lower frequency in Asians.[33,48] Recently, *gsp* gene mutation has been reported in about 10% of tumors of patients with sporadic acromegaly in Brazil.[51]

TABLE 1: Genetic alterations implicated in GH-secreting adenomas

Alteration	Associated Disorder
Gene	Inherited or Familial Tumor
Menin (11q13)	MEN-1
PRKR1A (17q22-24)	CNC
gsp (20q13.3)	McCune-Albright syndrome
AIP (11q13)	FIPA
	Sporadic Tumor
gsp (20q13.3)	mostly in DGGH cell adenomas (10%–40% of cases)
CREB (2q32.3-q34)	cAMP response element-binding protein, transcription factor, constitutive phosphorylation†
Oncogene/Tumor Suppressor Gene	Result
*PTTG (5q22)**	pituitary tumor–transforming protein, securin protein, overexpression‡
*GADD45G (9q22.1-q22.2)**	growth arrest & DNA damage–inducible 45γ, proapoptotic factor, epigenetic silencing§
*ODC1 (2p25)**	ornithine decarboxylase-1, overexpression¶
*BAG1 (9p12)**	Bcl-2-associated athanogene, overexpression**
*CDKN2C (1p32)**	cyclin-dependent kinase inhibitor 2C (p18), underexpression**
*WIF1 (12)**	Wnt inhibitory factor-1, underexpression††

* Genetic alterations not specific to GH-secreting adenomas.
† According to Bertherat et al.
‡ According to Pei and Melmed.
§ According to Zhang et al.
¶ According to Evans et al.
** According to Morris et al.
†† According to Elston et al.

TABLE 2: Animal models for GH-secreting adenomas in the literature*

Authors & Year	Gene	Model	Pituitary Lesion
Asa et al., 1992, & Mayo et al., 1988	*GHRH*	transgenic	mammosomatotroph hyperplasia & adenoma
Fedele et al., 2002	*HMGA2*	transgenic	mixed GH/PRL adenoma
Fedele et al., 2005	*HMGA1*	transgenic	mixed GH/PRL adenoma
Abbud et al., 2005	*αGSU.PTTG*	transgenic	plurihormonal hyperplasia & occasional microadenoma (including GH)
Donangelo et al., 2006	*αGSU.PTTGxRb +/-*	bitransgenic	plurihormonal hyperplasia, higher incidence of adenomas (including GH), & intermediate lobe ACTH tumors
Egashira et al., 2008	*Prop1*	transgenic	GH, PRL, TSH, &/or gonadotrophin-adenomas

* ACTH = adrenocorticotropic hormone; TSH = thyroid stimulating hormone.

The presence of *gsp* mutation in a GH cell adenoma does not appear to correlate with patient's age, sex, tumor size, or circulating GH levels.[48] However, patients appear to have higher circulating levels of α-subunit of glycoproteins. Moreover, *gsp*-mutated adenomas have better response to somatostatin analogs drugs. Growth hormone–secreting tumors with *gsp* mutations, although indistinct from tumors without *gsp* mutations from a morphological point of view, are typically DGGH cell adenomas.[48]

Unlike DGGH cell adenomas that most likely exhibit the *gsp* gene mutation as mentioned previously, SGGH cell adenomas have been demonstrated by some as having preferentially a somatic histidine-to-leucine substitution in codon 49 of the extracellular domain of the GH receptor.[2] This genetic dissimilarity may explain the low response of SGGH cell adenomas to somatostatin analog drugs.[2]

The *gsp* oncogene mutation is very rare in other pituitary tumor subtypes, occurring in only 10% of clinically nonfunctioning pituitary adenomas and in 5% of corticotroph adenomas.[48] As mentioned previously, activating mutation of *gsp* represents the basis of the McCune-Albright syndrome, which is characterized by somatotroph hyperplasia and polyostotic fibrous dysplasia of the bones.[55]

Since mutational events are rare in GH-secreting adenomas, the identification of other candidate genes of significance in the adenoma tumorigenesis has been intensively explored. Several studies have used microarray-based, high-throughput gene profiling for identification of candidate genes and pituitary-specific signaling pathways that may be participate in pituitary tumorigenesis, including studies analyzing GH-secreting adenomas.[19,20,36,43] Except for genes linked to adenoma subtype, including *GH* and *GHRH-R*,[36,43] the majority of identified genes with potential tumorigenic effect are not unique to GH-secreting adenomas and seem to contribute to the pathogenesis of most adenomas (Table 1).

Animal Models for GH-Secreting Pituitary Tumorigenesis

Several animal models have been developed for the understanding of pituitary tumorigenesis by overexpressing oncogenes or knocking out tumor suppressor genes known to play a role in human disease. However, these animal models do not completely recapitulate pituitary human tumorigenesis because animal tumor formation is frequently preceded by hyperplasia, an unlikely event in human pituitary tumor formation. Animal models resulting in GH-secreting adenomas have been well characterized since the late 1980s, particularly with the description of the transgenic mouse for human GHRH[34] that, under extended exposure to GHRH, leads to mammosomatotroph hyperplasia and adenoma formation.[3] Table 2 shows some of the current animal models that develop GH hyperplasia and/or tumors.

Disclosure

The author reports no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Manuscript submitted June 15, 2010.
Accepted July 26, 2010.

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Neurosurg Focus 29 (4):E3, 2010

Craniometric changes in patients with acromegaly from a surgical perspective

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Object. The objective of this study was to evaluate and analyze morphometric and volumetric changes of the skull due to acromegaly in areas relevant for neurosurgical practice, focusing on the surgical implications.

Methods. On preoperatively acquired CT scans, cephalometric and volumetric measurements were performed on 45 patients with acromegaly (Group A) and 45 control patients (Group B). The authors determined thickness of the cranial vault, inner and outer diameters of the skull, and the diameter of sphenoidal and maxillary sinus, as well as frontal and maxillary sinus volumetry. The morphometric and volumetric CT data of the patients with acromegaly were compared with the data of a control group and correlated with clinical parameters.

Results. Cranial vault thickness differed significantly ($p < 0.0001$) between the 2 groups. A correlation of the vault thickness with preoperative human growth hormone, insulin-like growth factor–I levels, and duration of clinical history in acromegaly could not be established. The outer anterior-posterior skull diameter of Group A (18.47 ± 0.94 cm) differed significantly ($p = 0.0146$) from Group B (17.98 ± 0.93 cm) and correlated significantly with preoperative human growth hormone ($r = 0.3277$; $p = 0.0299$) and insulin-like growth factor-–I serum levels ($r = 0.3756$; $p = 0.0120$). Measurements of the anterior-posterior diameter of the sphenoidal sinus differed significantly ($p = 0.0074$) between patients with acromegaly and controls. Volumetric analysis of the frontal sinus resulted in a statistically significant difference ($p = 0.0382$) between patients with acromegaly (14.89 ± 10.85 cm^3) and controls (10.06 ± 6.93 cm^3).

Conclusions. Significant craniometric changes and volumetric remodelling of the paranasal sinus occur in acromegaly. The bone alterations are of surgical importance for using the transsphenoidal approach. Detailed preoperative diagnostic examination and planning as well as selection of appropriate instruments are mandatory for safe and successful pituitary adenoma removal in patients with acromegaly. *(DOI: 10.3171/2010.7.FOCUS10152)*

Key Words • **acromegaly** • **paranasal sinus** • **volumetry** • **craniometric change** • **growth hormone** • **insulin-like growth factor**

Patients with acromegaly are recognizable by the pathognomonic phenotype of somatic overgrowth and craniofacial disproportions. Excessive IGF-I levels cause a periosteal new bone formation resulting in characteristic nasal bone hypertrophy, mandibular overgrowth, maxillary widening, and frontal bossing. Craniometric changes have been analyzed in the literature.[3,5,7] Recently our group reported on a reduced intercarotid artery distance (distance between left and right carotid arteries) in acromegaly.[4]

The vast majority of these patients harbors a pituitary adenoma and potentially may be cured through neurosurgical intervention. Typically a transsphenoidal approach is chosen. However, certain growth patterns with extensive intradural tumor extension necessitate transcranial surgery.[6] The aim of the present study was to evaluate and analyze morphometric and volumetric changes of the skull in areas relevant for neurosurgical practice in these patients, focusing on the surgical implications.

Methods

Study Population

Forty-five consecutive patients referred to our department for primary surgery of a GH-secreting pituitary adenoma were studied prospectively (Group A). All patients showed the characteristic clinical signs of acromegaly and the presence of a pituitary adenoma was neuroradiologically confirmed. Endocrinologically, all patients had elevated

Abbreviations used in this paper: GH = growth hormone; IGF = insulin-like growth factor.

sex- and age-adjusted IGF-I levels and pathological GH secretion during an oral glucose tolerance test. A control group (Group B) consisted of 45 patients who were examined with CT scans (Sensation 16, Siemens AG) for a reason other than a disease of the pituitary gland. The controls were age-matched with the patients. Computed tomography scans were acquired preoperatively in all patients. A helical data set was available for 32 in each group.

Data Analysis

Forty-five metric measurements on transversally oriented, orbitomeatally inclined slides were performed with SIENET Sky-VA50B (Siemens AG). Volumetric analysis of 32 frontal and maxillary sinuses was performed using the BrainLAB Workstation (BrainLAB AG). The distances assessed on transversal bone window reconstructions at the Siemens workstation and volumetric assessments are reported in Table 1 and illustrated in Figs. 1 and 2.

The morphometric and volumetric CT data of the patients with acromegaly were compared with the data of the control group. Anamnestic data, preoperative human GH and IGF-I values, and secondary diagnoses were determined. The preoperative endocrinological data were assessed immediately preoperatively or prior to medical treatment in those patients who underwent short-term preoperative pretreatment. All patients underwent operations using the transsphenoidal route and histopathological examination confirmed the diagnosis of human GH-producing adenoma.

Statistical Methods

Statistical analysis was performed with JMP statistical discovery software (version 7.0.2, SAS). The mean values of continuous variables in the 2 groups were compared with the 2-sample t-test if the variances did not differ significantly ($p < 0.05$). We used the Welch test for significantly different variances. Normally distributed data are summarized by their means and SDs. For variables that were not normally distributed we provide medians and ranges. We calculated the Pearson correlation coefficients for the assessment of associations between continuous variables. In the case of human GH, IGF-I, and duration of clinical history, the values were log-transformed to obtain bivariate normal distribution.

TABLE 1: Assessed craniometric and volumetric measurements*

Localization	Distance
skull (rt & lt)	diameter of frontal skull
	diameter of occipital skull
	outer diameter longitudinal
	inner diameter longitudinal
	outer diameter transversal
	inner diameter transversal
maxillary sinus (rt & lt)	longitudinal diameter
	transversal diameter
	volume (cm^3)
sphenoidal sinus	longitudinal diameter
	transversal diameter
frontal sinus	volume (cm^3)

* All measurements in centimeters unless otherwise indicated.

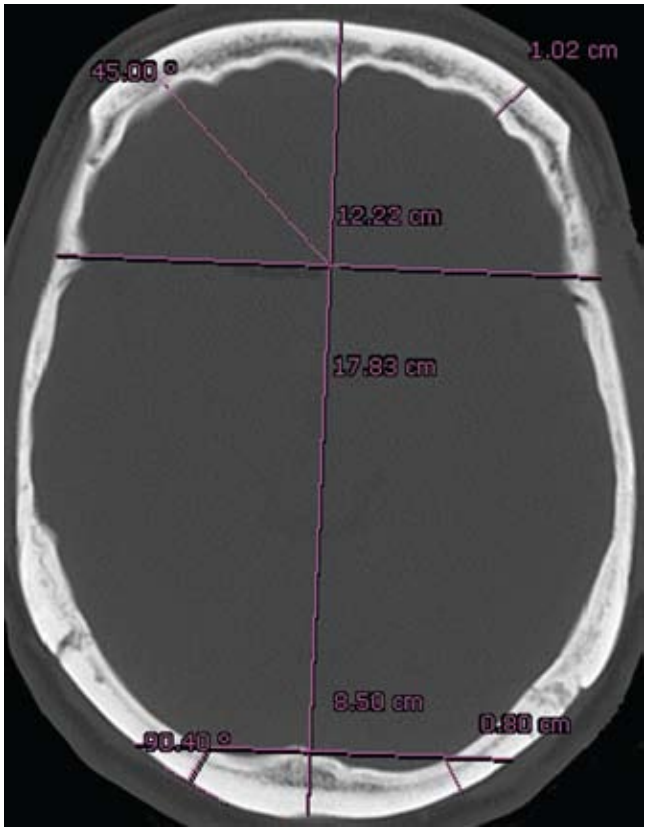

Fig. 1. Axial CT scan illustrating the method used for measuring frontal and occipital cranial vault thickness. Measurements were performed on the highest slice where the spur of the sphenoidal wing was still observed. First, a transversal line connecting the spurs and a vertical line at a right angle were drawn. Then a bisecting line was drawn from the intersection toward the frontal skull to determine the frontal vault thickness. For standardized measurement of the occipital vault thickness, a transversal line was drawn orthogonally to the main vertical line where the latter reaches the occipital skull. Where the lateral part of the transversal line touches the bone, the vault thickness was measured at a right angle to a tangent on the outer surface.

Results

Twenty-four patients with acromegaly were female and 21 were male. The control group consisted of 20 females and 25 males. The median age of the 45 patients with acromegaly was 49 years (range 9–80 years), and 52 years (range 8–82 years) in the control group.

Cranial Vault

In the patients with acromegaly (Group A), the mean thickness of the frontal cranial vault was 1.12 ± 0.43 cm. In the control group (Group B), the mean thickness was 0.67 ± 0.27 cm (Fig. 3). The difference between groups was highly significant ($p < 0.0001$; Fig. 4). In patients with acromegaly, the mean thickness of the occipital cranial vault was 0.75 ± 0.28 cm, whereas in the control group the

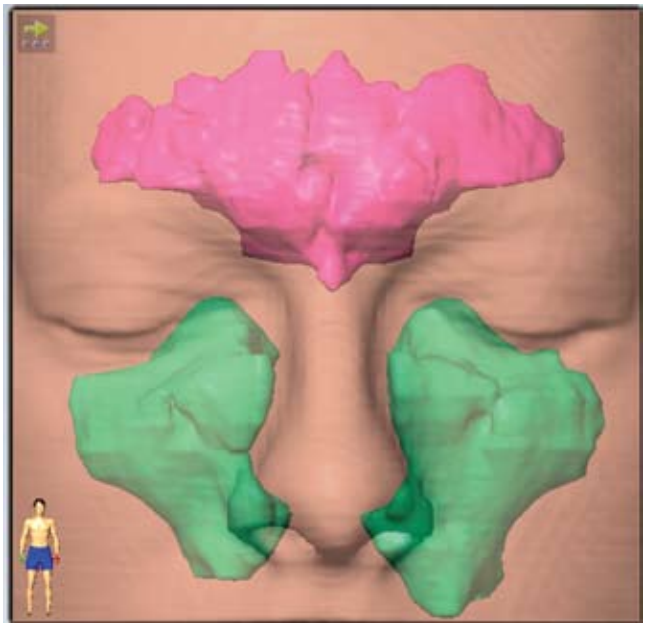

Fig. 2. Three-dimensional image showing volume rendering of frontal *(red)* and maxillary *(green)* sinuses detailed on the BrainLAB workstation. Figure at lower left shows orientation of the 3D reconstruction.

mean thickness was 0.55 ± 0.14 cm ($p < 0.0001$). While the outer anterior-posterior skull diameter of Group A (18.47 ± 0.94 cm) differed significantly ($p = 0.0146$) from Group B (17.98 ± 0.93 cm), no statistical difference could be demonstrated regarding the inner anterior-posterior diameter of the skull (15.80 ± 0.82 cm [Group A] vs 15.97 ± 0.95 cm [Group B]; $p = 0.3759$).

There was a statistically significant difference ($p = 0.0411$) between the outer lateral-lateral (right side to left side) diameter in patients with acromegaly (14.49 ± 0.66 cm) compared with controls (14.20 ± 0.66 cm). However, this difference was not as great as the difference in the outer anterior-posterior skull diameter. There was no difference ($p = 0.6057$) in the inner lateral-lateral diameter between Group A (13.52 ± 0.83 cm) and Group B (13.43 ± 0.66 cm).

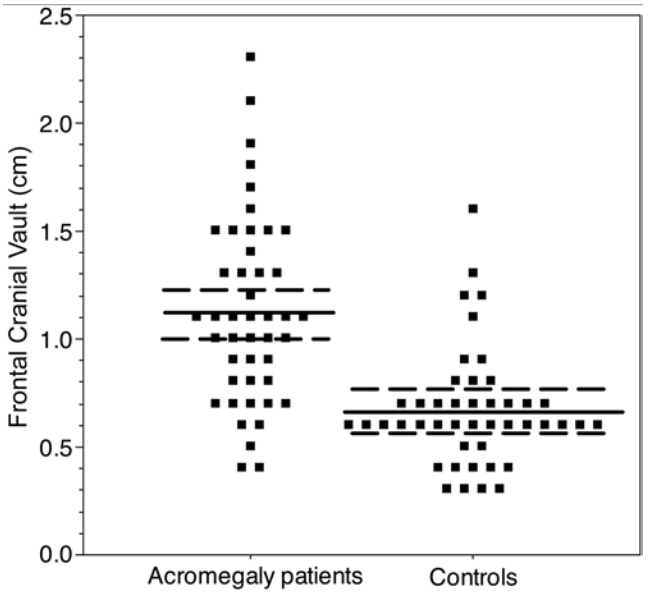

Fig. 3. Scatterplot showing the difference in frontal vault thickness between patients with acromegaly (Group A) and controls (Group B). *Dashed horizontal lines* in graph represent standard deviation, *solid line* represents the mean value.

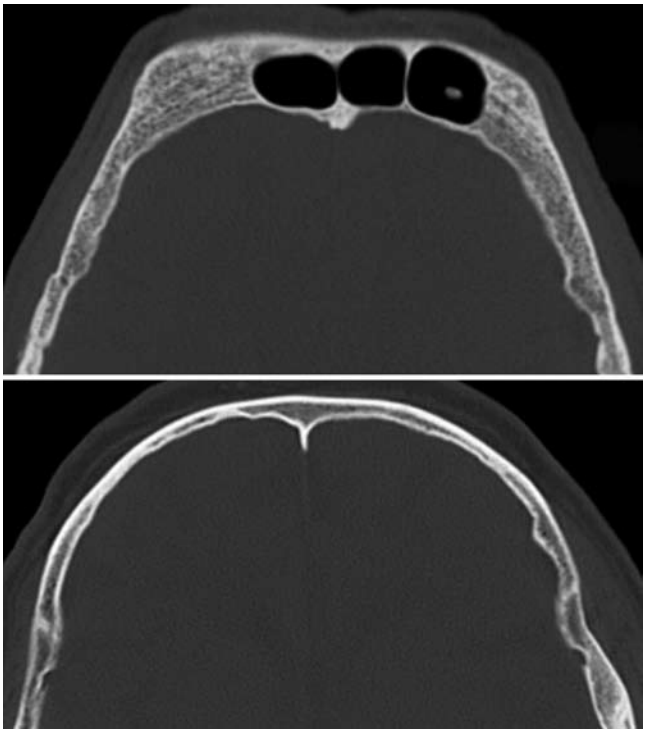

Fig. 4. Axial bone window CT scans show markedly increased frontal bone thickness in a patient with acromegaly **(upper)** in contrast to the frontal bone of a patient from the control group **(lower)**.

A correlation of the vault thickness with preoperative GH, IGF-I levels, and duration of clinical history in acromegaly could be established neither at the frontal bone ($r = 0.039$, $p = 0.8021$; $r = 0.1362$, $p = 0.3780$; and $r = -0.047$, $p = 0.7934$, respectively) nor at the occipital bone ($r = 0.2806$, $p = 0.0650$; $r = 0.2413$, $p = 0.1145$; and $r = 0.019$, $p = 0.9133$, respectively). The anterior-posterior length of the skull in patients with acromegaly correlated significantly with preoperative human GH ($r = 0.3277$, $p = 0.0299$) and IGF-I serum levels ($r = 0.3756$, $p = 0.0120$) as well as with duration of clinical history ($r = 0.2939$, $p = 0.500$). A correlation of these parameters with the lateral-lateral diameter could not be established (human GH $r = -0.1590$, $p = 0.3082$; IGF-I $r = -0.1361$, $p = 0.3839$; and duration of clinical history $r = -0.1705$, $p = 0.2683$).

Sinus Diameter

The sinuses showed a marked difference in longitudinal expansion. Measurements of the anterior-posterior diameter of the sphenoidal sinus differed significantly ($p = 0.0074$) between patients with acromegaly (3.31 ± 0.62 cm) and controls (2.92 ± 0.71 cm). Human GH ($r = 0.240$, $p = 0.1251$) and IGF-I ($r = 0.093$, $p = 0.5569$) at presentation were not correlated with the anterior-posterior sinus diameter. Similarly, the anterior-posterior diameter of the

maxillary sinus was significantly longer ($p = 0.0042$) in the acromegaly group (4.22 ± 0.30 cm) than in the control group (4.06 ± 0.24 cm). Preoperative human GH values ($r = 0.115$, $p = 0.4590$) and duration of clinical history ($r = 0.212$, $p = 0.1624$) did not correlate with maxillary sinus length.

The width of the evaluated sinuses did not differ significantly between patients with acromegaly and controls. The lateral-lateral diameter of the sphenoidal sinus was 3.53 ± 1.03 cm in Group A and 3.30 ± 0.63 cm in Group B ($p = 0.2199$). The lateral-lateral diameter of the maxillary sinus was 2.33 ± 0.27 cm in Group A and 2.40 ± 0.24 cm in Group B ($p = 0.1766$).

Sinus Volumetry

Volumetric analysis of the maxillary sinus resulted in a measurement of 19.47 ± 7.02 cm^3 in the patients with acromegaly. The maxillary sinus was only slightly smaller in the control group with a volume of 17.64 ± 4.19 cm^3 ($p = 0.2117$). Furthermore, duration of clinical history ($r = -0.131$, $p = 0.5134$) and preoperative hormone levels (human GH $r = 0.058$, $p = 0.7521$; IGF-I $r = 0.127$, $p = 0.4897$) were not correlated with the maxillary sinus volume. However, a positive correlation between maxillary sinus volume and the variables tumor diameter ($r = 0.374$, $p = 0.0348$) and patient age ($r = -0.474$, $p = 0.0061$) was noted.

Volumetric analysis of the frontal sinus resulted in a statistically significant difference ($p = 0.0382$) between patients with acromegaly (14.89 ± 10.85 cm^3; Fig. 5) and controls (10.06 ± 6.93 cm^3). Within the group of patients with acromegaly, no statistically significant association of frontal sinus volume with duration of clinical history ($r = 0.028$, $p = 0.8899$) and tumor diameter ($r = 0.266$, $p = 0.1418$) was detected. A slight correlation was found between preoperative hormone levels and size of the frontal sinus (GH $r = 0.289$, $p = 0.1089$; IGF-I $r = 0.342$, $p = 0.0554$). However, this correlation did not reach statistical significance.

Discussion

Patients with acromegaly are characterized by a pathognomonic phenotype. The excess of human GH and IGF-I has ubiquitous effects on all tissues throughout the body. This excess results in the clinical features of acral enlargement, colon polyps, cardiovascular problems, sleep apnea, visceromegaly, and endocrine and metabolic alterations. In more than 95% of patients, acromegaly is derived from a pituitary adenoma.[10]

The shape and size of the head changes during the lifetime of not only patients with acromegaly, but also in healthy patients.[3] Using lateral radiographs, Macho[9] showed in his study of 353 patients that the viscerocranium increases up to the 4th decade of life and thereafter decreases, while the height of the neurocranium progressively decreases during an adult life. However, the effects of acromegaly on the patient's head are much more striking. The viscerocranium is affected in terms of prognathism, malocclusion, maxillary widening, widened tooth gap, and nasal bone hypertrophy. At the neurocranium, the phenomenon of frontal bossing is well known because it gives a characteristic appearance to affected

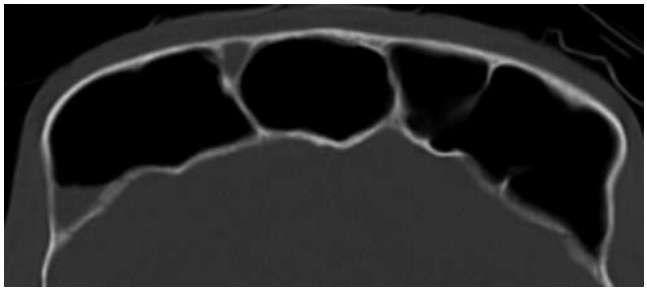

Fig. 5. Axial bone window CT scan shows an impressively enlarged frontal sinus in a patient with acromegaly.

patients. Further, mucosal changes both in the nose and the paranasal sinuses in terms of mucosal hypertrophy and polyposis are reported occurrences in acromegaly.[14] It is logical to assume that these morphological alterations have repercussions in microsurgical therapy. The transsphenoidal route is direct and safe for the majority of pituitary adenomas and thus represents the standard approach for pituitary surgery. In acromegaly, however, two issues related to the pathological anatomical alterations have to be taken into consideration when considering pituitary surgery.

First, the reduced intercarotid artery distance in the C5 and C4 segment narrows the habitual working space,[4,12] increasing the risk of a potentially life-threatening vascular complication. Therefore, we have recommended bone window CT scan of the cranial base during preoperative diagnostics in patients with acromegaly scheduled for transsphenoidal surgery.[4] In difficult cases, additional use of neuronavigation can be considered. Magnetic resonance imaging depicts the course of carotid arteries well. However, the chronic excess of human GH and IGF-I significantly distorts bone anatomy, which is better visualized by CT. Additionally, drilling of bone is often required for transsphenoidal exposure. Therefore, it is justified to add a CT scan to the preoperative workup. In acromegaly, it is important to know the position and proximity of the internal carotid arteries before surgery; even then, a very narrow intercarotid working space does not preclude the transsphenoidal intervention.[4]

Second, our data show that the anterior-posterior diameter of the sphenoid sinus is extended in patients with acromegaly compared with the control group. This diameter elongates the depth of the working corridor through the transsphenoidal route (Fig. 6). Saeki et al.[13] studied morphological differences of the nasal cavity between patients with and without acromegaly and also found a narrower and deeper operating access in human GH-secreting adenomas. Osseous changes and pathological cartilaginous overgrowth of viscerocranium and neurocranium have implications for the selection of instruments for surgery.[11]

One-stage complete transsphenoidal resection is achievable in most pituitary adenomas. In selected cases, however, adenomas are more amenable to a transcranial approach. The degree of vertical intracranial extension as well as an irregular and multilobular configuration are important predictors of incomplete transsphenoidal resection.[6] Pituitary adenoma removal is then performed through a

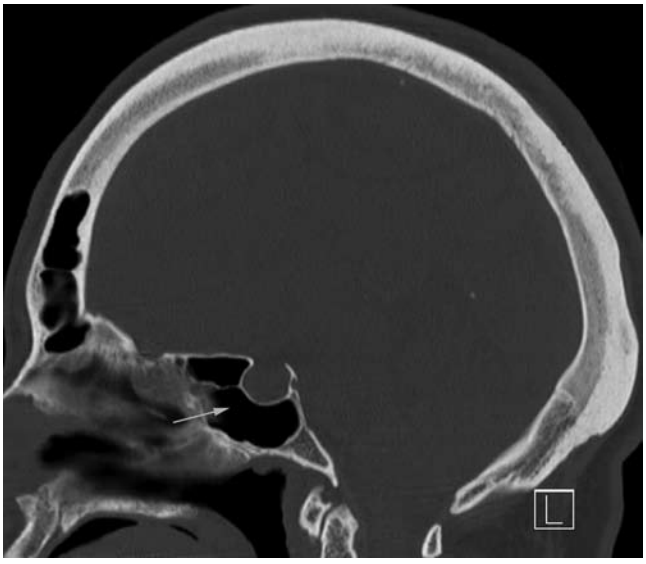

Fig. 6. Sagittal bone window CT scan showing voluminous sphenoidal sinus *(arrow)* in a patient with acromegaly. The increased anteroposterior diameter lengthens the transnasal working distance to the floor of the sella turcica. Note the increased thickness of the cranial vault and the prominent frontal sinus.

pterional or frontolateral approach. In this context, the reported increase of frontal sinus volume and thickness of the cranial vault are of surgical interest. The issue might be not to injure the enlarged frontal sinus to prevent a CSF fistula or secondary infection. In addition, increased effort during craniotomy can be anticipated due to the almost double thickness of the frontal vault in patients with acromegaly compared with those patients without this condition.

Increase of cranial vault diameter and sinus volume also influences the required radiation dose. However, these changes are without clinical relevance in the era of modern radiation algorithms with correction of incompatibility based on individual CT examinations. An association of acromegaly and Chiari malformation has been reported in the literature.[1,2,8] A hypothesis for this association might be that the bony overgrowth reduces posterior fossa volume.[2] At least supratentorially, we could not confirm this phenomenon: both the outer anterior-posterior and lateral-lateral skull diameters increased but not the corresponding inner diameters, thus the intracranial volume itself does not appear to diminish.

Conclusions

Significant craniometric changes and volumetric remodelling of the paranasal sinus occur in acromegaly. The bone alterations are of surgical importance for the transsphenoidal approach. Detailed preoperative diagnostic examination and planning as well as selection of appropriate instruments are mandatory for safe and successful pituitary adenoma removal in patients with acromegaly.

Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Ebner, Bültmann, Nägele, Honegger. Acquisition of data: Kürschner. Analysis and interpretation of data: Ebner, Kürschner, Honegger. Drafting the article: Ebner. Critically revising the article: Honegger. Reviewed final version of the manuscript and approved it for submission: Ebner, Nägele, Honegger. Statistical analysis: Dietz. Administrative/technical/material support: Ebner, Bültmann, Nägele, Honegger. Study supervision: Ebner, Honegger.

Acknowledgment

The authors thank Dr. F. Paulsen, Department of Radiooncology, Eberhard-Karls-University Tübingen, for professional and courteous advice regarding radiooncologic implications.

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Manuscript submitted June 10, 2010.
Accepted July 19, 2010.
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Neurosurg Focus 29 (4):E4, 2010

Patterns of extrasellar extension in growth hormone–secreting and nonfunctional pituitary macroadenomas

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Object. Growth patterns of pituitary adenomas have been observed to vary by histopathological subtype. The authors aimed to analyze variations in the patterns of extrasellar extension of nonfunctional macroadenomas (NFMAs) and growth hormone (GH)–secreting macroadenomas.

Methods. A retrospective review was conducted of data obtained in 75 patients who underwent transsphenoidal operations for histologically confirmed NFMAs (50 patients) and GH-secreting macroadenomas (25 patients) at the Brigham and Women's Hospital over an 18-month period. Patients with microadenomas and prior operations were excluded from the analysis. Preoperative MR images were reviewed to assess patterns of extrasellar extension in the varying tumor subtypes.

Results. The mean maximal tumor diameter in NFMAs and GH-secreting macroadenomas was 26 and 16 mm, respectively ($p < 0.0001$). Extension of the NFMAs occurred into the following regions: infrasellar, 23 patients (46%); suprasellar, 41 patients (82%); and cavernous sinus, 20 patients (40%). Extension of GH-macroadenomas occurred into the following regions: infrasellar, 18 patients (72%); suprasellar, 4 patients (16%); and cavernous sinus, 4 patients (16%). Compared with GH-adenomas, NFMAs were more likely to develop suprasellar extension (82% vs 16%, $p < 0.0001$), cavernous sinus extension (40% vs 16%, $p = 0.04$), and isolated suprasellar extension (30% vs 4%, $p = 0.0145$). GH-macroadenomas had higher overall rates of infrasellar extension (72% vs 46%, $p < 0.05$), and isolated infrasellar extension (52% vs 6%, $p < 0.0001$). Of the 13 GH-macroadenomas with isolated infrasellar extension, 5 (42%) met WHO criteria for atypical adenomas.

Conclusions. Substantial differences in extrasellar growth patterns were observed among varying histological subtypes of pituitary macroadenomas. Despite smaller tumor diameters, GH-macroadenomas demonstrated a proclivity for infrasellar extension, whereas NFMAs exhibited preferential extension into the suprasellar region.
(DOI: 10.3171/2010.7.FOCUS10155)

Key Words • **sella turcica** • **transsphenoidal surgery** • **pituitary adenoma** • **acromegaly** • **growth hormone** • **invasion** • **clivus**

Pituitary adenomas are frequently occurring neoplasms of the sellar region that typically become symptomatic due to mass effect on surrounding structures and/or hormonal oversecretion. Invasion of the surrounding dura mater and extension into parasellar compartments occur in a significant proportion of these tumors and have been correlated with patient age, tumor size, and histopathological subtype.[12,14,17] The degree of resection, as well as the incidence of subsequent tumor recurrence, has also been reported to correlate, in part, with the degree of invasion into surrounding regions.[1,2,19] In tumors that extend into the cavernous sinuses, suprasellar space, or clivus, gross-total resection can be challenging, if not impossible, without resulting in significant morbidity. Because subtotal resection is frequently an expected outcome in many patients with tumor invading the para-, infra-, or suprasellar regions, a commonly implemented treatment paradigm is to perform a subtotal tumor resection followed by adjunctive stereotactic radiosurgery and/or continued medical management as a means of achieving long-term control of tumor growth and/or neuroendocrinological remission.[18]

It has been reported that varying histopathological adenoma subtypes demonstrate preferential growth patterns of dural invasion and extension from their sellar origins.[12,16]

Abbreviations used in this paper: GH = growth hormone; NFMA = nonfunctional macroadenoma.

For instance, the classic imaging description of a nonfunctional pituitary macroadenoma is a "dumbbell-shaped" tumor with suprasellar extension through the aperture of the diaphragma sellae, resulting in the appearance of a "waist" at this point. Another example is that GH-secreting adenomas are frequently noted to invade the sphenoid sinus and clivus.[6,13] In this study, we aimed to analyze patterns of tumor extension on MR imaging studies of these 2 most commonly treated macroadenomas at our institution (GH-secreting and nonfunctional macroadenomas) to better understand the proclivity of these tumors to preferentially invade various parasellar regions.

Methods

We conducted a retrospective review of the Brigham and Women's Hospital Pituitary Center database to identify all patients who underwent transsphenoidal surgery performed by the senior author (E.R.L.) between April 2008 and September 2009. Approval for the study was granted by the institutional review board. Of the 177 consecutive transsphenoidal procedures performed for all sellar-region lesions, pathology was consistent with a pituitary adenoma in 111 patients (63%). Patients with microadenomas and a history of transsphenoidal surgery were excluded from the analysis. Furthermore, patients with macroprolactinomas and adrenocorticotropic hormone macroadenomas were not included due to insufficient sample size. Following exclusion, 75 patients with newly diagnosed GH-secreting (25 patients) and nonfunctional pituitary (50 patients) macroadenomas were included in the analysis. Preoperative MR images were reviewed to assess for the pattern of tumor extension, and findings were subsequently correlated with histopathological diagnosis following tumor resection.

Imaging Analysis

Based on standard preoperative 3-T MR imaging performed with and without contrast administration, a macroadenoma was defined as a tumor with a maximal diameter of greater than or equal to 10 mm, whereas microadenomas were defined by a maximal diameter of less than 10 mm. Invasion of the cavernous sinuses was defined as extension beyond the line corresponding to the lateral tangents of the 2 components of the intracavernous internal carotid artery, as defined by Knosp et al.[8] Suprasellar invasion was defined as clear tumor growth through the diaphragma sella or above the plane of the inferior optic chiasm. Finally, infrasellar invasion was determined by clear tumor growth through the sellar floor and into the sphenoid sinus or clivus. "Isolated" extension was defined as extrasellar extension into only one of these regions.

Statistical Analysis

Analysis of the data was performed using GraphPad Statistical Software. Categorical data were compared using a 2-tailed Fisher exact test, and continuous data were analyzed using a 2-tailed unpaired t-test. Statistical significance was defined as $p < 0.05$.

Results

Of the 75 patients with GH-secreting macroadenomas and NFMAs, overall extension was noted into the following regions: suprasellar, 45 patients (60%); infrasellar, 41 patients (55%); cavernous sinus, 24 patients (32%); and no extension, 9 patients (12%). Sixteen patients (21%) had tumors with isolated infrasellar extension. Of these, 13 (81%) were GH-secreting tumors and 3 (19%) were NFMAs. Sixteen patients (21%) had tumors with isolated suprasellar extension. Of these, 15 (94%) were NFMAs and 1 (6%) was a GH-secreting tumor. Four patients (5%), all with NFMAs, had tumors with isolated cavernous sinus extension.

Of the 25 patients with GH-secreting macroadenomas, extension was noted into the following regions (Table 1): infrasellar, 18 patients (72%); suprasellar, 4 patients (16%); cavernous sinus, 4 patients (16%); and no extension (intrasellar macroadenoma), 6 patients (24%). Compared with nonfunctional macroadenomas, GH-secreting adenomas had significantly higher rates of infrasellar extension (72% vs 46%, respectively; $p < 0.05$). Patients with GH-secreting adenomas were over 8 times more likely to have isolated infrasellar extension than were patients with NFMAs (52% vs 6%, respectively; $p < 0.0001$) (Fig. 1). Furthermore, of the 13 GH-secreting adenomas with isolated infrasellar extension, 5 (42%) met WHO diagnostic criteria for an atypical pituitary adenoma (MIB-1–labeling index greater than 3%, excessive p53 immunostaining, and high mitotic figures) (Fig. 2).

Of the 50 patients with NFMAs, extension was noted into the following regions (Table 1): infrasellar, 23 patients (46%); suprasellar, 41 patients (82%); cavernous sinus, 20 patients (40%); and no extension, 3 patients (6%). Nonfunctional macroadenomas were over 5 times more likely to have suprasellar extension than GH-secreting macroadenomas (82% vs 16%, respectively; $p < 0.0001$). Addition-

TABLE 1: Patterns of extrasellar extension of GH-secreting and nonfunctioning macroadenomas in 75 patients undergoing transsphenoidal operations*

Variable	No. of Patients (%)		p Value
	GH Adenomas	NFMAs	
no. of patients	25	50	
mean maximal tumor diameter (mm)	16	26	<0.0001
any invasion	19 (76)	47 (94)	NS
cavernous sinus invasion			
any	4 (16)	20 (40)	0.04
isolated	0 (0)	4 (8)	NS
suprasellar extension			
any	4 (16)	41 (82)	<0.0001
isolated	1 (4)	15 (30)	0.015
infrasellar invasion			
any	18 (72)	23 (46)	0.049
isolated	13 (52)	3 (6)	<0.0001
multiple regions of extension	5 (20)	25 (50)	0.012

* NS = not significant.

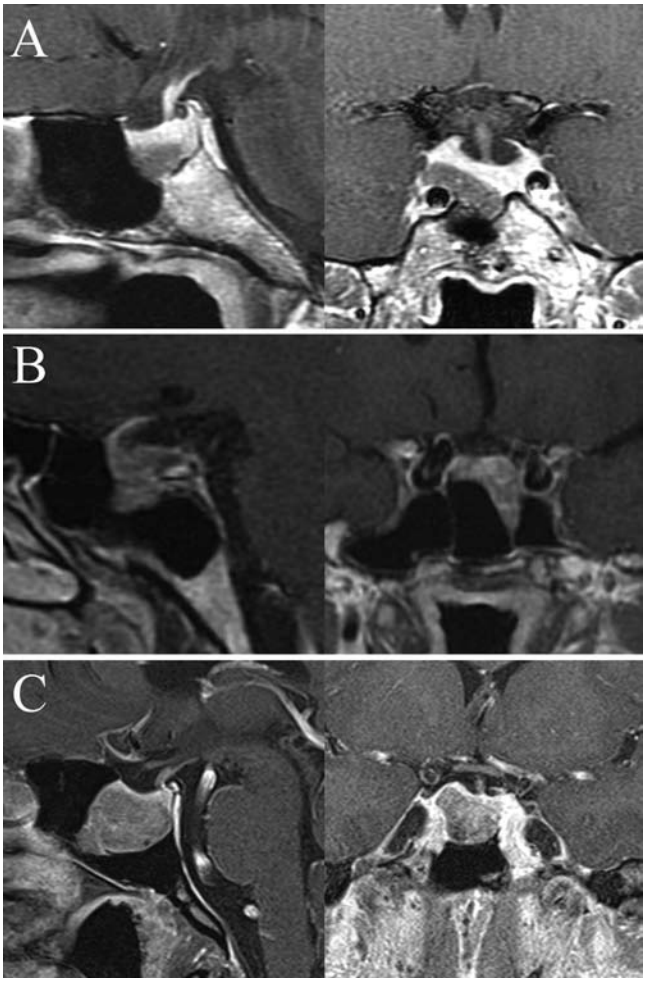

Fig. 1. A–C: Sagittal and coronal contrast-enhanced MR images of GH-secreting macroadenomas showing isolated infrasellar extension.

ally, NFMAs were more likely to demonstrate cavernous sinus extension than were GH-secreting adenomas (40% vs 16%, respectively; $p = 0.04$). Finally, NFMAs were over 7 times more likely to exhibit isolated suprasellar extension than GH-secreting macroadenomas (30% vs 4%, respectively; $p = 0.0145$) (Fig. 3). No statistical differences were noted in the size or patterns of invasion between null-cell adenomas and silent gonadotropin adenomas.

The same analysis was then performed after controlling for tumor size. Patterns of extrasellar extension were analyzed for the 20 largest GH-secreting macroadenomas and 20 smallest NFMAs. The mean maximal diameter of the GH group was 17.4 mm and that in the NFMA group was 18.1 mm ($p > 0.05$). These groups demonstrated no statistically significant differences in the overall incidence of invasion or that of cavernous sinus invasion. The incidence of suprasellar extension, however, was higher in NFMAs than GH-secreting macroadenomas (65% vs 20%, respectively; $p < 0.01$). Furthermore, the incidence of infrasellar extension was higher in GH-secreting macroadenomas than NFMAs (70% vs 30%, respectively; $p < 0.03$). Finally, the incidence of isolated infrasellar extension was 5 times higher in GH-secreting macroadenomas than NFMAs (50% vs 10%, respectively; $p < 0.02$).

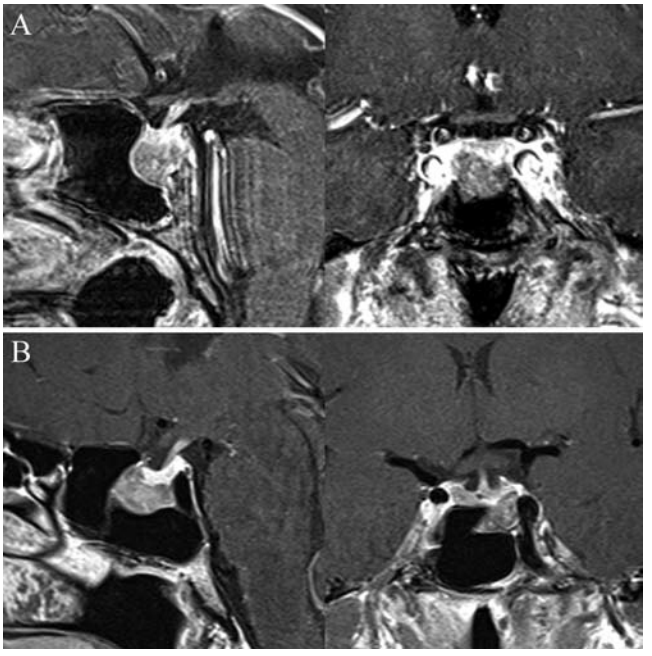

Fig. 2. A and B: Sagittal and coronal contrast-enhanced MR images of WHO atypical GH-secreting macroadenomas, which comprised 42% of all GH-secreting adenomas demonstrating isolated infrasellar extension.

Discussion

Extrasellar extension of pituitary macroadenomas into the surrounding supra-, para-, or infrasellar compartments is noted in over 90% of resected macroadenomas.[2,19] A thorough assessment of the pattern of extrasellar extension on preoperative MR images is mandatory prior to attempting transsphenoidal resection of pituitary adenomas, to define which regions pose the greatest limitation for tumor resection and are likely to retain residual tumor that may cause subsequent disease progression or serve as targets for postoperative radiation. The goal of the current study was to assess whether the 2 most commonly resected macroadenomas at our institution, GH-secreting and nonfunctional subtypes, exhibited preferential patterns of tumor growth into various parasellar compartments. The salient findings of this study are as follows: 1) GH-secreting adenomas, despite being smaller tumors on average, demonstrate preferential extension into the infrasellar region, and the majority of tumors (81%) exhibiting isolated infrasellar extension are GH-secreting adenomas; 2) NFMAs demonstrate preferential extension into the suprasellar region, and the majority of tumors (94%) demonstrating isolated suprasellar extension are NFMAs; and 3) atypical GH-secreting adenomas have an even higher predisposition for isolated invasion of the infrasellar region. Commensurate with our data is clinical evidence from previous series of patients with GH-secreting adenomas, which have reported visual loss as a presenting symptom in only 9%–14% of patients with acromegaly,[9,10] compared with 49%–72% of patients with nonfunctioning adenomas.[2,3,11]

The implications of these extension patterns of various histopathological subtypes of pituitary adenomas may provide some insight into the tumor biology contributing to the

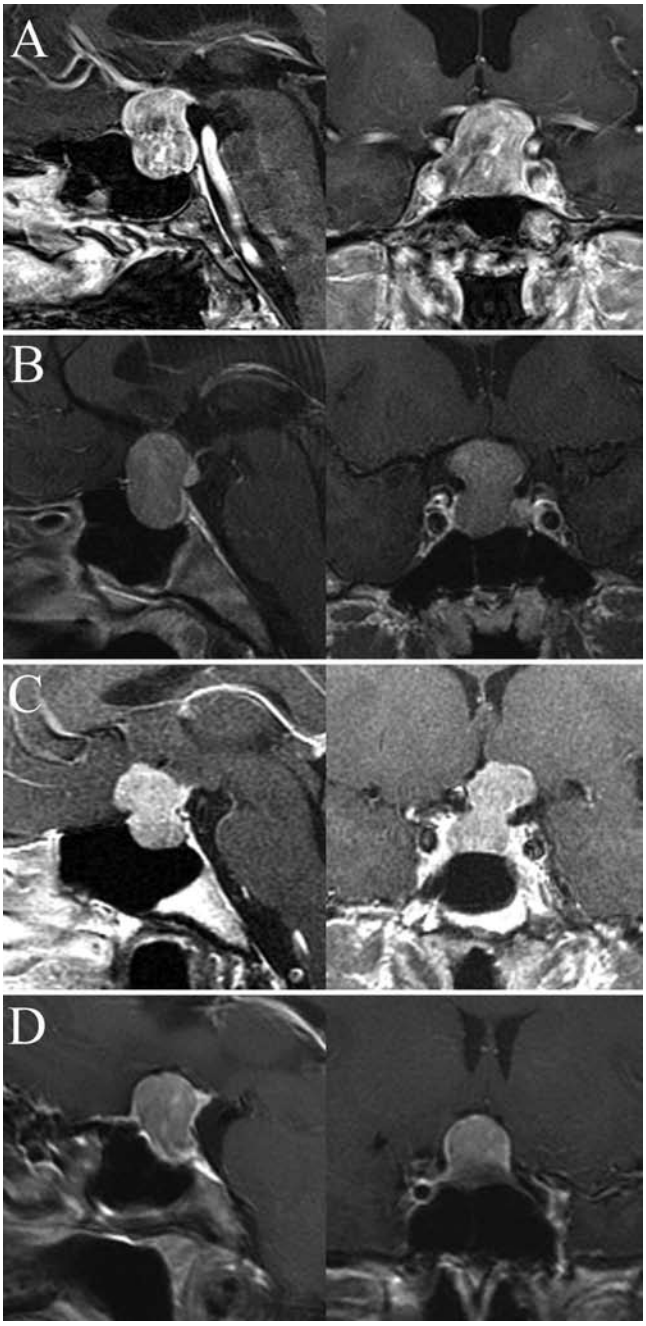

Fig. 3. A–D: Sagittal and coronal contrast-enhanced MR images of typical NFMAs demonstrating suprasellar extension. A characteristic "dumbbell" or "sand-glass" shape with constriction, or a "waist," at the diaphragma sellae is noted in panels **B** and **C**.

process of dural and bony invasion, and it remains speculative why GH-secreting adenomas exhibit an increased proclivity for infrasellar invasion. One possibility is that this phenomenon is related to the anatomical topography of somatotrophs in the caudal and lateral aspect of the pituitary gland, which is likely to explain why GH-secreting microadenomas often arise in this location on MR imaging studies.[13] Some authors have suggested that GH may thicken the soft tissue of the diaphragma sellae while enlarging the sellar space, thus making the sellar floor thinner and

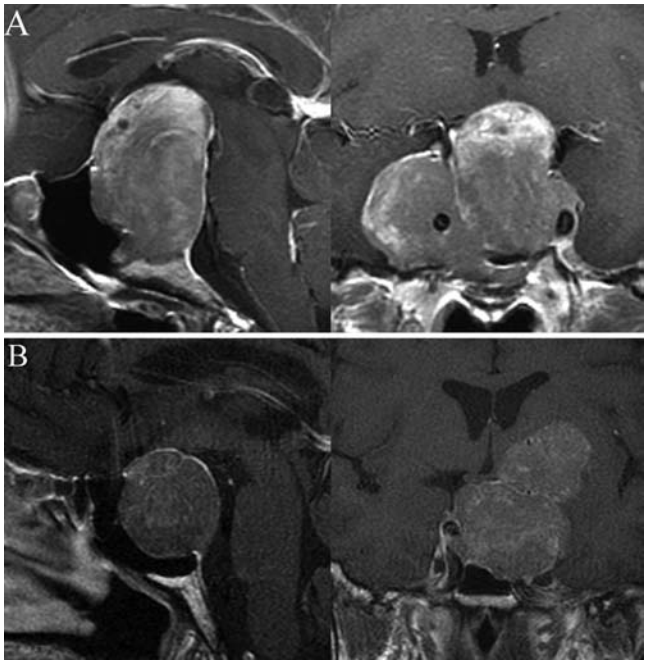

Fig. 4. A and B: Sagittal and coronal contrast-enhanced MR images of WHO atypical null-cell macroadenomas, with invasion of multiple compartments.

more prone to tumor penetration.[6] Alternatively, the biology of GH-secreting adenomas may enable them to more easily invade surrounding dural and/or bony structures, perhaps due to differential expression of proteins involved with degradation, such as matrix metalloproteinases.[5,7,15] Consistent with this reasoning is that GH-secreting adenomas with a more aggressive inherent tumor biology that met the WHO criteria for atypical adenomas demonstrated especially peculiar patterns of isolated extension through the sellar floor and into the clivus, comprising 5 of the 13 GH-secreting adenomas with such growth. However, nonfunctional adenomas are typically larger tumors at the time of diagnosis and tend to grow through the diaphragmatic aperture and into the suprasellar cistern without primarily invading bony structures or the cavernous sinus, until they become larger tumors.[12,14,17] Atypical nonfunctional adenomas, however, are typically aggressive macroadenomas that often invade multiple surrounding compartments (Fig. 4). From a clinical standpoint, the implications of identifying residual GH-secreting adenoma are of paramount importance. To ultimately achieve normalization of delayed insulin-like growth factor levels following transsphenoidal surgery, many patients with residual GH-secreting tumor may require multimodal management strategies, often consisting of maintained somatostatin-analog therapy, pegvisomant, and/or stereotactic radiosurgery or external beam radiotherapy to treat the residual tumor burden. A priori knowledge of residual tumor in the clivus or sellar floor may aid in the postoperative targeting of residual lesions.

The designation of atypical pituitary adenoma was added to the WHO classification for pituitary adenomas in 2004. It is based on the following criteria: 1) MIB-1 labeling index greater than 3%, 2) increased p53 immunostaining, and 3) increased mitotic figures. In the cur-

rent study, 5 (39%) of the 13 GH-secreting adenomas demonstrating isolated infrasellar extension were atypical tumors. Although the long-term outcomes of patients harboring atypical adenomas remain to be determined, previous studies have reported a correlation between Ki 67 labeling index and degree of invasion and hormonal remission in patients with acromegaly.[4]

A previous study by Hagiwara et al.[6] compared MR imaging features and growth patterns of GH-secreting and nonfunctional adenomas. The authors also noted increased proportions of infrasellar invasion in GH-adenomas compared with nonfunctional adenomas, but growth patterns based on isolated extension were not reported. The authors used an index called the Suprasellar Extension Index to quantify this growth patterns, which was defined as the height of suprasellar extension minus the depth of infrasellar extension.[6] In their study, nonfunctional adenomas had a suprasellar extension value of +5.7 mm, compared with −0.8 mm in GH-secreting adenomas. The current study lends support to the theory that GH-secreting adenomas have a predisposition for inferior invasion of the bony sellar floor and clivus.

Conclusions

Substantial differences in extrasellar growth patterns are observed among varying histological subtypes of pituitary macroadenomas. Despite their smaller size, GH-macroadenomas demonstrate a propensity for infrasellar extension, whereas NFMAs demonstrate preferential extension into the suprasellar region. Preferential invasion through the bony sellar floor may provide some insight into the tumor biology of GH-secreting adenomas and is important to note as a potential locus for tumor recurrence or targeting for postoperative radiation.

Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Zada, Laws. Acquisition of data: Zada, Lin. Analysis and interpretation of data: Zada, Lin. Drafting the article: all authors. Critically revising the article: Lin, Laws. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Zada. Study supervision: Laws.

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Manuscript submitted June 11, 2010.
Accepted July 28, 2010.

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Neurosurg Focus 29 (4):E5, 2010

Outcomes after a purely endoscopic transsphenoidal resection of growth hormone–secreting pituitary adenomas

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Object. Using strict biochemical remission criteria, the authors assessed surgical outcomes after endoscopic transsphenoidal resection of growth hormone (GH)–secreting pituitary adenomas and identified preoperative factors that significantly influence the rate of remission.

Methods. A retrospective review of a prospectively maintained database was performed. The authors reviewed cases in which an endoscopic resection of GH-secreting pituitary adenomas was performed. The cohort consisted of 26 patients who had been followed for 3–60 months (mean 24.5 months). The thresholds of an age-appropriate, normalized insulin-like growth factor–I concentration, a nadir GH level after oral glucose load of less than 1.0 μg/l, and a random GH value of less than 2.5 μg/l were required to establish biochemical cure postoperatively.

Results. Overall, in 57.7% of patients undergoing a purely endoscopic transsphenoidal pituitary adenectomy for acromegaly, an endocrinological cure was achieved. The mean clinical follow-up duration was 24.5 months. In patients with microadenomas (4 cases) the cure rate was 75%, whereas in patients harboring macroadenomas (22 cases) the cure rate was 54.5%. Cavernous sinus invasion (Knosp Grades 3 and 4) was associated with a significantly lower remission rate ($p = 0.0068$). Hardy Grade 3 and 4 tumors were also less likely to achieve biochemical cure ($p = 0.013$). The overall complication rate was 11.5% including 2 incidents of transient diabetes insipidus and 1 postoperative CSF leak, which were treated nonoperatively.

Conclusions. A purely endoscopic transsphenoidal approach to GH-secreting pituitary adenomas leads to similar outcome for noninvasive macroadenomas compared with traditional microsurgical techniques. Furthermore, this approach may often provide maximal visualization of the tumor, the pituitary gland, and the surrounding neurovascular structures. *(DOI: 10.3171/2010.7.FOCUS10153)*

Key Words • **growth hormone** • **pituitary adenoma** • **endonasal resection** • **endoscopic** • **outcome** • **acromegaly**

Pituitary tumors are the underlying pathological entity in approximately 99% of cases of acromegaly and are nearly always benign. These lesions chronically produce supraphysiological levels of GH and IGF-I.[39] Elevated GH and IGF-I levels are considered to be responsible for a wide range of cardiovascular, respiratory, endocrine, and metabolic morbidities.[19,45] In a meta-analysis of 16 previously published studies surveying the mortality effects of acromegaly, Dekkers et al.[23] found an overall 72% increase in deaths in patients with acromegaly compared with the general population.

Acromegaly is a relatively rare disorder; the incidence is roughly 4 new cases per million annually.[4] Clinically, acromegaly is characterized by slowly progressive somatic disfigurement (mainly involving the face and extremities) and systemic manifestations. Ultimately, the rheumatological, cardiovascular, respiratory, and metabolic consequences determine prognosis.[11] However, given the typical indolent presentation of the disease, the diagnosis of acromegaly is often delayed. The authors of many older series have reported a delay in the diagnosis of 7–10 years after the onset of signs and symptoms.[24] However, in a recent retrospective study Nachtigall et al.[50] reported a decrease in this interval to roughly 2–3 years. Given that tumor size has been established as an important predictor of surgical outcome, early recognition and treatment are considered keys to achieving high rates of remission and avoiding long-term comorbidities.[16,49]

Total surgical removal of GH-secreting tumors offers the possibility of hormonal control of acromegaly as well as amelioration in the associated multisystem morbidities.[48] As such, recent consensus guidelines recom-

Abbreviations used in this paper: GH = growth hormone; IGF = insulin-like growth factor; LOS = length of stay; OGTT = oral glucose tolerance test.

mend surgery for the management of acromegaly as the first-line therapy in cases involving tumors likely to be controlled by surgery.[25,46,48] Thus, in patients with acromegaly, the goals of surgical treatment are to normalize biochemical markers, eliminate morbidities associated with the disease, relieve mass effect, and subsequently normalize the overall mortality rate.[46,63] While the microsurgical transsphenoidal route has historically been the favored approach to these lesions, the addition of the endoscope to this procedure represents a recent innovation, allowing the surgeon a panoramic view irrespective of the width and depth of the access.[22,52] We report our experience with the resection of each consecutive GH-secreting pituitary adenoma presenting over a 50-month period; all tumors were excised via an entirely endoscopic transsphenoidal approach.

Methods

Patient Population

After obtaining the approval of the Thomas Jefferson University institutional review board, we performed a retrospective review of a prospectively maintained database and evaluated the medical records of 27 consecutive patients who presented with GH-secreting adenomas from June 2005 to September 2009. One patient relocated abroad postoperatively and was subsequently lost to follow-up. This patient underwent microadenoma resection, was discharged on postoperative Day 2, and had an initial unremarkable postoperative visit; however, laboratory evaluations and longer-term results were not available. Of the remaining 26 patients, ages ranged from 20 to 69 years (mean 45.7 years) (Table 1). There were 14 men and 12 women, all of whom presented with clinical signs of acromegaly. Hypertension was the most common associated symptom (42.3%), with obstructive sleep apnea, headache, and arthralgias being reported in 38.5% of patients (Table 1). If decreased acuity or visual fields were noted on the initial screening examination, patients were referred for formal ophthalmological evaluation before and after surgery. The follow-up duration ranged from 3 to 60 months (mean 24.5 months).

TABLE 1: Baseline demographic in 26 patients with acromegaly*

Factor	No. of Patients (%)
sex	
male	14 (53.8)
female	12 (46.2)
age at diagnosis (yrs)†	
20–29	3 (11.5)
30–39	4 (15.4)
40–49	7 (26.9)
50–59	9 (34.6)
60–69	3 (11.5)
mean initial IGF-I (μg/l)	814.1
mean initial GH (μg/l)	18.9
associated diseases & symptoms	
OSA	10 (38.5)
DM	5 (19.2)
headache	10 (38.5)
visual field defect	7 (26.9)
abnormal visual acuity	4 (15.4)
arthralgia	10 (38.5)
hypertension	11 (42.3)
hyperprolactinemia	3 (11.5)

* OSA = obstructive sleep apnea; DM = diabetes mellitus.
† Mean age of the population was 45.7 years.

Endocrine Evaluation

All patients underwent full preoperative endocrine laboratory evaluations, which were repeated at 3, 6, and 12 months postoperatively and annually thereafter. Criteria for endocrine remission were adopted from the literature as follows: normal age- and sex-matched IGF-I concentration and a nadir GH level during oral glucose load of less than 1.0 μg/l and a random GH value of less than 2.5 μg/l.[55] We considered early remission to have been achieved if these parameters were met. The results of the additional follow-up visits were reviewed to evaluate recurrence.

Imaging Evaluation and Tumor Classification

All patients underwent thin-cut preoperative CT and MR imaging (MR imaging). Postoperative MR imaging was performed within 24 hours of surgery and repeated at 3 and 12 months to confirm the extent of tumor removal. All pituitary adenomas were classified by size and extension on postcontrast MR imaging. Tumors less than 1 cm were classified as microadenomas, while those greater than or equal to 1 cm were recorded as macroadenomas (Table 2). Volumetric analysis of the tumor was calculated using the diameter method.[61] Parasellar extension was recorded using both Hardy classification and Knosp scoring.[32,37]

Treatment Protocol

All patients were treated using identical surgical procedures. All operations were performed or supervised by the senior neurosurgeons (J.J.E. and D.W.A.) using a purely endoscopic endonasal approach, which has been described in detail elsewhere in the literature.[6,22,43,56] No transcranial procedures were performed in this series. Patients in whom sufficient biochemical relief was not achieved postoperatively received adjuvant treatment on the basis of residual tumor burden, endocrine studies, available medical and radiosurgical treatment options, and patient preference.

Statistical Analysis

Data analysis was performed using SPSS 8.0 software (SAS Institute). The differences in outcome in relation to tumor volume, biochemical cure, extent of invasion, extent of resection, and preoperative GH levels were investigated by calculating Fisher exact or chi-square tests. A probability value of less than 0.05 was considered statistically significant.

TABLE 2: Tumor characteristics and outcome at last follow-up

Factor	No. of Patients/Value (%)
size of adenoma	
<10 mm	4 (15.4)
≥10 mm	22 (84.6)
tumor volume (cm^3)	
mean	14.11
range	0.03–57.37
Knosp score	
mean	1.8
range	0–4
Hardy class	
mean	2.4
range	0–4
revision op	5 (19.2)
gross-total resection	19 (73.1)
intraop lumbar drainage	2 (7.7)
CSF leak	1 (3.8)
LOS (days)	
mean	2.8
range	2–7
endocrine remission	15 (57.7)
microadenomas	3 (75.0) of 4
macroadenomas	12 (54.5) of 22
postop radiosurgery	2 (7.7)
postop medical treatment	9 (34.6)
follow-up (mos)	
mean	24.5
range	3–60

Results

Surgical Results

The overall rate of endocrinological remission in the group of 26 patients who underwent endoscopic transsphenoidal surgery was 57.7% (that is, remission in 15 of 26 patients). The surgical outcomes are reported in Table 2. A gross-total resection was accomplished in 19 patients (73.1%). Five patients (19.2%) presented after having 1 or 2 previous microscopic transsphenoidal resections by other surgeons. Of these 5 patients, 2 met the criteria for cure postoperatively. Postoperative radiosurgery was performed in 2 patients (7.7%) with residual tumor in the cavernous sinus. Ultimately, both of these patients required continued medical therapy. Medical therapy (primarily octreotide) was administered in 9 patients (34.6%) in whom a biochemical cure was not achieved by surgery or radiosurgery. One patient was concomitantly treated with octreotide and bromocriptine.

Seven patients (26.9%) presented with visual field defects as demonstrated by formal perimetry and visual field testing. While 5 patients noted an improvement postoperatively, 2 did not. No patient experienced a decrease in visual field or acuity postoperatively. The LOS ranged from 2 to 7 days (mean 2.8 days). Nearing the conclusion of the study period, patients were routinely discharged on the 2nd postoperative day.

Remission Rate by Size and Invasion

Clinical follow-up ranged from 3 to 60 months (mean 24.5 months). The best endocrinological results were achieved in patients with microadenomas; in 3 (75%) of 4 these patients, a biochemical cure was achieved. For those with macroadenomas, a postoperative remission was noted in 54.5% (Table 2). Tumor volume, as calculated by the diameter method, ranged from 0.3 to 57.37 cm^3 (mean 14.11 cm^3) (Table 3). In patients with larger tumor volumes, a biochemical cure or a gross-total resection was significantly less likely ($p = 0.0076$ and $p < 0.0001$, respectively). Parasellar extension was grouped into Grades 0–4 based on Knosp and Hardy classification systems.[32,37] The mean Knosp score was 1.8 and mean Hardy classification was 2.4. Patients with Knosp or Hardy Grade 3 or 4 were less likely to experience a cure ($p = 0.0068$ and $p = 0.013$, respectively). Table 4 provides a summary of the results of univariate analysis of factors associated with the lack of postoperative remission.

TABLE 3: Tumor characteristics and outcome*

Case No.	Age (yrs), Sex	Tumor Dimension (mm)			Biochem Cure
		Transverse	Craniocaudal	Anteropst	
1	44, F	24	32	19	no
2	50, M	16	10	11	yes
3	39, M	32	30	30	no
4	53, F	12	9	11	no
5	47, M	8	8	12	yes
6	39, F	4	7	5	yes
7	51, M	12.5	10.6	9.4	yes
8	22, F	2.8	2.5	2.2	no
9	53, M	16	14	16	yes
10	34, F	35	29	27	no
11	61, M	12	12	13	yes
12	53, F	28	25	19.7	yes
13	69, F	13	7	10	yes
14	44, F	8	9	11	no
15	33, M	15	17	19	yes
16	41, F	16	23	21	no
17	51, F	28	34	28	no
18	49, M	15	16	12	no
19	51, M	1.5	3	2	yes
20	53, M	21	18	30	yes
21	60, M	8	9	7	yes
22	47, F	10	13	9	yes
23	50, M	12	14	11	no
24	20, M	7	10	11	yes
25	29, M	23	17	27	yes
26	45, F	25	27	15	no

* Anteropst = Anteroposterior; Biochem = Biochemical.

TABLE 4: Univariate analysis of factors associated with the lack of a biochemical cure after endoscopic resection of a GH-secreting adenoma

Factor	p Value
initial GH level	0.4279
tumor volume	0.0076
subtotal resection	<0.0001
Hardy Class 3 or 4	0.0130
Knosp Grade 3 or 4	0.0068

Surgical Complications

There were no major complications, but minor complications occurred in 3 patients (11.5%). Transient postoperative diabetes insipidus was observed in 2 patients and was treated medically with desmopressin. One patient required 3 doses, and the other required treatment with a nightly dose for 1 month prior to resolution. A postoperative CSF leak occurred in 1 patient after resection of a macroadenoma with a high-flow cranial base defect. This CSF leak resolved after insertion of a lumbar drain, no morbidity occurred. No deaths or cases of meningitis were observed.

Discussion

Therapy for acromegaly is directed at the control of tumor growth, restricting GH hypersecretion, and normalizing IGF-I levels and the long-term objective is to reduce the morbidity and mortality rate to a level comparable to that of the general population.[48] To objectively measure postoperative GH function, typically after an OGTT, IGF-I is measured to assess the biochemical response to treatment. However, there has been considerable debate as to the accepted criteria to define biochemical remission.[2,28,41,60] In the past, random GH levels less than 5 μg/l and/or an OGTT suppression of GH less than 2 μg/l were acceptable thresholds for the remission of the disease.[1,41] In 2000, the Acromegaly Treatment Workshop presented international consensus criteria that defined biochemical control as a normal IGF-I for age and sex as well as a GH less than 1.0 μg/l during an OGTT.[30,47] However, the validity of this boundary was questioned in 2005 by a consensus workshop that determined that GH nadir values should more closely approximate those of healthy individuals, and thus GH after OGTT should fall below 0.4 μg/l.[46] Ronchi et al.[55] reevaluated 70 patients meeting international consensus criteria for control and reported no significant difference in clinical, biochemical, and hormonal parameters in patients in whom GH was suppressed after OGTT at 0.4 μg/l or 1.0 μg/l upon long-term follow-up. While many postoperative patients will be considered "cured" by the current criteria, OGTT GH nadir often remains higher than what is observed in healthy controls, the significance of which remains uncertain.

Several authors have suggested that a purely endoscopic approach to sellar pathology offers improved visualization, preservation of sinonasal function and superior patient comfort while decreasing hospital LOS compared with traditional microscopic transsphenoidal techniques.[8,33,51] Furthermore, many posit the use of angled endoscopes provides a field of view that is significantly larger and may enhance the identification of critical neurovascular structures, allow for a better assessment of the extent of the resection, and subsequently decrease the complication rate.[59,62] The authors of several series have retrospectively contrasted their results after using a purely endoscopic approach with the current "gold standard" traditional microscopic approaches.[9,12,21,22,27,65] Although we are not aware of any randomized studies, a few studies present retrospective outcome data after microscopic and endoscopic approaches before and after the investigators adopted the endoscope into routine practice. For secretory adenomas Cho and Liau[12] reported a control rate of hormonal hypersecretion of 73% after microscopic surgery, but the cure rate was 64% and the complication rate was significantly lower after these authors transitioned their practice patterns to using the endoscopic procedure. Conversely, D'Haens et al.[21] reported an increased cure rate (to 65% from 50%) with endoscopic removal of secretory adenomas, with a slightly higher rate of CSF leakage. While endoscopic approaches provide many theoretical benefits over standard microscopic techniques, recent publications have not consistently shown improvement in resection and complication rates in the endoscopic group.[58] However, high-volume endoscopic studies with long-term follow-up data (similar to those available in the microscopic literature) will ultimately be required to draw relevant conclusions.

Purely endoscopic approaches to pituitary adenomas have been described as a safe and effective alternative to the traditional microscopic procedure.[21,22,27,31] The authors of series dedicated to outcomes after the microsurgical treatment of GH-secreting adenomas have described biochemical cure rates after microscopic procedures ranging from 42% to 67%, using the most recent criteria.[3,29,36,40,42,52,63] To assess biochemical cure rates after a purely endoscopic resection, the results typically must be separated from endoscopic series reporting data on all adenomas (Table 5). In these series, cure rates range from 57% to 100%.[7,10,13,21,22,27,31,33,34,44,57,66] We are aware of only one early study that focused specifically on outcomes after endoscopic resection in the setting of acromegaly.[44] In this early study the authors reviewed the cases of 5 patients with mostly microadenomas and reported a cure rate of 100% using a liberal cure benchmark. In comparing the results of the traditional series with endoscopic counterparts, bias may be introduced by the use of a short follow-up period, as GH-secreting adenomas in a previously assumed cured patient may recur after many years of follow-up.[15,38,52] In these lumped endoscopic series, precise reporting of tumor volume, frequency of follow-up, use of adjuvant medical therapy, and stereotactic radiosurgery for those in the acromegaly subset are often not defined, making comparison across studies difficult. Additionally, the number of patients with suprasellar and cavernous sinus invasion also varies when reported. The results of the present series are slightly less robust compared with the previously reported endoscopic series. However, the baseline patient characteristics in this study included 84.6% macroadenomas, 19.2% revisions, and an overall mean Knosp grade of 2.4, which represents more invasive disease at presentation than in most other series.

TABLE 5: Summary of cure rates after endoscopic transsphenoidal resections of GH-secreting adenomas reported in the literature*

Authors & Year	No. of Cases	Total Cure Rate (%)	Lesion Size		Definition of Cure
			<10 mm	≥10 mm	
Jho, 2001†	9	78	NR	NR	normal postop IGF-1 levels
Lui et al., 2001	5	100	NR	NR	GH ≤2 μg/l (OGTT)
Cappabianca et al., 2002†	36	NR	6	30	basal GH ≤2.5 μg/l, GH ≤1 μg/l (OGTT), normal IGF-I level
Rudnick et al., 2005†	12	83.3	4	8	normal postop GH serum & IGF-I levels
Kabil et al., 2005†	48	85	NR	NR	normal postop IGF-I levels
Frank et al., 2006†	83	70	24	59	basal GH <2.5 ng/ml or GH <1 μg/l (OGTT) or normal IGF-I level
Dehdashti et al., 2008†	34	71	8	26	basal GH ≤2.5 μg/l, GH ≤1 μg/l (OGTT), normal IGF-I level
Choe et al., 2008†	9	88.8	NR	NR	basal GH ≤2.5 μg/l, GH ≤1 μg/l (OGTT), normal IGF-I level
Yano et al., 2009†	31	70.9	NR	NR	GH ≤1 μg/l (OGTT), normal IGF-I level
D'Haens et al., 2009†	13	62	2	11	GH ≤1 μg/l (OGTT), normal IGF-I level
Gondim et al., 2010†	58	70.6	11	47	GH ≤1 μg/l (OGTT), normal IGF-I level
Ceylan et al., 2010†	7	57	NR	NR	GH ≤1 μg/l (OGTT), normal IGF-I level
present study	26	57.7	4	22	basal GH ≤2.5 μg/l, GH ≤1 μg/l (OGTT), normal IGF-I level

* NR = not reported.

† Data obtained from an overall endoscopic series.

Overall, the complication rates have typically been commensurate between endoscopic and microsurgical techniques.[22,53] In a study of two groups of 25 patients undergoing microscopic approaches and endoscopic approaches, O'Malley et al.[53] described similar complication rates between the groups for both CSF leak and incidence of diabetes insipidus, with a trend toward less diabetes insipidus in the endoscopic group. Overall complications realized in this cohort of patients were 11.5% with no major complication requiring return to the operating room, permanent deficit, or treatment. Transient diabetes insipidus occurred in 2 patients (7.7%), while no permanent diabetes insipidus was noted. This result is significantly lower than the 7.6% rate of persistent diabetes insipidus in the historical microscopic cohort.[14] One patient (3.8%) experienced a postoperative CSF leak, which resolved after 3 days of lumbar cistern drainage. This result is similar to others in the literature; Dehdashti et al.[22] reported a rate of 3.5% as compared with the 3.9% historical average in large microscopic series. In this series, no patient experienced a worsening of visual fields or acuity, while 5 patients noted an improvement.

Invasion of the cavernous sinus occurs in roughly 6%–10% of pituitary adenomas and is an arduous challenge in the management of these tumors.[26,37,64] In this situation, Couldwell[20] noted that microscopic transsphenoidal exposures are profoundly limited because of the narrow midline corridor around the sella. However, endoscopic techniques may allow for a more accommodating approach to the medial and inferior walls of the cavernous sinus and thus may increase the rates of total excision in this scenario.[10] In the current series, we noted significant difficulty in resolving hormonal hypersecretion in patients with extensive cavernous sinus and parasellar invasion despite the endoscopic access. Complete resection and hormonal resolution occurred in few patients in this category (Fig. 1). Overall, surgery in patients with Knosp Grade 3 or 4 adenomas was significantly less likely to achieve a biochemical cure ($p = 0.0068$). Management of pituitary lesions with extrasellar extension is a source of ongoing controversy. A significant proportion of patients with large macroadenomas extending outside the sella will experience persistently elevated GH levels postoperatively, often requiring subsequent medical therapy and/or radiosurgery to gain satisfactory biochemical control.[5,18] Some authors have argued primary medical therapy may be used for patients with GH-secreting macroadenomas with extrasellar extension, which makes complete surgical resection unfeasible.[5,18] However, other authors have asserted that initial operative debulking of these macroadenomas may increase the proportion of patients that subsequently attain hormonal control with adjunctive therapy, particularly if more than 75% of the initial tumor volume is resected.[17,35,48,54]

To demonstrate safety and efficacy an attempt was made to carefully evaluate and report the biochemical results of endoscopic resection of GH-secreting adenomas in the current series. However, there are several important limitations of this study. This is a retrospective single-institution study with no direct comparison between the traditional microscopic and endoscopic groups. The mean follow-up period was 24.5 months and no cases of biochemical relapse were noted. In microscopic surgical series, long-term follow-up has consistently identified relapse rates ranging from 0.6% to 10%.[15,38,52] It remains unresolved and untested as to whether the endoscopic technique can result in a similar or lower incidence of delayed recurrence.[22] We evaluated 26 consecutive patients presenting over a 50-month period. It is unclear if the demographics of this patient population (the relatively high number of revision cases [19.2%], tumor volume, and extent of parasellar extension) are comparable to other reported series with regard to outcome after endoscopic resections (Table 5).

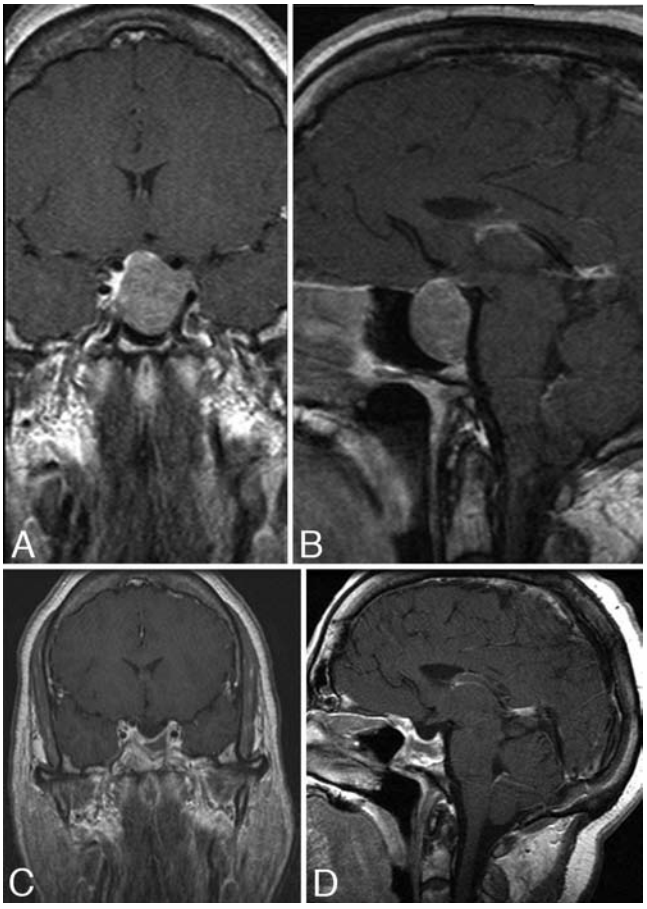

Fig. 1. A and B: Sagittal and coronal contrast-enhanced MR images obtained in a 53-year-old woman who presented with clinical signs of acromegaly and a macroadenoma extending into the cavernous sinus and suprasellar cistern. **C and D:** Six-month postoperative contrast-enhanced MR images revealing postoperative changes but no residual tumor in this patient in whom a biochemical cure was achieved.

Conclusions

To the best of our knowledge, this is the first study aimed solely at reporting the outcomes after an endoscopic endonasal resection of GH-secreting adenomas. The results authenticate the efficacy and safety of endoscopic pituitary surgery in the setting of acromegaly. While long-term results are needed to ultimately define tumor control, a favorable comparison with historical results supports the continued use of endoscopic techniques. We believe the advantages of endoscopic approaches, including minimal postoperative discomfort, the associated development of expanded approaches, the relative ease of reoperation if necessary, and superior visualization provided by 3D and angled endoscopes, will ultimately position this technique as the favored approach for the future treatment of pituitary adenomas.

Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Campbell, Yadla, Evans. Acquisition of data: Campbell, Kenning, Andrews, Rosen, Evans. Analysis and interpretation of data: Campbell, Kenning, Evans. Drafting the article: Campbell, Yadla. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: Campbell, Andrews, Evans. Statistical analysis: Campbell. Administrative/technical/material support: Campbell. Study supervision: Campbell.

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Manuscript submitted June 10, 2010.
Accepted July 7, 2010.
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Neurosurg Focus 29 (4):E6, 2010

Endoscopic endonasal transsphenoidal surgery for growth hormone–secreting pituitary adenomas

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Object. The aim of this study was to determine the preoperative predictors of the extent of resection and endocrinological remission following endonasal endoscopic removal of growth hormone (GH)-secreting pituitary adenomas.

Methods. The authors analyzed a prospectively collected database of 24 consecutive acromegalic patients who underwent endoscopic endonasal transsphenoidal surgery. The extent of resection was evaluated on postoperative contrast-enhanced MR imaging. Endocrinological remission was defined as normal insulin-like growth factor I (IGF-I) serum levels and either a nadir GH level of < 0.4 ng/ml after an oral glucose load or a basal GH serum level < 1 ng/ml.

Results. The majority of acromegalic patients (83%) had macroadenomas > 1 cm in maximum diameter. Gross-total resection was achieved in 17 (71%) of 24 patients. Notably, endoscopic transsphenoidal surgery allowed complete resection of all lesions without cavernous sinus invasion, regardless of the suprasellar extent. Biochemical remission was achieved in 11 (46%) of 24 patients. A smaller tumor volume and a postoperative reduction in GH serum levels were associated with a higher rate of biochemical cure ($p < 0.05$). During a 23-month follow-up period 5 patients (21%) underwent Gamma Knife treatment of any residual disease to further reduce excess GH production. Twenty patients (83%) reported significant relief of their symptoms, while 3 (13%) considered their symptoms stable. Two patients (8%) with large macroadenomas experienced postoperative panhypopituitarism, and 2 patients (8%) suffered from CSF leaks, which were treated with lumbar CSF diversion.

Conclusions. A purely endoscopic endonasal transsphenoidal adenoma resection leads to a high rate of gross-total tumor resection and endocrinological remission in acromegalic patients, even those harboring macroadenomas with wide suprasellar extension. Extended approaches and angled endoscopes are useful tools for increasing the extent of resection. *(DOI: 10.3171/2010.7.FOCUS10173)*

Key Words • **endoscopy** • **acromegaly** • **growth hormone** • **insulin-like growth factor I** • **minimally invasive procedure** • **transsphenoidal surgery** • **skull base**

Acromegaly is most commonly caused by GH-secreting pituitary adenomas. This rare but very serious condition carries at least twice the mortality rate compared with that in the general population.[3,26,28,34] Excessive secretion of GH causes cardiovascular disease, musculoskeletal deformity, diabetes mellitus, and an increased incidence of malignancies. Cardiovascular and cerebrovascular accidents are common causes of death in acromegalic patients. Importantly, the normalization of GH levels alleviates symptoms and reduces mortality rates to those in the general population. Thus, a definition of cured acromegaly involves the normalization of excessive GH secretion as determined by circulating IGF-I and nadir GH of < 0.4 ng/ml after an oral glucose load.[12,13,23] Although somatostatin analogs and the GH receptor antagonist pegvisomant are increasingly prescribed as adjuvant or even primary therapy, resection remains the first-line treatment. In patients with intrasellar microadenomas, microsurgical removal alone provides biochemical control with the normalization of IGF-I in 75%–95% of patients; control rates decrease to 40%–68% of patients with macroadenomas.[21,25,33] Resection can be performed either alone or in combination with the administration of medical treatment as wells as radiotherapy.[22]

Abbreviations used in this paper: GH = growth hormone; GKS = Gamma Knife surgery; GTR = gross-total resection; IGF-I = insulin-like growth factor I; STR = subtotal resection.

In the current study we describe our experience with a purely endoscopic endonasal transsphenoidal approach in 24 patients with GH-secreting pituitary adenomas. Our aim was to analyze predictors of biochemical and clinical outcomes after the endoscopic resection of such lesions.

Methods

Patient Demographics

We reviewed a prospectively collected database of all endoscopic endonasal surgeries for GH-secreting pituitary adenomas performed at Weill Cornell Medical College, New York–Presbyterian Hospital, Geisinger Neurosciences Institute, and Temple University School of Medicine between February 2004 and May 2010 as a collaboration between the Departments of Neurosurgery and Otolaryngology. Patients selected for this study all underwent surgery during which an endoscopic endonasal transsphenoidal approach was used. In 3 patients an extended transsphenoidal approach with removal of the tuberculum sellae and planum sphenoidal was performed.[18] All patients underwent preoperative MR imaging. All tumors were analyzed using contrast-enhanced MR images on postoperative Day 1, at 3 months after surgery, and then at a yearly interval. Tumor volume was approximated by an ellipsoid model by using the product of the maximal anteroposterior, lateral, and rostrocaudal radii.[2,17,36] Invasion of the cavernous sinus was diagnosed according to the following criteria: three-fourths or more encasement of the internal carotid artery, obliteration of the carotid sulcus venous compartment, or crossing of the lateral intercarotid line by the tumor.[6] For each surgery, the pathology, duration of surgery, estimated blood loss, type of exposure, use of intraoperative fluorescein and lumbar drainage, technique of closure, and complications were recorded. The institutional review board at both institutions approved the study.

Surgical Technique

Following the induction of general anesthesia, antibiotics, glucocorticoids, and intrathecal fluorescein are given.[27] BrainLAB neuronavigation is routinely used. A detailed description of the procedure has already been published.[18,31] Briefly, after topical exposure of the nasal mucosa to cocaine and injection of the mucosa of the middle turbinates with a mixture of lidocaine 1% and epinephrine (1:100,000), the sphenoid ostia are bilaterally identified and the bony opening is enlarged. The posterior third of the nasal septum adjacent to the vomeric bone and maxillary crest is resected with a tissue shaver. The anterior wall of the sella is opened using a high-speed drill and curettes. In more recent cases with large macroadenomas, a nasoseptal flap may be harvested at the start of the case. For the resection of microadenomas, an attempt is made to remove the tumor en bloc. For macroadenomas, the lesion is first internally decompressed by removing the inferior portion of the tumor followed by the lateral portions to prevent the suprasellar arachnoid from herniating down into the sella and obstructing the view. The suprasellar component is resected last. Exposure of this region may require an extended approach including removal of the tuberculum sellae and planum sphenoidale. Tumor is dissected off the medial wall of the cavernous sinus. Angled endoscopes are used to enter the cavernous sinus and remove tumor that can easily be dissected from this area. Closure is performed in a multilayer fashion.[20]

Endocrinological Evaluation

Basal fasting levels of GH and IGF-I were measured in the serum of patients preoperatively, postoperatively, and at the time of the last follow-up. Biochemical remission was evaluated according to IGF-I serum levels combined with an oral glucose tolerance test in 10 patients. A glucose tolerance test was considered normal if serum GH levels were suppressed to < 0.4 ng/ml following a 75-g oral glucose load. In the remaining 14 patients, biochemical remission was evaluated by IGF-I levels combined with basal GH levels. Random basal GH serum levels of ≤ 1 ng/ml were considered normal. Insulin-like growth factor I was always evaluated according to age-related diagrams. Our goal is to attempt an oral glucose test to determine cure in all patients, but this test is not always possible in patients referred from outside endocrinologists who may not comply or follow up reliably at our institution.

Statistical Evaluation

Continuous variables are displayed as the means ± SD and the range. Categorical values are shown as percentages. Associations between the effect of tumor size, invasion of the cavernous sinus, extension into the suprasellar cistern, or preoperative GH serum levels on endocrinological remission and the extent of resection were calculated using a chi-square test for categorical variables and the Pearson correlation coefficient for continuous variables. Postoperative GH serum levels were compared using a Mann-Whitney U-test. Outcome predictors were determined with binary logistic regression modeling. A p value < 0.05 was considered significant.

Results

Patient Characteristics

Twenty-four patients who underwent purely endoscopic transsphenoidal resection of GH-secreting pituitary adenomas were included in the series. The cohort consisted of 13 males and 11 females with a mean age of 50.7 ± 14.7 years (range 22–75 years; Table 1). Approximately half of these patients presented with increases in ring and shoe size as well as the typical coarse acromegalic facial features. Fewer patients sought medical attention for bone and joint pain or amenorrhea. The majority of lesions were macroadenomas defined by a maximum diameter > 1 cm. However, presenting symptoms were attributable to excess hormonal production in all but 1 patient, who presented with diplopia caused by tumor invasion of the cavernous sinus. None of the patients demonstrated impairment on preoperative visual field testing. Assessment of preoperative contrast-enhanced MR imaging revealed a cavernous sinus invaded by tumor in 10 patients.

TABLE 1: Summary of characteristics in 24 patients with acromegaly*

Characteristic	No. (%)
sex	
M	13 (54.2)
F	11 (45.8)
mean age (yrs)	50.7 ± 14.7
previous op	
yes	4 (16.7)
no	20 (83.3)
presenting symptoms	
increased ring & shoe size	11 (45.8)
bone & joint pain	4 (16.7)
amenorrhea	2 (8.4)
max tumor diameter	
microadenoma (<1 cm)	4 (16.7)
macroadenoma (>1 cm)	19 (83.3)
invasion of the CS	
yes	10 (41.7)
no	14 (58.3)
suprasellar tumor extension	
yes	7 (29.2)
no	17 (70.8)
GTR	
yes	17 (70.8)
no	7 (29.2)
mean FU (mos)	23.2 ± 25.4

* CS = cavernous sinus; FU = follow-up.

TABLE 2: Summary of operative details in 24 patients with acromegaly

Parameter	No. (%)
mean op time (min)	181.6 ± 57.3
mean estimated blood loss (ml)	153.1 ± 206.4
extended approach	
yes	3 (12.5)
no	21 (87.5)
intrathecal fluorescein	
yes	18 (75.0)
no	6 (25.0)
intraop CSF leak	
yes	13 (54.2)
no	11 (45.8)
closure of skull base defect	
fat	13 (54.2)
vomer	10 (41.6)
fascia lata	2 (8.3)
DuraSeal	24 (100.0)
lumbar drain	
yes	3 (12.5)
no	21 (87.5)
mean hospital stay (days)	3.6 ± 1.8

The tumor extended into the suprasellar cistern in 7 patients. The average duration of the follow-up period from resection to laboratory testing was 23 months (range 1–74 months).

Surgical Results

Purely endoscopic transsphenoidal surgeries lasted an average of 182 minutes (range 104–326 minutes). The estimated blood loss was 153 ml (range 30–800 ml). An extended transsphenoidal approach was performed in 3 patients with suprasellar tumor expansion and invasion of the cavernous sinus. In more than two-thirds of the cases, intrathecal fluorescein was given to label the CSF, which is an institutional protocol at Weill Cornell Medical College. Intraoperative CSF leaks were encountered in approximately one-half of the patients (Table 2). In 83% of the cases with intraoperative CSF leaks, abdominal fat was harvested for the enforcement of a multilayer closure. Twenty-five percent of these patients also underwent spinal CSF drainage for 3 days to facilitate watertight closure of the skull base defect. Postoperative MR imaging revealed that GTR was achieved in 71% of the cases. Two factors were associated with STR; greater tumor volume and cavernous sinus invasion were linked to a higher rate of residual tumor ($p < 0.01$ and $p < 0.001$, respectively; Fig. 1). Gross-total tumor resection was achieved in all patients who did not have invasion of the cavernous sinus and in 3 of the 10 patients who did have cavernous sinus invasion. Thus, residual tumor was identified in the cavernous sinus of 7 patients. In 1 of these patients residual tumor was also found in the frontal lobe, and in another patient tumor was left in the suprasellar cistern. Note, however, that tumor expansion into the suprasellar cistern was not correlated with a higher rate of STR. Only tumor volume was a significant predictor for GTR, according to a logistic regression model ($p < 0.05$). Five patients who underwent STR and had poor control of their GH serum levels underwent GKS. One of these patients achieved biochemical remission following adjuvant medical therapy. Another 2 patients had near complete restoration of GH and IGF-I levels and did not require medical treatment. However, 2 of these 5 patients who underwent GKS continued to have poor control of excess GH secretion despite adjuvant medical therapy.

Endocrinological Outcome

Preoperative serum GH levels of 31 ng/ml (range 1–150 ng/ml) decreased to 4 ng/ml (range 0–36 ng/ml) postoperatively. Insulin-like growth factor I levels of 806 ng/ml prior to surgery (range 15–1321 ng/ml) decreased to 462 ng/ml (range 6–937 ng/ml) postoperatively (Table 3). At 23 months after resection, 11 patients (46%) had a biochemical cure. Considering only patients with macroadenomas (maximum diameter > 1 cm), the rate of endocrinological remission decreased to 42%. A smaller tumor volume was associated with a higher rate of biochemical cure by endoscopic transsphenoidal surgery (p

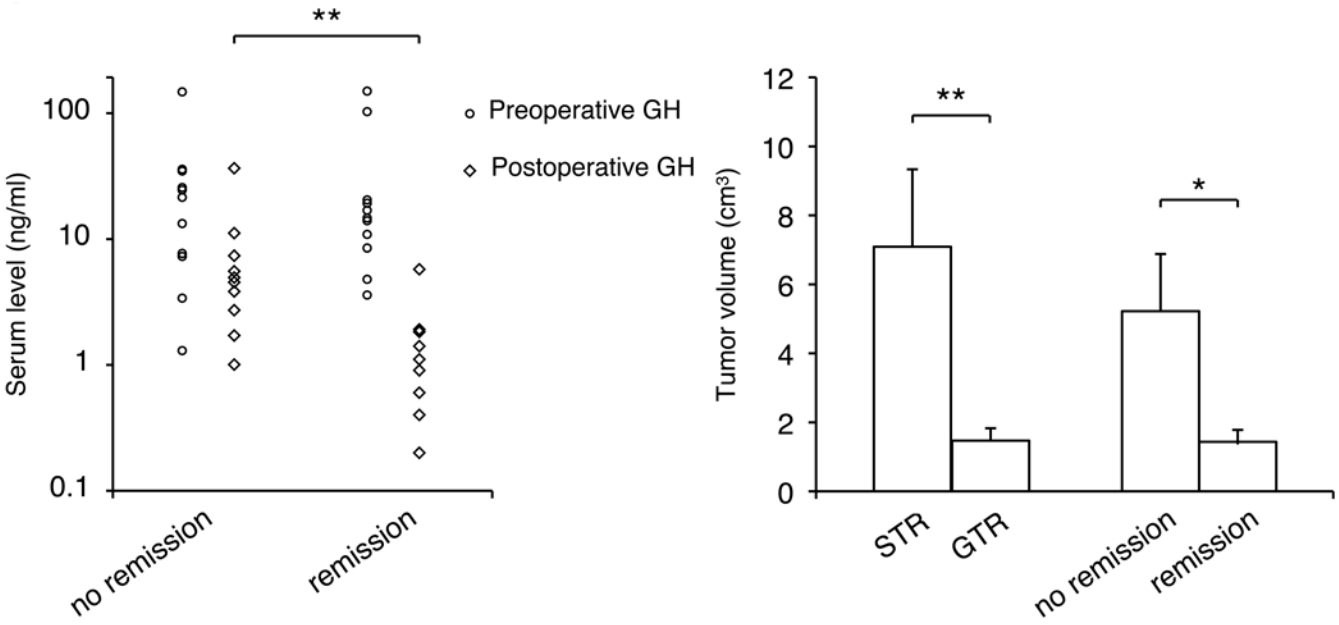

Fig. 1. Graphs showing the association between GH levels or tumor size and endocrinological remission. Comparison of pre- and postoperative GH serum levels in patients with and without endocrinological remission **(left)**. *Horizontal line* indicates the median. Lesions associated with GTR and endocrinological remission are significantly smaller than lesions for which no GTR or remission was achieved **(right)**. Values are shown as the means. *Error bars* represent the SEM. *$p < 0.05$ and **$p < 0.01$.

< 0.05; Fig. 1). While preoperative GH serum levels did not differ significantly between patients who demonstrated an endocrinological remission and those who did not, postoperative GH serum levels were significantly lower in patients who had a remission ($p < 0.01$). Thus, postoperative GH serum level was a significant predictor of endocrinological remission in a logistic regression model ($p < 0.05$). Of 11 patients in biochemical remission, 9 were cured by resection alone. One patient achieved endocrinological remission by a combination of resection, GKS, and adjuvant medical therapy, and 1 patient by resection and adjuvant medical therapy (Table 3). Seven of the 13 patients who did not achieve endocrinological remission required medical therapy for elevated GH serum levels. The other 6 patients had GH levels close to normal so that their endocrinologist selected conservative treatment with serial GH and IGF-I serum level checks.

Clinical Outcome and Complications

Twenty-three months after resection, 25% of the patients believed that their initial presenting symptoms had normalized and another 58% experienced significant improvement in their condition (Table 4). The remaining patients felt no change in their symptoms, and 1 patient with severe bone and joint paint believed that he had gotten worse following surgery.

Two patients who had an intact hypothalamic-pituitary axis prior to the procedure demonstrated panhypopituitarism following resection of their adenoma. Notably, the lesions in both of these cases were macroadenomas. Cerebrospinal fluid rhinorrhea developed in 2 patients after the resection of a GH-secreting macroadenoma. Both CSF leaks were successfully treated with 3–4 days of lumbar CSF drainage. Two patients suffered from sinusitis following the procedure and were treated with oral antibiotics. Transient diplopia was noticed by a patient who underwent resection of a recurrent pituitary macroadenoma with invasion of the cavernous sinus. Immediately after the procedure the patient demonstrated cranial nerve VI paresis ipsilateral to the side of invasion.

Discussion

Resection is currently the first-line treatment for GH-secreting adenomas. While endocrinological remission leads to symptom relief and the restoration of normal life expectancy, some patients are not cured by surgical treatment alone. Analysis of the determinants of a failed endoscopic transsphenoidal technique may assist in appropriate patient selection and further refinement of the procedure.

During the last few decades, the criteria for endocrinological remission have been constantly revised.[12,13] In early series, GH levels < 5 ng/ml were used to define biochemical remission.[1,29] Using these criteria, Abosch et al.[1] report that 76% of 254 patients had endocrinological remission after transsphenoidal pituitary resection. Similarly, Ross and Wilson[29] found GH levels < 5 ng/ml in 79% of 165 patients at the 76-month follow-up. However, basal GH levels are an unreliable marker for endocrinological remission given the pulsatile nature of GH secretion and the changes in serum levels with sleep, age, and nutritional status of a patient.[14] For that reason, subsequent studies included an assessment of the absolute nadir in levels of GH after an oral glucose load. Using a nadir level < 2 ng/ml, Fahlbusch et al.[8] reported a 57% rate of endocrinological remission after transsphenoidal surgery. More recent studies have used stricter criteria such as a

TABLE 3: Treatment characteristics and endocrinological outcome of 24 patients with GH-secreting pituitary adenomas*

Case No.	Age (yrs) & Sex	Preop GH	Preop IGF-I	Postop GH	Postop IGF-I	GKS	Adjuvant Medical Therapy	Last FU GH	Last FU IGF-I	OGTT†	Endocrin Cure	FU (mos)
1	48, F	13.3	624	4.5	261	yes	none	1.7	274	NA	no	10
2	56, M	NA	15.4	3.8	6.4	yes	none	4.8	267	NA	no	47
3	55, M	7.7	NA	1.0	422	no	none	NA	NA	NA	no	44
4	37, F	NA	773	5.7	506	yes	bromocriptine, cabergoline, Sandostatin	0.9	180	NA	yes	61
5	48, M	4.8	940	0.2	530	no	none	0.1	118	NA	yes	74
6	35, F	1.3	411	1.7	288	no	none	1.7	120	NA	no	13
7	60, M	35.9	567	2.7	313	no	none	2.7	313	NA	no	53
8	58, M	103	757	0.9	190	no	none	0.9	165	NA	yes	66
9	65, M	8.5	902	1.1	635	no	none	0.8	191	normal	yes	21
10	66, F	10.9	534	1.4	85	no	none	0.017	87	NA	yes	24
11	65, F	3.6	836	0.4	547	no	none	0.056	148	NA	yes	31
12	39, M	19.3	855	0.2	597	no	none	0.1	135	NA	yes	4
13	69, M	24.6	895	4.9	478	no	Sandostatin	2.2	200	NA	no	69
14	65, F	14.7	1012	1.8	526	no	cabergoline	0.98	260	normal	yes	6
15	60, M	16.9	NA	1.9	539	no	none	1.9	289	abnormal	no	5
16	44, M	7.3	1251	1.0	602	yes	octreotide	0.3	394	normal	no	4
17	26, F	148	1022	11	841	yes	octreotide	3.4	655	abnormal	no	5
18	22, F	25.7	660	36	756	no	octreotide	18	884	NA	no	1
19	56, F	150	626	0.4	87	no	none	0.7	145	NA	yes	1
20	58, M	20.5	896	0.6	407	no	none	7.0	198	normal	yes	3
21	40, M	34.8	1297	7.3	937	no	Sandostatin	3.1	290	abnormal	no	2
22	75, M	14	1241	1.1	494	no	none	0.9	140	normal	yes	5
23	26, F	21.5	1321	2.7	900	no	Sandostatin	3.9	799	abnormal	no	3
24	44, F	3.4	296	5.5	147	no	Sandostatin	3.4	193	abnormal	no	4
average		31.4	806.0	4.1	462.0			2.7	286.8			23.2
SD		43.4	330.0	7.3	255.5			3.9	216.6			25.4

* All serum hormone levels are expressed in ng/ml. Abbreviations: Endocrin = Endocrinological; NA = not applicable; OGTT = oral glucose tolerance test.

† Test is considered normal if serum GH is lower than 0.4 ng/ml following a 75-g oral glucose load.

nadir level < 1 ng/ml.[3,19,25] But a nadir level < 1 ng/ml would miss the diagnosis of acromegaly in up to 25% of patients.[7,11] Given the widespread availability of ultrasensitive GH assays, a recent consensus statement proposed a nadir level < 0.4 ng/ml as the criterion for an endocrinological cure.[13] An additional criterion for endocrinological cure also includes an assessment of IGF-I serum levels, which reflects integrated 24-hour GH secretion and remains relatively constant over the day. Normalization of IGF-I levels has been demonstrated following the successful treatment of acromegaly.[5,15,30] Consequently, normal IGF-I levels and a nadir level < 1 ng/ml of GH after a glucose load were proposed by a consensus statement in 2000 as criteria for an acromegaly cure.[12] The application of these criteria yielded endocrinological remission rates of 57%–67% after microsurgical transsphenoidal approaches.[3,19,25] When considering only pituitary macroadenomas (diameter > 1 cm), Nomikos et al.[25] reported an endocrinological remission in 51% of patients, and Beauregard et al.[3] documented remission in 47%. Using more stringent criteria for endocrinological remission as proposed by a consensus statement from 2010,[13] we report a 46% endocrinological remission rate in our patients with GH-secreting pituitary adenomas.

In the current series a purely endoscopic transsphenoidal technique was used. In accordance with microscopic transsphenoidal series, we found that tumor volume was a predictor of resectability and an endocrinological cure.[3,25] Using a purely endoscopic technique, we found residual suprasellar tumor in only 1 of 7 patients with suprasellar tumor extension. In contrast, tumor was left in 7 of 10 patients with invasion of the cavernous sinus. This finding contrasts with that in a study by Bohinski and colleagues,[4] who investigated the extent of macroadenoma resection via a microsurgical technique by using intraoperative MR imaging. In that series, residual tumor was

TABLE 4: Clinical outcomes and complications in 24 patients with acromegaly

Parameter	No. (%)
adjuvant medical treatment	
yes	9 (37.5)
no	15 (62.5)
GKS	
yes	5 (20.8)
no	19 (79.2)
endocrinological remission	
yes	11 (54.2)
no	13 (45.8)
clinical outcome	
asymptomatic	6 (25.0)
improved	14 (58.3)
stable	3 (12.5)
worse	1 (4.2)
complication	
panhypopituitarism	2 (8.4)
CSF leak	2 (8.4)
sinusitis	2 (8.4)
diplopia	1 (4.2)

detected both in the suprasellar cistern and adjacent to the cavernous sinus in 66% of all cases. A similar rate of residual tumor was reported by Nimsky and colleagues.[24] In their series, intraoperative MR imaging detected residual disease in 41.5% of all macroadenomas treated with a microsurgical transsphenoidal technique. The superiority of the endoscopic technique for visualizing the pathology in the suprasellar cistern was very recently demonstrated by Theodosopoulos et al.,[35] who performed intraoperative MR imaging after purely endoscopic transsphenoidal tumor resections. In a series of 27 patients, these authors were able to detect tumor remnants in the suprasellar cistern in 2 of 5 cases utilizing the endoscopic technique. These results are similar to those of Schwartz et al.,[32] who found residual tumor with intraoperative MR imaging in only 20% of patients after endoscopic surgery. The endoscopic technique offers the advantage of a wider field of view, better illumination, and the possibility of looking around corners using angled scopes. The ability to visualize and resect lesions in the suprasellar cistern was corroborated in the current series. However, tumor invasion of the cavernous sinus remains associated with a high rate of STR and poor disease control. Nevertheless, more aggressive surgery within the cavernous sinus by using endoscopic techniques has been shown to lead to a higher rate of endocrinological cure.[9,10,16]

While the current series demonstrates a high rate of endocrinological remission after endoscopic macroadenoma resection, additional larger studies using the most recent criteria for endocrinological cure are needed to corroborate our findings. Larger studies may also allow for subgroup analysis with regard to various tumor sizes and grades. Our results may be skewed by the adjuvant radiation and/or medical therapy that more than one-third of our patients received, but this limitation is inherent to the retrospective nature of our study. Mounting a controlled study of the separate use of resection, radiation, or medical therapy would be barely feasible.

Conclusions

In summary, an endoscopic transsphenoidal approach for the resection of GH-secreting pituitary adenomas leads to endocrinological remission in 46% of patients. Procedure-associated morbidity is low and three-fourths of our patients experienced improvement of their clinical symptoms. While the endoscopic technique greatly facilitates the resectability of lesions in the suprasellar cistern, resection of a tumor in the cavernous sinus remains a challenge.

Disclosure

Dr. Kennedy is a principal investigator for Lilly and Novo Nordisk Diabetes Clinical Trials. The authors report no other conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Schwartz, Hofstetter, Dehdashti. Acquisition of data: all authors. Analysis and interpretation of data: Hofstetter, Dehdashti. Drafting the article: Hofstetter, Mannaa, Mubita. Critically revising the article: Schwartz, Anand, Dehdashti. Reviewed final version of the manuscript and approved it for submission: Schwartz, Anand, Dehdashti. Statistical analysis: Hofstetter. Study supervision: Schwartz.

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Manuscript submitted June 21, 2010.
Accepted July 23, 2010.

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Neurosurg Focus 29 (4):E7, 2010

Pure endoscopic transsphenoidal surgery for treatment of acromegaly: results of 67 cases treated in a pituitary center

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Object. Acromegaly is a chronic disease related to the excess of growth hormone (GH) and insulin-like growth factor–I secretion, usually by pituitary adenomas. Traditional treatment of acromegaly consists of surgery, drug therapy, and eventually radiotherapy. The introduction of endoscopy as an additional tool for surgical treatment of pituitary adenomas and, therefore, acromegaly represents an important advance of pituitary surgery in the recent years. The aim of this retrospective study is to evaluate the results of pure transsphenoidal endoscopic surgery in a series of patients with acromegaly who were operated on by a pituitary specialist surgeon. The authors discuss the advantages, outcome, complications, and factors related to the success of the endoscopic approach in cases of GH-secreting adenomas.

Methods. The authors retrospectively analyzed data from cases involving patients with GH-secreting adenomas who underwent pure transsphenoidal endoscopic surgery at the Department of Neurosurgery of the General Hospital in Fortaleza, Brazil, between 2000 and 2009. Tumors were classified according to size as micro- or macroadenomas, and tumor extension was analyzed based on suprasellar/parasellar extension and sella floor destruction. All patients were followed up for at least 1 year. The criteria of disease control were GH levels < 1 ng/L after oral glucose tolerance test and normal insulin-like growth factor–I levels for age and sex.

Results. During the study period, 67 patients underwent pure endoscopic transsphenoidal surgery for treatment of acromegaly. Disease control was obtained in 50 cases (74.6%). The rate of treatment success was higher in patients with microadenomas (disease control achieved in 12 [85.7%] of 14 cases) than in those with larger lesions. Suprasellar/parasellar extension and high levels of sella floor erosion were associated with lower rates of disease control ($p = 0.01$ and $p = 0.02$, respectively). Complications related to the endoscopic surgery included epistaxis (6.0%), transitory diabetes insipidus (4.5%), and 1 case of seizure (1.5%).

Conclusions. Endoscopic transsphenoidal surgery represents an effective option for treatment of patients with acromegaly. High disease control rates and a small number of complications are some of the most important points related to the technique. Factors related to the success of the endoscopic surgery are lesion size, suprasellar/parasellar extension, and the degree of sella floor erosion. Although presenting important advantages, there is no conclusive evidence that endoscopy is superior to microsurgery in treatment of GH-secreting adenomas.
(DOI: 10.3171/2010.7.FOCUS10167)

Key Words • acromegaly • pituitary • adenoma • transphenoidal surgery • endoscopic surgery

Acromegaly was first described by Pierre Marie in 1886[6] as a syndrome characterized by the abnormal growth of extremities associated with the enlargement of the pituitary gland. Later on, it was described as associated not with a diffuse enlargement of the gland, but with the development of specific areas of hyperplasia of GH-secreting cells in the anterior lobe of the pituitary gland.

Clinically, acromegaly is characterized as a chronic disease related to high levels of GH and IGF-I.[18] Its prevalence is estimated to be around 40–70 cases per million inhabitants, with an annual incidence of 3–4 new cases per million inhabitants.[4] The main signs and symptoms are related to the somatic disfigurement secondary to hormonal imbalance, such as the abnormal growth of hands

Abbreviations used in this paper: ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; GH = growth hormone; IGF-I = insulin-like growth factor–I; LH = luteinizing hormone; TSH = thyroid-stimulating hormone.

and feet and facial alterations.[4,18] Cardiovascular, metabolic, respiratory, and bone alterations are usually also present, which complicates management.[23] Such alterations are related to the increased mortality observed in acromegalic patients,[8] who have a 32% increased risk for all-cause mortality.[20] According to previously published series, 60% of patients die of cardiovascular disease, 25% from respiratory complications, and 15% from cancer.[4,14] High GH/IGF-I levels and heart disease are the main factors related to poor outcome in these patients.[19]

Treatment options for acromegaly include surgery, medical therapy, and radiotherapy. The development of drug therapy for the control of acromegaly represents an important step toward hormonal control in patients with GH-secreting adenomas. Some of the options include the use of somatostatin analogs and pegvisomant, which are considered to represent useful options mainly for tumors that present characteristics associated with a small chance of surgical success. However, the costs of such treatment and the occurrence, in some cases, of major side effects, represent important limitations of the medical therapy.[2,4,12]

Surgical treatment, which provides rapid control of GH/IGF-I levels and lower costs, remains, therefore, the first line of treatment for GH-secreting adenomas according to different neuroendocrinology societies and pituitary centers.[12,13] Classically, transsphenoidal microsurgery has been considered the best surgical approach for most GH-secreting adenomas. However, in the last decade, the endoscopic approach to the treatment of sellar lesions has become an important option for resection of pituitary adenomas.[9,12,24] Some of the advantages of such an approach include improved visualization, less nasal trauma, increased patient comfort, and, potentially, better results with respect to total tumor resection.[7,12,24]

In the current study, we aim to describe the results of endoscopic transsphenoidal surgery for the treatment of acromegaly in our center from 2000 to 2009. We also analyze the current literature related to endoscopic treatment of acromegaly and the role of surgery in the management of such cases.

Methods

Study Design

We performed a retrospective analysis of data from 67 cases involving patients with GH-secreting adenomas who had been referred to the neuroendocrine department of Fortaleza General Hospital in Fortaleza, Brazil. All of the patients underwent transsphenoidal endoscopic adenomectomy for acromegaly between 2000 and 2009. The median duration of follow-up was 2 years (range 12 months–6 years). Earlier results were reported for a subset of these patients in a previous paper.[12] The operations were all performed using the transsphenoidal endoscopic technique,[11] and the aim of treatment was to remove the tumor in its totality without causing hypopituitarism. The study was performed under the authorization of the ethics committee of Fortaleza General Hospital, and all patients agreed with the proposed treatment after careful explanation of all options for the management of acromegaly.

Patient Population

The inclusion criteria used in the study were as follows: clinical diagnosis compatible with acromegaly (GH > 1 mU/L, IGF-I level greater than the normal age- and sex-adjusted level), presence of GH-secreting pituitary adenoma, tumor determined to be positive for GH marker through histological examination, no previous treatment, surgery performed by the senior author (J.A.G.), and at least 1 year of follow-up. Data were analyzed according to patient age and gender. Clinical outcome was defined according to the presence or absence of compressive signs and/or endocrinological control.

Endocrinological Assessment

The following pre- and postoperative endocrinological investigations were performed at our hospital: multiple measurements of plasma GH (normal value < 1 μg/L for adults) and IGF-I. The normal age- and sex-adjusted ranges for IGF-I are determined in our laboratory using in-house results obtained from healthy controls. Other endocrinological findings were assessed with respect to the following reference ranges: prolactin, 1.5–30 μg/L; ACTH, 30–60 pg/ml, and serum cortisol levels; TSH, 0.3–4 mU/ml; LH, 6–34 mIU/ml; and FSH, 2–2.2 mIU/ml. The evaluation of gonadal function was further evaluated based on menstrual history in female patients and on testosterone levels in male patients. Endocrinological evaluation was performed before surgery, 3 months after surgery, and every 6 months thereafter. Six patients (5 with macroadenomas and 1 with a microadenoma) had elevated prolactin levels (range 52–1000 μg/L). Five patients with macroadenomas had multiple hormone deficiency (ACTH, LH, and FSH deficiency in 2 cases; TSH, LH, and FSH in 2; and ACTH, TSH, FSH, and LH in 1). Four men had testosterone deficiencies. Immunohistochemical analysis of resected tumor tissue was performed in all cases.

Neuroimaging Examination

All patients underwent tumor evaluation by means of MR imaging. We used 1.5-T MR imaging with T1- and T2-weighted spin echo sequences obtained before and after administration of Gd-based contrast medium. Tumor size was classified according to maximum tumor diameter in 2 categories: microadenoma (≤ 10 mm) and macroadenomas (> 10 mm). Based on the Hardy classification, according to the suprasellar/parasellar extension of the tumor, pituitary adenomas were classified as: A, lesion limited to the sella; B, lesion with minimal suprasellar extension and no considerable optic nerve compression; C, lesion presenting important suprasellar extension and optic nerve compression; or D, lesion with considerable parasellar extension. According to the presence of sella floor erosion and tumor extension, the lesions were classified as: 1, no floor destruction; 2, minimal floor destruction with no sphenoid sinus invasion; 3, minimal sphenoid sinus invasion; or 4, diffuse destruction of the sella floor with sphenoid sinus invasion.

A facial CT scan was used in all patients to evaluate the paranasal sinuses (septal anatomy, sphenoidal, and maxillofacial anatomy) for surgical planning. Follow-up

MR imaging studies were performed 3 months after surgery and every 6 months thereafter.

Tumor Removal

The success of tumor removal was determined on the basis of both the MR imaging findings obtained 3 months after surgery and the surgeon's intraoperative observation. A tumor was considered to be totally removed when the surgeon's observation and the MR imaging examination documented no residual tumor. Resection was considered subtotal when part of the tumor remained in situ.

Surgical Procedure

After induction of general anesthesia, the patient is placed in the supine position on the operating table with the back elevated 30° and the head tilted back 20° and toward the left shoulder 25°. The surgeon is positioned on the right side of the patient. Normally, the left nostril is used, but the choice is based on nasal anatomy. A 30°, or less frequently 45° or 70°, rigid endoscope (180/4 mm) is used. The nasosphenoidal phase of the procedure is performed holding the endoscope with the nondominant hand. The endoscope is navigated into the nasal cavity. The floor of the sella is located approximately 1 cm above the inferior margin of the middle turbinate. The space between the middle turbinate and the nasal septum is gently widened, and a large opening is made in the anterior wall of the sphenoid sinus. Inside the sphenoid sinus, the sella is then localized, the endoscope is fixed, the anterior wall of the sella and the dura mater are opened widely with a high-speed drill or Kerrison rongeur, and the tumor is removed. For the reconstruction of the sellar region, we used a combination of fascia lata, abdominal fat, mucoperiosteum, and fibrin sealants.

Disease Control

The aim of treatment was to remove the tumor in its entirety without causing hypopituitarism. The success of tumor removal was based on the surgeon's intraoperative observations as well as contrast-enhanced MR images obtained 3 months after surgery. The tumor was considered to be totally removed when the surgeon's intraoperative report and the MR imaging examination documented an absence of residual tumor. The criteria used for acromegaly control were the current internationally accepted criteria for biochemical "cure" of the disease: the nadir GH level after oral glucose administration should be less than 1 ng/ml, and the IGF-I level should correspond to the appropriate age- and sex-adjusted reference values.

Results

Between 2000 and 2009, 367 patients underwent endoscopic transsphenoidal surgery for treatment of skull base lesions at the Department of Neurosurgery of the Fortaleza General Hospital. Pituitary adenomas were the most common lesions treated, representing 82% of the 367 cases. In the group of functioning pituitary adenomas, the most common subtype was GH-secreting adenomas.

During the study period, 67 GH-secreting pituitary adenomas were treated by pure transphenoidal endoscopic surgery in Fortaleza General Hospital of Fortaleza by the senior author (J.A.G.). The mean age (± SD) of the 67 patients was 44.8 ± 12.4 years (range 20–76 years); 32 (47.8%) of the patients were male, and 35 (52.2%) were female.

Five patients with macroadenomas had multiple hormone deficiencies preoperatively. These patients were being treated with hormone replacement therapy—3 of them with glucocorticoids (20–30 mg hydrocortisone), 3 with levothyroxine (0.1–0.15 mg/day), and 4 men with depot testosterone (200–300 mg, intramuscularly, per 3–4 weeks); no patient was receiving desmopressin treatment. A total of 6 patients (5 with macroadenomas and 1 with a microadenoma) had elevated prolactin levels at the preoperative evaluation: in 3 of these patients (2 with macroadenomas and 1 with a microadenoma), the prolactin levels normalized after surgery; in the 3 others (all of whom had macroadenomas) the prolactin levels were stabilized with the use of dopamine agonists.

All pituitary adenomas were anatomically analyzed based on MR imaging findings. The mean size of the lesions was 21.5 ± 10.1 mm (range 8–49 mm). All lesions were classified as micro- or macroadenomas (Table 1). Microadenomas were present in the minority of cases, representing only 20.9% of the cases (14 patients). Macroadenomas, therefore, were responsible for the symptoms of the patients in most of the cases (53 patients [79.1%]). Extension of the tumor, usually considered an important factor related to the success of resection, was analyzed based on the degree of suprasellar and parasellar extension, according to the Hardy classification. Based on this variable, 27 (40.3%) of the lesions were classified as Class A, 18 (26.9%) as Class B, 10 (14.9%) as Class C, and 12 (17.9%) as Class D. Based on sella floor erosion and tumor extension, tumors were classified as Grades 1–4, as follows: 10 lesions (14.9%) were classified as Grade 1 pituitary adenomas, 45 (67.1%) as Grade 2, 7 (10.4%) as Grade 3, and 5 (7.5%) cases as Grade 4. Most of the pitu-

TABLE 1: Characteristics of 67 cases of GH-secreting adenoma

Characteristic	No. of Cases (%)
tumor size	
microadenoma	14 (20.9)
macroadenoma	53 (79.1)
suprasellar/parasellar extension	
Class A	27 (40.3)
Class B	18 (26.9)
Class C	10 (14.9)
Class D	12 (17.9)
sella floor erosion	
Class I	10 (14.9)
Class II	45 (67.1)
Class III	7 (10.4)
Class IV	5 (7.5)
cystic component	
not present	60 (89.6)
present	7 (10.4)

itary adenomas were completely solid (60 cases, 89.6%). Cystic areas, therefore, were present only in a minority of cases (7 patients [10.4%]).

Complications associated with endoscopic pituitary surgery and, therefore, surgical treatment for acromegaly include CSF leak, diabetes insipidus, meningitis, pituitary dysfunction, nasal lesions, and death.[7,13,24] In the current study, 8 patients (11.9%) had minor complications related to the surgical procedure. Epistaxis was observed in 4 cases (6.0%), transitory diabetes insipidus in 3 cases (4.5%), and 1 case (1.5%) of seizures in the immediate postoperative time. No major complications related to the procedure, such as meningitis, CSF leaks or carotid lesions were observed in our study. There was no case of death related to the surgical approach. Thyroid hormone deficiency was observed in 5 patients who underwent endoscopic surgery for treatment of macroadenomas. These patients were treated with levothyroxine.

Disease control was achieved in most of the cases (50 patients [74.62%]); however, in 17 cases (25.4%) surgical treatment did not provide adequate control of acromegaly. Adequate postoperative disease control was achieved in 12 (85.7%) of the 14 patients who had microadenomas. In the group of patients with macroadenomas the rate of adequate disease control obtained with surgery was somewhat lower, with success achieved in 38 cases (71.7%). With respect to the correlation of suprasellar/parasellar tumor extension and sella floor erosion grades with the success of treatment, pituitary adenomas with higher levels of extrasellar extension and sella floor destruction were associated with a lower disease control index ($p = 0.01$ and $p = 0.02$, respectively) (Figs. 1 and 2). There was no significant difference in the outcome of patients that presented lesions with cystic areas (adequate control was achieved in 6 of 7 patients with cystic adenomas and in 44 of 60 patients with noncystic adenomas, $p = 0.31$). Four patients underwent a second operation after presenting with residual tumors considered to be easily resected by the transsphenoidal endoscopic technique. All of those patients had a favorable outcome (adequate endocrinological control) after the second procedure.

Discussion

Transsphenoidal surgery for treatment of acromegaly

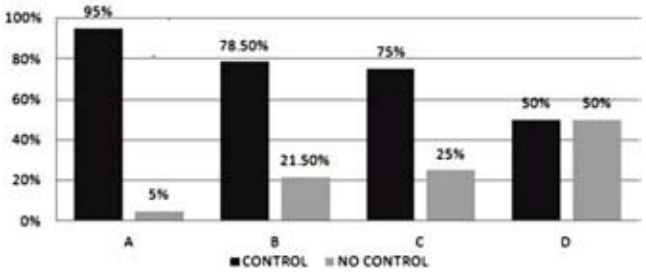

Fig. 1. Disease control in patients with acromegaly according to the degree of suprasellar/parasellar extension of the lesion. Based on the Hardy classification, extension was classified as follows: A, lesion limited to the sella; B, lesion with minimal suprasellar extension and no considerable optic nerve compression; C, lesion presenting important suprasellar extension and optic nerve compression; or D, lesion with considerable parasellar extension.

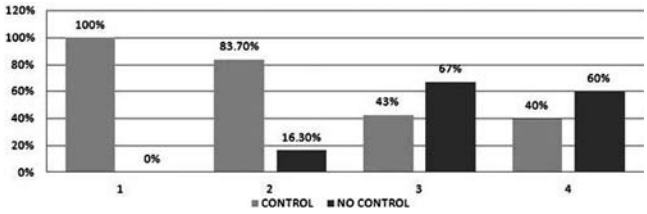

Fig. 2. Disease control in patients with acromegaly according to the degree of sella floor erosion and pituitary tumor extension. Lesions were classified as follows: 1, no floor destruction; 2, minimal floor destruction with no sphenoid sinus invasion; 3, minimal sphenoid sinus invasion; or 4, diffuse destruction of the sella floor with sphenoid sinus invasion.

has been used since the initial work of Schloffer[17] and Cushing.[5] Characterized by lower morbidity and mortality rates than with the transcranial approach, transsphenoidal microscopic surgery (either sublabial or endonasal) has been considered the gold standard surgical treatment for acromegaly in recent decades. However, this type of approach presents considerable limitations, including: limited visual field during surgery, nasal lesions associated to the septum dissection, and important cosmetic limitations if a sublabial approach is used.[7,13,22]

The introduction of endoscopy represents one of the most important advances in pituitary surgery in recent years. In 1970, Messerklinger[21] developed the endoscopic technique. Thereafter, surgeons started to use the endoscope in skull base surgery and in procedures involving the sellar and parasellar region.[7,13] In 1992, Jankowski et al.[15] introduced the endoscope in the pituitary surgery field, describing the use of the endonasal transsphenoidal endoscopic technique for removal of 3 pituitary adenomas. Transsphenoidal endoscopically guided pituitary surgery was standardized in actual clinical practice by Jho and Carrau[16] and by Cappabianca et al.[3] The development of neuroendoscopy and the popularization of transsphenoidal endoscopically guided pituitary surgery have been associated with better tumor resection results, which are often related to better visualization of the sella, less nasal dissection, and improvement in the resection of suprasellar and parasellar components of the adenoma.[10,13] Although endoscopic surgery provides better illumination and visualization of the lesions, no report has definitively proved the superiority of endoscopic surgery over microsurgery in the surgical treatment of pituitary lesions so far.

The success of endoscopic transsphenoidal surgery in the treatment of acromegaly has been studied by different authors.[7,13,24] According to our review, the current study presents the largest series of GH-secreting adenomas surgically treated by a single neurosurgeon using the pure endoscopic approach. In our center, all cases of GH-secreting adenomas are initially treated with endoscopic surgery, unless large cavernous sinus invasion is observed in the preoperative MR imaging or the patient has clinical comorbidities that do not allow for surgery. In those cases, medical therapy based on the use of somatostatin analogs is usually attempted.

Microadenomas represented 20.9% of the cases treated by our team. Lesion size, which usually has been considered an important factor related to disease control, was a major variable regarding to the success of the treatment,

with small lesions presenting a trend toward higher levels of disease control. The difference between the outcome in patients with microadenomas and those with macroadenomas, however, was not great enough to be considered statistically significant (85.7% control rate for microadenomas vs 71.7% for macroadenomas, $p = 0.284$). The overall rate of surgical success in our study (74.6%), is comparable to the rates presented in recent papers, which vary from 52% to 85%.[7]

Most of the patients in our study had large macroadenomas (53 cases [79.1%]), lesions that have been associated with poor disease control in some series.[24] We believe the variable of size is not the only factor related to the poor clinical control found in cases of larger lesions. Therefore, we analyzed the tumor extension according to suprasellar/parasellar extension and the extension of sella floor erosion, based on the Hardy scale. According to our data, the presence of higher levels of suprasellar and parasellar extension were related to a lower chance of disease control ($p = 0.01$). Major limitation was associated with lesions with parasellar extension in close relation with the internal carotid artery and the cavernous sinus (Class D, with only a 50% rate of clinical control after surgery). In cases in which surgery did not provide adequate control, somatostatin agonists were prescribed to achieve lower levels of GH/IGF-I. In one patient who presented with major cavernous sinus invasion, radiotherapy was attempted secondarily, but no hormonal control has been obtained to date. Considering specifically the variable of sella floor erosion, pituitary adenomas with greater extent of sellar destruction were associated with poor clinical control ($p = 0.02$). Tumors associated with large erosions had more extensive posterior, inferior, and anterior components, which require an overall larger opening of the skull base. Such procedures are more complex since the surgeon usually has to deal with regions situated peripherally to the sella—such as the clivus and the anterior fossa—and their neurovascular structures, which could justify, at least in part, the lower chances of clinical control in those cases. The presence of cystic areas inside the lesion was not an important factor related to disease control ($p = 0.31$). However, in cases with large/predominant cystic areas, we believe resection might be easier to accomplish because the resection of cystic lesions is usually simpler than the resection of solid masses. We believe a larger study, with more cases of cystic lesions, is needed to demonstrate such an association.

Different management options exist for GH-secreting adenomas that do not respond to surgery as a first-line treatment,[20] including a second surgical procedure, radiotherapy, and medical therapy. In 17 patients (25.4%) in our series, surgery did not result in clinical control. Most of these patients (12 cases) were treated with somatostatin analogs postoperatively to obtain reduction of GH/IGF-I levels. One patient was treated with radiotherapy after unsuccessful resection. Four patients underwent a second endoscopic surgery because they were considered to have residual tumor that could be easily removed by a new approach.

Economically, the endoscopic transsphenoidal procedure also represents an interesting option for management of acromegaly. As described previously,[12] a center with experience in the surgical treatment of patients with acromegaly will result in considerable cost savings to the health system. Moreover, treating uncomplicated acromegaly by means of transsphenoidal surgery has been reported to be less expensive than medical treatment or a course of radiotherapy.[2,3,25] In the hands of an experienced pituitary surgeon, transsphenoidal surgery is associated with a high cure rate with few postoperative complications and a low recurrence rate.[1,7,13,25]

Conclusions

Acromegaly is a chronic clinical condition related to high levels of GH and IGF-I. Endoscopic transsphenoidal surgery represents one of the most effective options for treatment of acromegalic patients. Presenting an improved panoramic visualization of the surgical field, superior close-up views of the anatomy, and different working angles for resection of the lesion, endoscopy has become an important tool for pituitary adenoma resection in recent years. High disease control rates and low rates of complications are some of the most important points related to the technique. Some of the factors related to the success of endoscopic surgery are lesion size, suprasellar/parasellar extension, and the degree of sella floor erosion. The cost of surgical treatment for acromegaly is usually lower than that of medical therapy and/or radiotherapy. Therefore, if an experienced pituitary surgeon is available, we advocate the use of endoscopic transsphenoidal surgery as the first-line treatment for GH-secreting adenomas that do not demonstrate major cavernous sinus invasion. So far, however, there is no definitive evidence that endoscopy is superior to microsurgery for treatment of acromegaly or any other pituitary adenoma.

Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Almeida, Gondim, Albuquerque, Gomes, Ferraz. Acquisition of data: Almeida, Gondim, Albuquerque, Gomes, Schops. Analysis and interpretation of data: Almeida, Gondim, Gomes, Ferraz. Drafting the article: Almeida, Gondim, Albuquerque, Schops. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Almeida, Gondim. Administrative/technical/material support: Gondim. Study supervision: Gondim, Gomes, Schops, Ferraz.

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Manuscript submitted June 15, 2010.
Accepted July 29, 2010.

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Transsphenoidal surgery in patients with acromegaly: operative strategies for overcoming technically challenging anatomical variations

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Object. In addition to difficulties with anesthetic and medical management, transsphenoidal operations in patients with longstanding acromegaly are associated with inherent intraoperative challenges because of anatomical variations that occur frequently in these patients. The object of this study was to review the overall safety profile and anatomical/technical challenges associated with transsphenoidal surgery in patients with acromegaly.

Methods. The authors performed a retrospective analysis of 169 patients who underwent endoscopic transsphenoidal operations for growth hormone–secreting adenomas to assess the incidence of surgical complications. A review of frequently occurring anatomical challenges and operative strategies employed during each phase of the operation to address these particular issues was performed.

Results. Of 169 cases reviewed, there was no perioperative mortality. Internal carotid artery injury occurred in 1 patient (0.6%) with complex sinus anatomy, who remained neurologically intact following endovascular unilateral carotid artery occlusion. Other complications included: significant postoperative epistaxis (5 patients [3%]), transient diabetes insipidus (5 patients [3%]), delayed symptomatic hyponatremia (4 patients [2%]), CSF leak (2 patients [1%]), and pancreatitis (1 patient [0.6%]). Preoperative considerations in patients with acromegaly should include a cardiopulmonary evaluation and planning regarding intubation and other aspects of the anesthetic technique. During the nasal phase of the transsphenoidal operation, primary challenges include maintaining adequate visualization and hemostasis, which is frequently compromised by redundant, edematous nasal mucosa and bony hypertrophy of the septum and the nasal turbinates. During the sphenoid phase, adequate bony removal, optimization of working space, and correlation of imaging studies to intraoperative anatomy are major priorities. The sellar phase is frequently challenged by increased sellar floor thickness, distinct patterns of tumor extension and bony invasion, and anatomical variations in the caliber and course of the internal carotid artery. Specific operative techniques for addressing each of these intraoperative challenges are discussed.

Conclusions. Transsphenoidal surgery in patients with longstanding acromegaly frequently poses greater challenges than operations for other types of sellar lesions, yet these challenges may be safely and effectively overcome with the anticipation of specific issues and implementation of various intraoperative techniques.
(DOI: 10.3171/2010.8.FOCUS10156)

Key Words • **sella turcica** • **transsphenoidal surgery** • **pituitary adenoma** • **acromegaly** • **growth hormone** • **endoscopy**

Acromegaly is a life-threatening systemic condition caused by excess production of GH, almost always from a functional pituitary adenoma, and it is associated with increased patient mortality if left untreated.[2,12,19] Transsphenoidal surgical intervention in patients with acromegaly has several inherent challenges, as it is a minimally invasive approach in patients with structural features that are generally enlarged. As a result of the chronic systemic disease, potential hurdles are frequently encountered in the anesthetic, surgical, and perioperative medical management in these cases.[5,9,16,18–20,26]

Abbreviations used in this paper: DI = diabetes insipidus; GH = growth hormone; ICA = internal carotid artery.

From an anatomical perspective, numerous pathological changes involving soft-tissue edema, nasal polyps, and bony remodeling often contribute to the complexity of the operation, as natural working corridors are typically more restricted and deeper than in other patients.[18,24,27] Because transsphenoidal surgery relies on the ability to visualize and identify key anatomical landmarks during each phase of the operation,[6,7] we aimed to characterize the particular anatomical characteristics and technical surgical considerations that arise frequently in patients with longstanding acromegaly. Particular pitfalls that may be prevented or avoided if awareness of these issues is maintained, and specific operative techniques that can be employed to overcome many of these challenges, are discussed.

Methods

The intraoperative observations and techniques reported in this review were derived from a retrospective analysis of 169 cases involving patients with GH-secreting pituitary adenomas treated in a combined series of 743 endoscopic transsphenoidal operations for pituitary adenomas at the Università degli Studi di Napoli Federico II and Brigham and Women's Hospital since January 2000.

The intention of this particular study is not to report the surgical or endocrinological outcomes associated with acromegaly. Rather, we aimed to assess the safety and complication rate associated with the endoscopic technique in patients with GH-secreting adenomas, and to identify some of the most pronounced anatomical features that are frequently encountered in patients with longstanding acromegaly that can make the operation more challenging than in patients with other types of pituitary adenomas. The aspects identified in this report were derived from the retrospective review of imaging data (CT and MR imaging), preoperative clinical assessments, operative reports, intraoperative observations, and video recordings in the 169 patients undergoing endoscopic transsphenoidal operations for GH-secreting adenomas.

Patient Characteristics and Complications

The patient characteristics and the complications are presented in Table 1. The mean patient age was 44 years (range 16–75 years). There was a slight male preponderance, with 54% of patients being male and 46% female. Reoperation for recurrent tumor was performed in 7% of the cases, with the endoscopic transsphenoidal procedures in the other 93% being primary operations. Macroadenomas were present in 61% of patients, and 39% had microadenomas.

There were no cases of operative mortality. Internal carotid artery injury occurred in 1 patient (0.6%), a 31-year-old man with a GH-secreting microadenoma and complex sphenoid sinus anatomy. Immediately following the injury, the area of hemorrhage was packed and the patient was immediately transported to the endovascular suite for balloon test occlusion and successful coil embolization of the left ICA. The patient had excellent collateral circulation and developed no neurological sequelae as a result of this injury. He was taken back to the operating room the same day for gross-total resection of the tumor.

TABLE 1: Characteristics and surgical complications in 169 patients undergoing endoscopic endonasal transsphenoidal surgery for GH-secreting adenomas*

Variable	Value
mean age in yrs (range)	44 (16–75)
sex	
male	91 (54)
female	78 (46)
tumor size	
microadenoma	66 (39)
macroadenoma	103 (61)
recurrence/reop	11 (7)
complications	
death	0 (0)
ICA injury	1 (0.6)
severe epistaxis	5 (3)
transient DI	5 (3)
symptomatic hyponatremia	4 (2)
pancreatitis	1 (0.6)
CSF leak	2 (1)

* Values represent numbers of patients (%) except as otherwise indicated.

No patient developed postoperative visual loss. Postoperative delayed epistaxis (arterial bleeding) developed in 5 patients (3%). Of these patients, 3 were treated successfully with nasal packing alone. The other 2 had refractory bleeding requiring endovascular occlusion. Transient DI developed in 5 patients (3%), with no cases of permanent DI. Four patients (2%) developed symptomatic delayed hyponatremia due to the syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH), which resolved with fluid restriction and no neurological sequelae in all cases. One patient (0.6%) developed transient pancreatitis thought to be secondary to medication administration. Two patients (1%) developed postoperative CSF leaks. One of these patients required reoperation for abdominal fat graft placement; in the other patient, the leak was successfully managed with temporary lumbar drainage. Two patients (1%) with acromegaly and atypical nasal anatomy underwent intraoperative conversion to a microscopic approach.

Operative Strategies for Endoscopic Transsphenoidal Surgery in Patients With Acromegaly

Based on our review of these cases, several challenges were identified at each particular phase of the operation that were highlighted as being more pronounced in patients with acromegaly (Table 2). These intraoperative observations and recommended intraoperative technical strategies to address them are discussed below.

Preoperative Considerations. As with all neurosurgical patients undergoing transsphenoidal pituitary surgery, a detailed preoperative assessment is a priority in patients with acromegaly. Because anesthesia-related complica-

TABLE 2: Clinical and anatomical features in acromegaly posing various challenges for endoscopic transsphenoidal operations

Op Phase	Intraop Challenges	Potential Recommendation/Modification
preop		
	airway/laryngeal edema	preop anesthesia evaluation
	cardiopulmonary dysfunction	plan for intubation (awake/fiberoptic)
	venous congestion	elevate thorax, head of bed to at least 15° to improve venous drainage
nasal		
	mucosal edema/redundant tissue	use of cottonoids soaked in vasoconstricting agent
	hypertrophic nasal turbinates	resection of nasal turbinate if necessary
	thick sphenoid rostrum, vomer	use of high-speed drill, chisel, or Jansen-Middleton rongeur
sphenoid		
	thickened sphenoid septa & mucosa	wide anterior sphenoidotomy
	restricted workspace, collision of instruments	generous posterior nasal septectomy
sellar		
	abnormal skull base bony anatomy	imaging–intraoperative anatomical correlation
	atypical caliber & tortuosity of ICAs	intraoperative neuronavigation
	microvascular changes in ICA & cavernous sinus dura	Doppler ultrasound, blunt ring curettes

tions are known to arise more commonly in patients with longstanding acromegaly, preoperative anesthesia, cardiac, and/or pulmonary evaluations are frequently warranted prior to any operation.[4,13,20] A cogent plan for intubation based on preoperative airway assessment should be discussed with the anesthesia team.[5,26] Plans for administration of antibiotics, hormone replacement, pretreatment with somatostatin analogs,[8] or any additional perioperative medications should also be addressed in advance. It is imperative that the correct neuroimaging modalities are used and that the studies are carefully and systematically reviewed preoperatively. Patients with acromegaly often have atypical vascular and bony anatomy that may warrant further imaging, such as CT or CT angiogram studies, in addition to standard MR imaging.[24] In patients with tumor recurrence, or complex vascular, sphenoid sinus, or sellar anatomy, plans for intraoperative neuronavigation should be made and images registered prior to the operation. Patient positioning for the operation may proceed as usual, however, elevation of the patient's thorax is recommended to facilitate optimal venous outflow from the cranial compartment.

The Nasal Phase: Maintenance of Visualization and Hemostasis. Several technical issues deserve particular consideration during the nasal phase of a transsphenoidal operation in patients with acromegaly, as the early exposure is critical in these patients and often lays the groundwork for a successful operation. The primary challenges during this stage are typically related to the edematous and/or redundant soft tissue of the nasopharynx, and enlarged, hypertrophic bony nasal turbinates, both of which may compromise endoscopic visualization and working space (Fig. 1). Furthermore, nasal polyps are a common finding in patients with acromegaly, and can generally be coagulated and removed with a nasal debrider or scissors at their pedicles early in the operation to improve visualization.[27] The size and rigidity of the nasal turbinates in patients with acromegaly often mandates more forceful lateral displacement using larger instruments than is typically required in other patients, which may result in increased bleeding if the integrity of the mucosa is compromised early in the operation. Maintaining hemostasis at this stage in the procedure is critical, and can be facilitated by routine placement of multiple cottonoids soaked in a vasoconstricting agent (such as lidocaine with epinephrine) medial to the middle turbinate, along the nasal septum. Lateral displacement of the middle turbinate by compression on the cottonoids, instead of the nasal mucosa itself, often minimizes mucosal injury and bleeding, and temporary packing with cottonoids helps maintain the lateral position of the turbinates once they are displaced. Although not routinely performed, resection of the middle turbinate is a viable option for improving visualization in cases where obscuration becomes a persistent issue. Identification of the sphenoid ostium, a key anatomical landmark during this phase that is typically located approximately 1.5 cm above the superior aspect of the posterior choanae, may be more challenging in patients with acromegaly, as the sphenoid ostia are often concealed by redundant nasal mucosa, polyps, bony overgrowth, or thickened mucosa from within the sphenoid sinus.[27] Variations in posterior nasal and sphenoidal bony anatomy, including sinus morphology and bone thickness, require additional consideration for achieving correlation of imaging with intraoperative findings (Fig. 2). Finally, the use of a high-speed drill or chisel may be more likely to aid in the anterior sphenoidotomy in these patients because of the increased bone thickness.

Because the intranasal working space is often narrow and restricted in a patient with acromegaly, the mobility and range of instruments may be limited, resulting in collision of instruments with the endoscope. A 2-nostril technique with a wide anterior sphenoidotomy and a more extensive posterior septectomy usually alleviates this particular issue, and docking of the endoscope in the superior aspect of the nasal cavity and sphenoid sinus is of paramount importance during the remainder of the operation

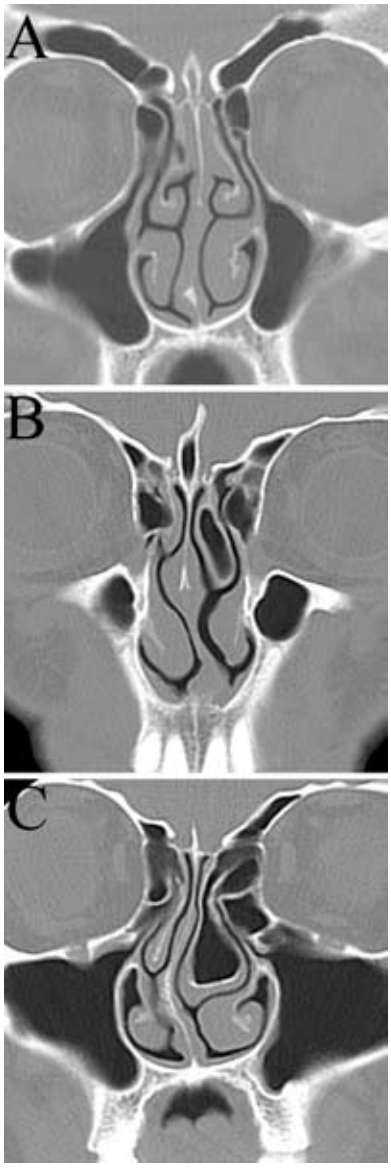

Fig. 1. Coronal CT images obtained in 3 patients with acromegaly. **A:** The patient has marked hypertrophy of the nasal turbinates, with very little working space within the nasal cavity. **B:** There is slight deviation of the nasal septum, a left middle turbinate concha bullosa, and very restricted workspace. **C:** There is marked septal deviation toward the right, a large left concha bullosa, and markedly reduced workspace.

to facilitate 2-handed microsurgical dissection via both nostrils. Realignment of a deviated nasal septum or resection of a septal bone spur may be required in a minority of cases to improve visualization and working room. Although rarely required, conversion to a microscopic or endoscope-assisted operation has been reported to provide some benefits of retraction and hemostasis of soft-tissue structures that may compromise the visualization necessary to complete the operation safely and accurately, especially in patients with acromegaly.[29] Delayed postoperative arterial epistaxis occurred in 3% of patients in the current series and may occur more frequently following endoscopic approaches than microscopic approaches.

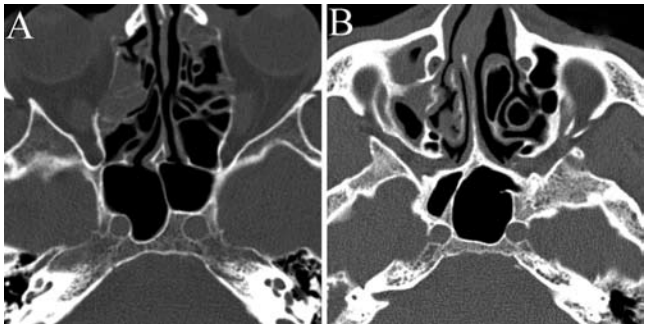

Fig. 2. Axial CT images obtained in 2 patients with acromegaly. **A:** Note the caliber of the ICAs, asymmetrical sphenoid sinus septum, and thickened skull base. **B:** Note the deviated nasal septum, asymmetrical sphenoid sinus anatomy, and thickened sphenoid sinus septum.

Bleeding from the sphenopalatine artery encountered during endoscopic approaches is preferably treated with bipolar cauterization.

The Sphenoid Phase: Maximizing Exposure and Workspace. During the sphenoid phase of the operation, the primary surgical challenges include atypical bony anatomy, achieving adequate exposure and working space within the sinus, and maintenance of hemostasis. Achieving correlation of imaging to intraoperative findings, such as the sphenoid septae, is critical during this phase, as the paranasal sinuses are frequently enlarged in patients with acromegaly, thus potentially giving the surgeon the impression that the sphenoid sinus and sellar face have been adequately exposed when in fact they have not. The use of more powerful rongeurs, such as the Jansen-Middleton rongeur, and/or a high-speed drill is often required to achieve adequate removal of the sphenoid rostrum and thickened sphenoid septa. The chisel can also be a useful instrument for detaching and removing a thick sphenoid rostrum, especially at its inferiormost aspect at the base of the vomer. Thickened sphenoid sinus mucosa and sinusitis are frequently encountered in patients with acromegaly,[24] and once stripped may cause venous bleeding from the sinus walls.[18] This bleeding can usually be readily controlled with saline irrigation, Gelfoam, Surgifoam, and/or compression with cottonoids. The anatomy of the sellar floor and clivus is often atypical in patients with longstanding acromegaly due to chronic bony remodeling, and opening of the sellar floor may also require the use of a chisel or drill. Tumors that secrete GH, however, are also known to have a proclivity for infrasellar extension through the sellar floor and into the sphenoid sinus and clivus, and tumor extension may often be noted early in the sphenoid phase of the approach.

The Sellar Phase: Identification of Key Vascular Structures and Safe Tumor Resection. Patients with longstanding acromegaly have been reported to develop anatomical changes in the caliber and tortuosity of the ICA that may come into play during the sphenoid and sellar phases of the operation (Fig. 3).[15,16,24] Because of these variations, it is critical to assess the course of the ICA within the parasellar nasal and cavernous sinuses prior to the operation, as extension of the ICA into the sphenoid sinus (Fig. 4) and a narrow intercarotid distance (Fig. 5)

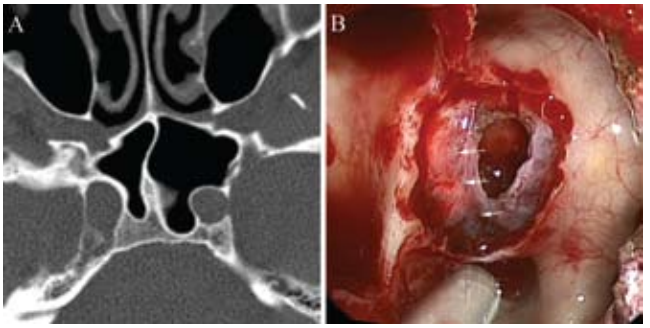

Fig. 3. Axial CT scan obtained preoperatively **(A)**, and intraoperative endoscopic photograph obtained following tumor resection **(B)** in a patient with acromegaly demonstrating increased caliber and tortuosity of the ICA. In panel **B**, the right ICA can be visualized immediately behind the sellar dura *(white arrows)*. The location and caliber of the ICA substantially increase the risks associated with dural opening and tumor resection.

are observed relatively frequently.[15,16,24] A small proportion of patients with acromegaly may have "kissing" carotid arteries, in which the surgical approach or plan may require reconsideration for safe tumor removal.[22] In addition, atypical anatomy of the ICA may be further complicated by complex bony sellar floor and sphenoid sinus anatomy, resulting in a higher likelihood of ICA injury (as occurred in the patient with ICA injury described in *Patient Characteristics and Complications*, above).

In addition to the macroscopic anatomical changes in parasellar vasculature that may be observed in patients with acromegaly, microvascular changes associated with chronic local and systemic GH excess may cause alterations in the structural integrity of surrounding structures, including the cavernous sinus dura and ICAs, that may contribute substantially to the risk associated with tumor resection.[16] Growth hormone–secreting adenomas have been implicated as causing local vascular changes that may be associated with deterioration of vessel endothelium and parasellar or intrasellar ICA aneurysm formation.[1,3,11,25,28] It should be remembered that ICA injury may be more likely to occur in patients with GH-secreting adenomas than in those with any other kind of pituitary adenoma as a result of the anatomical and microvascular changes mentioned. For this reason, use of the Doppler microprobe and intraoperative neuronavigation are useful intraoperative adjuncts for improving the safety profile associated with dural opening and tumor resection in some patients with acromegaly undergoing transsphenoidal surgery.[14,17]

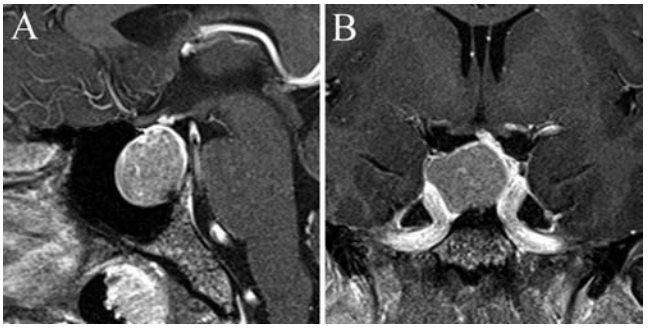

Fig. 4. Sagittal **(A)** and coronal **(B)** postcontrast MR images obtained in a patient with a GH-secreting macroadenoma and acromegaly. Note the caliber and tortuosity of the ICAs and their extension into the sphenoid sinus in panel **B**.

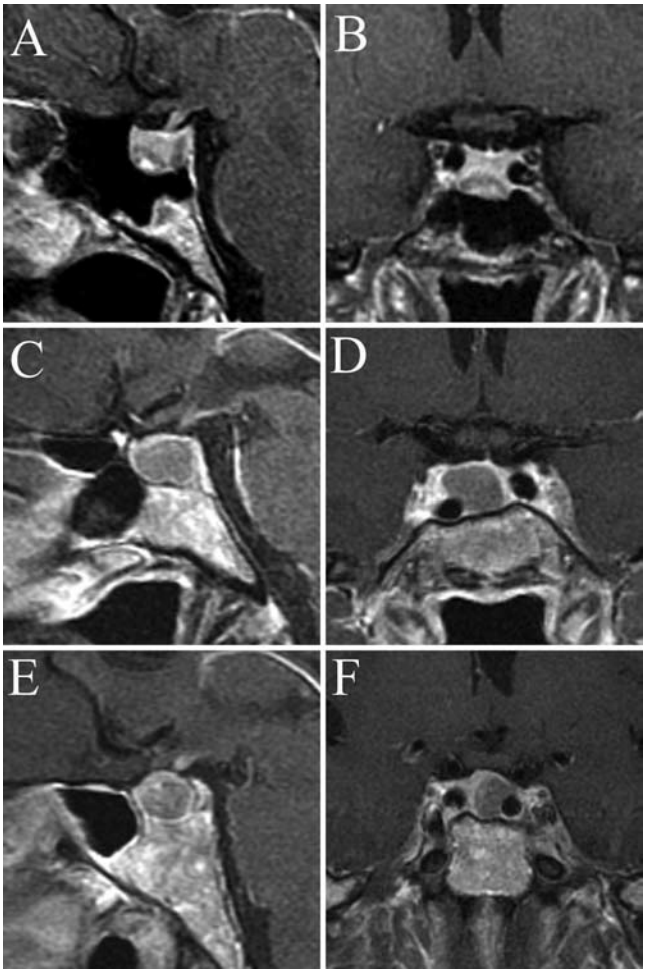

Fig. 5. Sagittal **(A, C, and E)** and coronal **(B, D, and F)** postcontrast MR images obtained in 3 patients with GH-secreting adenomas. Note the asymmetry of the parasellar ICAs and narrowed inter-ICA distance in all 3 cases.

Growth hormone–secreting adenomas are often noted to have a whiter color than other types of adenomas, which may aid in differentiating them from the anterior pituitary gland (Fig. 6). Growth hormone–secreting microadenomas often arise in a lateral and inferior location in the gland, and larger GH-secreting adenomas have a proclivity for inferior invasion of the bony sellar floor. In tumors invading the clivus and sellar floor, the surgeon should be mindful that the dorsum sella may be eroded. Tumor resection typically proceeds using ring curettes, suction, and tumor forceps, taking care to preserve the normal gland at all times. The use of blunt angled ring curettes in the lateral aspects of the sella and cavernous sinus is typically a safe way of mobilizing tumor medially into the sellar exposure for subsequent removal. Reconstruction of the sellar floor does not differ remarkably from the techniques used in patients with other tumor types although the tortuosity and position of the ICAs

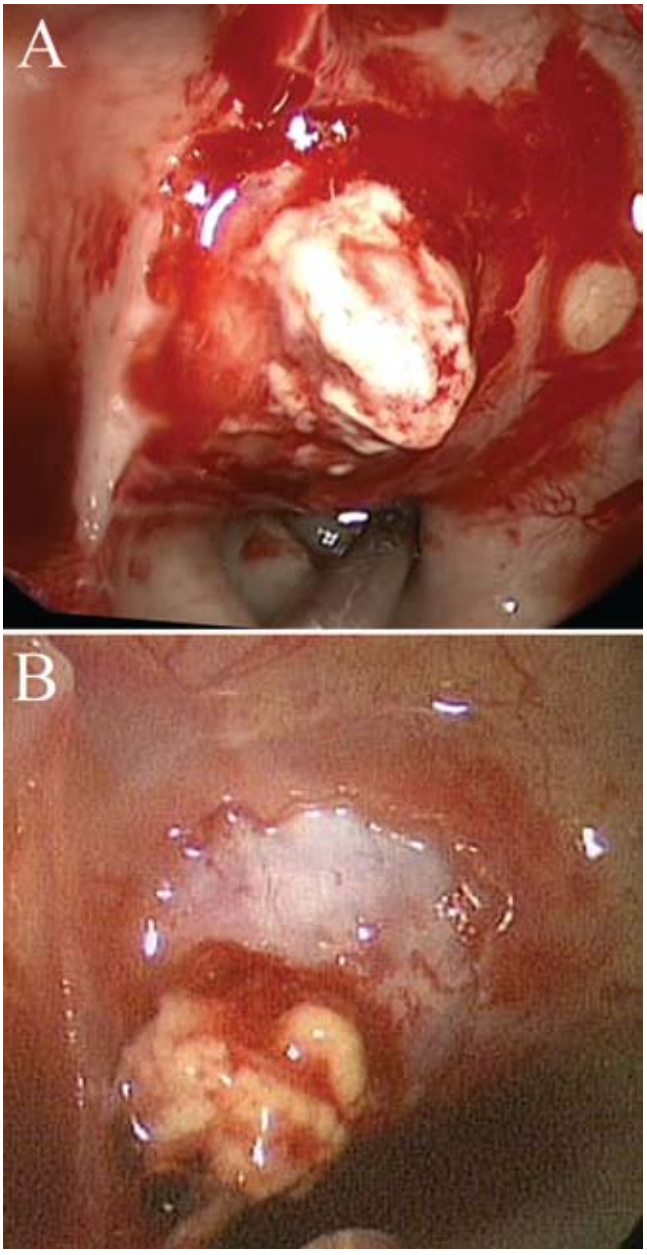

Fig. 6. Intraoperative photos obtained during endoscopic resection in 2 patients with GH-secreting adenomas. Note the bright white **(A)** or mild yellow **(B)** color of the tumors.

should be considered at all times if insertion of a rigid buttress for reconstruction is planned.[10]

Immediate Postoperative Considerations in Patients With Acromegaly

Although the majority of patients with acromegaly and preoperative laryngeal edema and/or obstructive sleep apnea will benefit from improved breathing following resection of a GH-secreting adenoma,[21,23] the surgeon and anesthesia team should maintain vigilance with regard to the patient's airway immediately after the operation. Although nasal packing is not typically used following endoscopic transsphenoidal procedures, it may be justified in selected cases for the purpose of maintaining hemostasis in patients with acromegaly in whom intraoperative bleeding was a concern. If nasal packing is a consideration, the use of a nasal trumpet on one side (and standard nasal packing on the other) is a useful technique for optimizing airflow and patient comfort following the operation. Finally, continuous positive airway pressure or bilevel positive airway pressure may be required for some patients with chronic or worsened sleep apnea in the early postoperative period. These types of therapy should not be employed, however, if there is any suspicion of a CSF leak.

In the first 24 hours following surgical treatment in patients with GH-secreting adenomas, brisk fluid diuresis is often noted that may mimic DI. In patients with successful treatment of GH-secreting adenomas and normalization of GH levels following surgery, this is often due to diuresis of soft-tissue edema rather than DI, and can be differentiated by obtaining serum sodium and osmolarity levels and urine specific gravity analysis.[30]

Conclusions

In addition to the systemic and cardiopulmonary challenges associated with anesthetic and surgical treatment of patients with GH-secreting adenomas, certain variations in the nasal, bony, and vascular anatomy of patients with acromegaly often pose increased technical challenges during transsphenoidal operations. Excess or redundant soft-tissue edema, abnormal bony anatomy and hypertrophy, and changes in the anatomical course and structural integrity of the ICA may pose remarkable challenges for visualization, exposure, and safe resection of adenomas. Close scrutiny of preoperative imaging studies and implementation of various intraoperative maneuvers may optimize the safety profile associated with these procedures.

Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Zada, Cavallo, Cappabianca, Laws. Acquisition of data: Zada, Esposito, Fernandez-Jimenez, Tasiou, De Angelis. Analysis and interpretation of data: Zada, Cavallo, Esposito, Fernandez-Jimenez, Tasiou, De Angelis, Cappabianca. Drafting the article: Zada, Tasiou. Critically revising the article: Cavallo, Esposito, Fernandez-Jimenez, Cafiero, Cappabianca, Laws. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Zada. Administrative/technical/material support: Cavallo, Esposito, Fernandez-Jimenez, Tasiou, De Angelis, Cafiero. Study supervision: Cappabianca, Laws.

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Manuscript submitted June 14, 2010.
Accepted August 5, 2010.
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Neurosurg Focus 29 (4):E9, 2010

Intraoperative magnetic resonance imaging–assisted transsphenoidal pituitary surgery in patients with acromegaly

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Object. Acromegaly is a rare disease, usually caused by a growth hormone (GH)–producing pituitary adenoma. If untreated, severe cardiovascular, metabolic, cosmetic, and orthopedic disturbances will result. Surgery is generally recommended as the first-line treatment. Transsphenoidal surgical techniques were recently extended by the introduction of intraoperative MR (iMR) imaging. In the present study, the contribution of ultra-low-field (0.15-T) iMR imaging to tumor resection, complication avoidance, and endocrinological and neurological outcome was analyzed.

Methods. A series of 39 consecutive transsphenoidal iMR imaging–guided (using the PoleStar N20 device) surgical procedures performed between September 2005 and August 2009 for GH-producing pituitary adenomas was retrospectively analyzed. In addition to the patients' clinical data, the following criteria were evaluated independently: duration of surgery; length of hospital stay; endocrinological parameters; results of neurological examinations; and pre-, post-, and intraoperative MR imaging results.

Results. Thirty-seven patients with acromegaly underwent 39 transsphenoidal surgeries for pituitary adenomas. During a median follow-up period of 30 months (range 9–56 months), the remission rate was 73.5% in 34 patients with primary surgery and 20% in 5 cases with previous surgery; overall the remission rate was 66.7%. There were no serious postoperative complications. Detection of tumor remnant on iMR imaging led to a 5.1% increase in remission rate.

Conclusions. In this largest study to date of GH-producing pituitary adenomas in which iMR imaging–guided transsphenoidal surgery was analyzed, the results suggest that this method is a highly effective and safe treatment modality, even compared with previously published surgical series in which high-field iMR imaging was used. Limitations of iMR imaging are the detection of small residual tumor in the cavernous sinus and persisting disease that could not be observed, even on diagnostic high-field follow-up MR images. This points to a general limitation regarding remission rates that can be achieved using iMR imaging. Nevertheless, iMR imaging led to an increase of the remission rate in this study. *(DOI: 10.3171/2010.7.FOCUS10164)*

Key Words • acromegaly • PoleStar N20 imager • intraoperative magnetic resonance imaging • pituitary adenoma • transsphenoidal surgery

Acromegaly is a rare disease, with an estimated incidence of approximately 4 cases per 1 million population. In most cases, it is caused by a GH-producing pituitary adenoma. If excessive output of GH is not normalized, severe cardiovascular and metabolic disturbances as well as cosmetic and orthopedic deformities will result. Previously published studies have shown a 2–3-fold increased mortality rate for treatment-resistant cases, compared with successfully treated patients and healthy individuals.[6,28,36] Correction of GH values to normal can restore life expectancy toward normal. Most studies and the international consensus conference[8,12,26,27] recommend surgery as the first-line treatment. Medication with somatostatin analogs can achieve biochemical control in up to 60% of cases, but without comparable tumor size reduction. The first surgical treatment in which a transnasal approach was used in a patient with acromegaly was performed by Dr. Schloffer in Vienna in 1907.[31] Two years later, Dr. Cushing did a partial hypophysectomy in a patient with acromegaly, assuming that the underlying pathological mechanism was a hypertrophy of the pituitary gland.[10] Surgical techniques and nonsurgical treatment options have been developing ever since.[23] Today, most patients receive surgery as the first-line treatment, via a transnasal, transsphenoidal ap-

Abbreviations used in this paper: fT3 and fT4 = free T3 and T4; GH = growth hormone; GTT = glucose tolerance test; IGF-I = insulin-like growth factor–I; iMR = intraoperative MR; PRL = prolactin; TSH = thyroid-stimulating hormone.

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proach that was introduced by Cushing and then reintroduced using microsurgical techniques by Hardy in 1979.[18] More recently developed refinements in this surgical approach include the introduction of endoscopy[3,9,20,22] for pituitary surgery, and iMR imaging.[4,14] In this largest study to date in which ultra-low-field iMR imaging was used in patients with GH-producing pituitary adenomas, we retrospectively analyzed a series of 39 consecutive cases that had been treated using a transnasal, transsphenoidal microsurgical iMR imaging–assisted approach with the PoleStar N20 unit (0.15 T).

Methods

Patient Demographic Data

Thirty-nine surgical interventions were performed in 37 patients (24 men and 13 women) suffering from GH-producing pituitary adenomas between September 2005 and August 2009 (Table 1). Two patients (1 man and 1 woman) were treated twice. All patients underwent transsphenoidal surgery performed by the senior author (R.L.B.) with the aid of ultra-low-field iMR imaging. The mean patient age was 47 ± 14 years (median 46 years, range 19–76 years). The median preoperative tumor size was 1319 mm^3 (mean 3360 mm^3, range 50–56,549 mm^3). Ten cases (25.6%) presented with microadenomas, 27 (69.2%) with macroadenomas, and 2 (5.1%) with giant adenomas. There were 5 patients (12.8%) with previous pituitary surgery. In 10 cases (25.6%) the tumor invaded the cavernous sinus. In 37 cases (94.8%), patients had symptoms of acromegaly, and 8 patients (20.5%) had cranial nerve symptoms, among them 5 with visual field deficits (Table 2).

Preoperative and Postoperative Management

Patients were seen as outpatients before surgery. After the decision to proceed with surgical treatment, patients were admitted to the hospital the day before surgery. Preoperative diagnostic tests included CT scanning and MR imaging for determination of the characteristics of the pituitary adenoma as well as bone and neurovascular structures. Preoperative and postoperative imaging studies were performed at the Department of Neuroradiology, University Hospital Zurich. The CT studies were performed on a 16-slice CT scanner (Siemens SOMATON Sensation), acquiring multislice imaging data with and without the addition of contrast material. The MR imaging studies were performed on a 1.5-T MR unit (Signa, General Electric).

Neurological and ophthalmological examinations were performed after admission. General patient data, additional diagnosis, medication at admission, and previous study results were noted. Patients underwent endocrinological examination, which included blood analysis for pituitary function in which GH, IGF-I, adrenocorticotropic hormone, cortisol, TSH, fT4, fT3, PRL, luteinizing hormone, follicle-stimulating hormone, and human chorionic gonadotropin were examined; testosterone was measured in male patients and estradiol in female patients, unless there was a history of recent menstrual bleeding or of contraceptive pill use (Table 3).

Patients signed consent forms for the surgical procedure and general anesthesia. On the day of surgery most patients received, for safety reasons, 100 mg of hydrocortisone (SoluCortef, Pfizer) 1 hour before operation; another 100-mg dose of hydrocortisone was adminstered perioperatively. After surgery, patients were transferred to an intermediate care unit. A postoperative CT scan was obtained in all patients approximately 6 hours after surgery to exclude major bleeding or serious complications. The next morning, patients were transferred to the general ward and mobilized. They received 100 mg of hydrocortisone on the 1st postoperative day and 50 mg on the 2nd postoperative day. On the morning of the 3rd postoperative day and/or before discharge, their pituitary function was reexamined. If patients' cortisol levels were < 200 nmol/L in early morning blood samples, they received 30 mg of hydrocortisone (Hydrocortone, Merck) per day until endocrinological follow-up evaluation as outpatients 4 weeks after surgery.

Surgery and Intraoperative Neuroimaging

All operations were performed after induction of general anesthesia. Patients were placed supine on a foldable standard operating table, with their heads slightly reclined. The head was then fixed in an MR imaging–compatible head holder, after adjusting the radiofrequency coil around the patient's head. Subsequently, the preoperative CT studies were referenced with the intraoperative navigation system (StealthStation, Medtronic Navigation). The iMR imager used in all patients was a PoleStar N20 (0.15 T, Medtronic Navigation). The position of the patient's head in the scanner was tested by performing a 24-second sagittal e-steady scan (8-mm slices) and adjusted if necessary. Before surgery, a 7-minute, T1-weighted, Gd-enhanced (20 ml; Dotarem, Guerbet), 4-mm-slice, coronal iMR image was obtained. These images were automatically loaded into the navigation system and merged with the preoperative imaging studies.

All parts of the surgical procedures were performed with the aid of an operating microscope (Pentero, Carl Zeiss). At the beginning of the operation, a self-retaining endonasal speculum was inserted in the nostril chosen for the surgical approach. The mucosa was incised and partially removed, the posterior bony part of the septum was removed, and the anterior wall of the sphenoid sinus was displayed. The anterior wall of the sphenoid sinus was then opened with punches, the intrasphenoidal mucosa and septum were removed, and the inferior and anterior surface of the sella turcica was displayed and opened with a chisel. The dura mater was opened in an X-shaped fashion, and the adenoma was removed by curettes, grasping forceps, and suction devices. Tumor material was sent for frozen sections and neurohistopathological examination.

After complete tumor removal was accomplished according to the surgeon's impression, a 3.5-minute, T1-weighted, Gd-enhanced, 4-mm-slice, coronal iMR image was obtained for resection control in all patients. For better visualization of possible tumor remnants, a glove-covered ball of bone wax was inserted into the resection cavity for hemostasis and improved interpretation of intraoperative images. The intraoperatively acquired images were automatically merged with the existing preoperative and intraoperative imaging studies. In cases of visible tumor

TABLE 1: Overview of data in 37 patients with acromegaly*

Case No.	Age (yrs), Sex	Prev Op	Dur of Op (min)	LOS (days)	Tumor Vol (mm^3)	HC	AR	Remnant at EOS	Remnant at FU	RS at FU (mm^3)	Preop Level (μg/ml)		Postop Level (μg/ml)		Pt in Remission
											GH	IGF-I	GH	IGF-I	
1	46, M	yes, 1	105	6	506	B	no	no	yes	220	1.44	281	6.13	371	no
2	29, M	no	180	7	268	E	no	no	no	NA	31.20	996	0.12†	328	yes
3	70, M	no	116	6	785	B	no	no	no	NA	14.00	544	3.30	19	no
4	66, F	no	90	7	523	A	no	no	no	NA	7.97	776	—	350	yes
5	64, M	no	60	8	829	B	no	no	no	NA	31.20	709	1.00†	152	yes
6	42, M	no	125	6	1,993	C	yes	no	yes	4	88.20	779	5.06	213	no
7	39, M	no	115	7	2,278	C	no	no	no	NA	25.40	859	0.45†	330	yes
8	52, M	no	95	8	1,334	B	no	no	no	NA	10.60	765	0.48	175	yes
9	32, M	no	120	6	3,364	C	no	no	no	NA	107.00	1,308	0.42	193	yes
10	64, M	no	50	6	91	A	no	no	no	NA	6.21	472	0.26	142	yes
11	43, F	no	60	12	226	A	no	no	no	NA	12.80	564	1.64	179	no
12	44, F	no	75	8	1,238	B	no	no	no	NA	20.30	461	0.48	218	yes
13	66, M	no	170	9	1,851	C	no	no	no	NA	24.90	848	<1.00†	304	yes
14	51, F	no	95	7	2,948	C	yes	no	no	NA	49.00	1,007	0.66†	431	yes
15	37, M	no	95	5	4,158	C	no	no	yes	168	28.40	1,307	3.09	405	no
16	38, M	yes, 1	60	7	167	A	no	no	no	NA	1.34	245	0.82	181	yes
17	38, F	no	40	8	1,319	B	no	no	no	NA	4.52	382	0.30	172	yes
18	19, F	no	100	17	13,722	D	yes	no	yes	147	438.00	900	6.84	835	no
19	20, F	yes, 1	140	7	307	B	yes	no	yes	52	15.90	702	4.39	735	no
20	32, M	no	85	8	4,576	C	no	no	no	NA	23.40	1,085	0.51	251	yes
21	49, M	no	105	8	5,091	D	yes	no	yes	4	39.00	926	1.51†	317	no
22	76, F	no	45	7	518	A	no	no	no	NA	24.60	580	0.08†	194	yes
23	74, M	no	55	8	691	B	no	no	no	NA	27.40	1,020	2.00	206	yes
24	53, F	no	100	7	2,741	B	yes	no	no	NA	47.00	932	0.84	196	yes
25	49, M	no	145	9	7,225	E	yes	no	yes	4	12.30	801	6.23	376	no
26	58, M	no	75	7	131	A	no	no	no	NA	23.00	140	1.38	409	no
27	45, M	no	140	9	50	A	no	no	no	NA	5.09	801	0.42	394	yes
28	54, M	no	50	6	424	A	no	no	no	NA	6.85	553	0.42	278	yes
29	44, F	no	30	7	2,356	C	no	no	no	NA	14.40	1,158	1.05	351	no
30	28, M	no	55	5	1,876	C	no	no	no	NA	84.50	992	0.10	345	yes
31	53, F	no	55	8	314	A	no	no	no	NA	5.42	527	0.85	170	yes
32	30, M	no	58	8	1,238	B	no	no	no	NA	47.90	1,349	<1.00†	603	yes
33	64, F	no	50	8	226	A	no	no	no	NA	4.13	403	0.85	151	yes
34	45, F	yes, 2	60	10	301	A	no	no	no	NA	1.53	447	1.40	439	no
35	30, M	no	70	6	1,810	B	no	no	no	NA	18.10	1,053	0.14	260	yes
36	53, F	no	115	7	3,064	C	no	no	no	NA	10.00	380	0.39†	165	yes
37	51, F	no	100	7	2,089	C	no	no	no	NA	19.50	1,112	0.52†	359	yes
38	41, M	yes, 1	235	7	56,549	D	yes	yes	yes	4691	15.40	1,081	3.90	480	no
39	48, M	no	60	6	1837	C	no	no	no	NA	6.58	807	0.04	137	yes

* Two patients underwent a second surgery. Abbreviations: AR = additional tumor removal after first iMR session for resection control; Dur = duration; EOS = end of surgery; FU = follow-up; HC = Hardy classification; LOS = length of stay; NA = not applicable; Pt = patient; RS = remnant size.
† Values are results of GTTs; other values are baseline results.

remnants, the resection cavity was reexamined and tumor remnants removed if possible. Another postresection, intraoperative, 3.5-minute, T1-weighted, Gd-enhanced, 4-mm-slice, coronal iMR image was obtained in those cases. The anterior wall of the sella turcica was reconstructed using the extracted posterior part of the bony nasal or intrasphenoidal septum. In cases of intraoperative CSF leakage, the sella was packed with abdominal fat, and fibrin sealant was used. No nasal packing was used. All operations were performed by the senior author (R.L.B.).

TABLE 2: Characteristics of 37 patients with acromegaly*

Characteristic	Value
no. of ops	39
median pt age, in yrs	46 [19–76]
male sex	24 (61.5%)
pts w/ previous pituitary op	5 (12.8%)
median preop tumor size, in mm^3	1319 [50–56,549]
infiltration of CS	10 (25.6%)
pts w/ microadenoma	10 (25.6%)
pts w/ macroadenoma	27 (69.2%)
pts w/ giant adenoma	2 (5.1%)
pts w/ symptoms of acromegaly	37 (94.8%)
pts w/ cranial nerve palsy	8 (20.5%)

* Numbers in brackets represent the range of values throughout. Abbreviation: CS = cavernous sinus.

Follow-Up Protocol and Classification of Findings

All patients were followed-up 4 weeks postoperatively as outpatients in the endocrinology clinic; hormone levels were analyzed and deficient hormones were replaced if necessary. Three months after surgery, patients underwent a postoperative MR imaging study for resection control, and were seen for neurosurgical follow-up and examination. Patients were only defined as being in remission if symptoms of acromegaly disappeared, IGF-I levels returned to the age-adjusted reference range, and GH levels decreased to < 1 μg/L. In cases of clinical improvement and normalization of IGF-I levels, but with GH levels between 1 and 5 μg/L, a GTT was performed. Patients suppressing GH to < 1 μg/L on the GTT were defined as being in remission as well.

Statistical Analysis and Neuroimaging

The statistical analysis was performed using Microsoft Excel (version 2003) and SPSS statistic software (version 16.0). All imaging studies were analyzed independently and the evaluators were blinded to the clinical outcome by using standardized software (picture archiving and communication system [PACS]). Tumor volume was calculated based on the diameter method (tumor volume = 4/3 * π * 1/2x * 1/2y * 1/2z), where x, y, and z are the maximum diameters in the 3 axes. Mean values are presented ± SDs.

TABLE 3: Median hormone levels pre- and postoperatively

Hormone	Level	
	Preop	Postop
GH, in μg/L	19.50 [1.34–438.00]	1.52 [0.04–6.23]
IGF-I, in μg/L	801 [140–1349]	282 [19–835]
cortisol, in nmol/L	376 [70–979]	363 [96–808]
TSH, in mU/L	1.63 [0.14–4.71]	1.59 [0.02–6.12]
fT4, in pmol/L	15.40 [9.90–20.30]	16.90 [11.90–22.00]
testosterone, in nmol/L	8.80 [3.30–19.40]	12.30 [2.60–20.60]
PRL, in μg/L	13.50 [3.00–52.30]	9.00 [2.30–227.00]

Results

Intraoperative Imaging Studies

Intraoperatively, a mean of 2.2 ± 0.53 imaging studies (median 2, range 1–4 imaging studies) were performed per case (Table 4). There was an iMR imaging session at the beginning of surgery in all cases, and in all cases a second iMR imaging study was performed before closing (Figs. 1 and 2 [illustrative case]). In 8 cases (20.5%), the second iMR imaging study revealed a tumor remnant, and further tumor removal was performed. In 7 of those 8 cases, a third imaging study was done. In 1 case, the third iMR imaging study revealed a tumor remnant, even after further tumor removal, that could not be safely resected; the remnant was therefore left in place. Of the 8 patients with additional tumor removal after the second iMR imaging session, 7 were considered free of tumor remnants after the second iMR imaging study. Five (71.4%) of those 7 patients showed tumor remnant on 3-month diagnostic follow-up high-field MR imaging studies. The median tumor remnant size in these patients was 4 mm^3 (range 4–147 mm^3). In comparison, only 2 (6.4%) of 31 patients who were considered free of tumor remnants after the first intraoperative imaging study showed a tumor remnant at the 3-month follow-up. In 2 patients (5.1%) in whom residual tumor was found on iMR imaging, the lesion was subsequently resected, and this led to endocrinological remission.

Duration of Surgical Procedures

The median duration of the surgical procedure, including iMR imaging, was 90 minutes (mean 91.7 minutes, range 30–235 minutes). Table 5 shows that the median duration of operations in patients with previous surgery (105 minutes, range 60–235 minutes) was longer than in patients with first-time surgery (median 88 minutes, range 30–180 minutes). The median duration of operations in patients with infiltration of the cavernous sinus (118 minutes, range 55–235 minutes) was prolonged in comparison with patients without infiltration (median 72.5 minutes, range 30–170 minutes). Acquisition of iMR images was responsible for interruption of the surgical procedure for between 5 and 10 minutes, depending on the different sequences. On average this added up to approximately 25 minutes, including 1 e-steady and 3 T1-weighted contrast-enhanced MR imaging studies.

TABLE 4: Results of surgical procedures and follow-up*

Variable	Value
median iMRI studies per pt	2 [1–4]
additional tumor removal after iMRI study for resection control	8 (20.5%)
visible tumor remnant at end of op	1 (2.6%)
median duration of op, in min	90 [30–235]
tumor remnant at 3-mo FU	8 (20.5%)
mean time of overall FU, in mos	29 [9–56]
median days of hospitalization	7 [5–17]
pts w/ normalized hormone levels	30 (76.9%)
pts in remission	26 (66.7%)

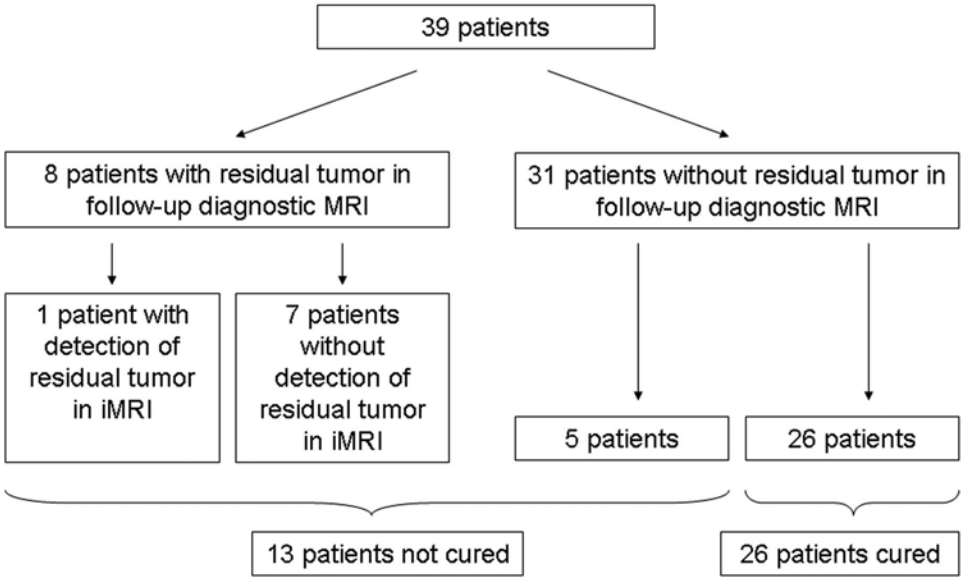

Fig. 1. Flowchart of residual tumor detection in diagnostic high-field MR imaging and iMR imaging.

Postoperative Course and Complications

The patients' median time of hospitalization was 7 days (range 5–17 days). The immunohistological examination revealed variable GH-positive adenoma tissue in all cases.

Postoperatively, 1 patient developed signs of CSF rhinorrhea and needed lumbar drainage for 5 days. Another patient developed diabetes insipidus and needed temporary treatment with desmopressin. There was no case of major postoperative hemorrhage or other complications needing a repeat operation.

Endocrinological Outcome

All patients were seen for endocrinological follow-up 4 weeks after surgery, and for surgical follow-up in the hos-

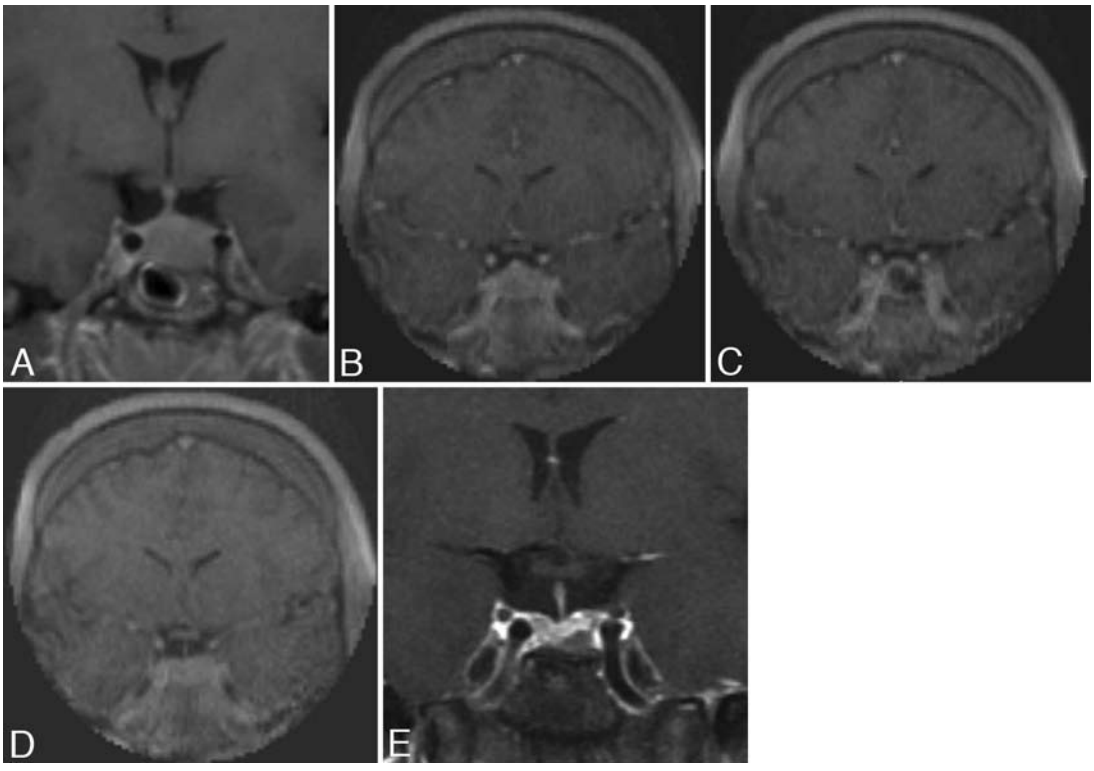

Fig. 2. Illustrative case. **A:** Preoperative coronal 1.5-T MR image. **B:** Coronal iMR image obtained before skin incision. All iMR imaging was performed with the PoleStar N20 unit. **C:** Coronal resection control iMR image obtained after tumor removal, showing residual tumor. **D:** Coronal iMR image obtained after at the end of the surgical procedure, showing no residual tumor. **E:** Postoperative coronal 1.5-T MR image.

TABLE 5: Patient parameters with potential influence on duration of surgical procedures

Comparisons Btwn Pt Groups	Duration of Op, in Min
median in pts w/ first-time op vs pts w/ previous op	88 [30–180] vs 105 [60–235]
median in pts in remission vs pts not in remission	72.5 [40–180] vs 105 [30–235]
median in pts w/ infiltration vs pts w/o infiltration of CS	118 [55–235] vs 72.5 [30–170]

pital's outpatient department after 12 weeks. At follow-up, there were 30 cases (76.9%) with normalization of preoperative GH and IGF-I excess. Applying the definition of remission according to the international consensus conference, the remission rate in our study patients was 66.7%. As shown in Table 3, the GH level dropped from a median of 19.50 μg/L (range 1.34–438.00 μg/L) preoperatively to a median of 1.52 μg/L (range 0.04–6.23 μg/L) at first follow-up (see Fig. 3). The IGF-I level dropped from a median of 801 μg/L (range 140–1349 μg/L) preoperatively to a median of 282 μg/L (range 19–835 μg/L) postoperatively. The other examined hormones remained at approximately their preoperative levels. The median level of cortisol was 376 nmol/L (range 70–979 nmol/L) at baseline and it was 363 nmol/L (range 96–808 nmol/L) after surgery. The median TSH level was 1.63 mU/L (range 0.14–4.71 mU/L) preoperatively and it was 1.59 mU/L (range 0.02–6.12 mU/L) postoperatively. The median PRL level was 13.50 μg/L (range 3.00–52.30 μg/L) before surgery and it was 9.00 μg/L (range 2.30–227.00 μg/L) after surgery. The median fT4 value was 15.40 pmol/L (range 9.90–20.30 pmol/L) before and 16.90 pmol/L (range 11.90–22.00 pmol/L) after surgery. There was no patient in need of cortisol or T4 (thyroxine) substitution postoperatively who had not received replacement therapy before.

Regarding gonadal function, the median testosterone level in male patients was 8.8 nmol/L (range 3.3–19.4 nmol/L) before and 12.3 nmol/L (range 2.6–20.6 nmol/L) after surgery. Three male patients were receiving testosterone replacement therapy at evaluation for surgery, and they remained gonadotropin deficient postoperatively. Eight female patients were postmenopausal at the time of surgery; in all of them, gonadotropin levels remained high following surgery. There was 1 female patient with insufficient menstrual function, and she also required estrogen replacement therapy following surgery.

In patients undergoing surgery for the first time, a remission rate of 73.5% was achieved, whereas in patients with previous surgery a 20% remission rate was found (Table 6). Patients referred for primary surgery without postoperative remission had higher mean baseline levels of GH and larger tumor volume (54.18 μg/L [range 1.44–438.00 μg/L] and 7181 mm^3 [range 132–56,549 mm^3], respectively) compared with patients subsequently experiencing remission (26.42 μg/L [range 1.34–107.00 μg/L] and 1449 mm^3 [range 50–4576 mm^3], respectively). Of the 26 patients in remission, there were only 3 (11.5%) with infiltration of the cavernous sinus, whereas 7 (53.8%) of 13 patients not in remission presented with infiltration of the cavernous sinus. There were no differences in general patient data, clinical symptoms, and IGF-I levels preoperatively between the patients who were in remission and those who were not.

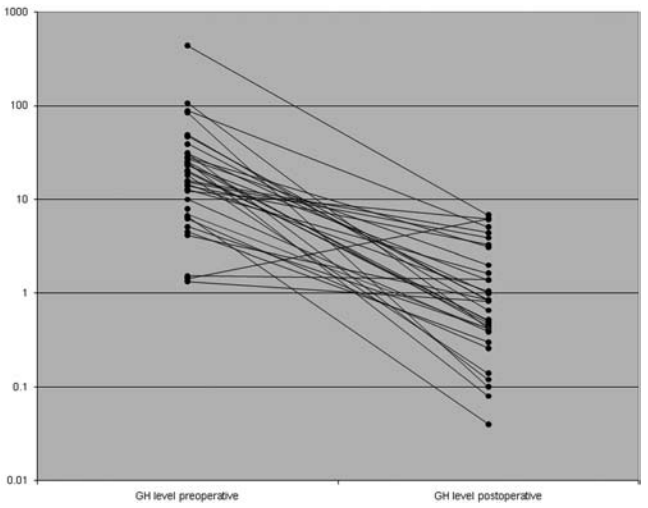

Fig. 3. Chart showing GH levels (in μg/L) before and after surgery for 37 patients (log scale).

Regarding the Hardy classification,[18] there were 11 patients in Stage A, 11 in Stage B, 12 in Stage C, 3 in Stage D, and 2 patients in Stage E. Remission rates were 72.3% for both Stages A and B patients, 75.0% for Stage C patients, 0.0% for Stage D patients, and 50.0% for Stage E patients.

Neuroradiological Follow-Up

At the 3-month follow-up there was no tumor remnant visible in diagnostic high-field MR imaging in 31 cases (79.5%; Table 6). Of those 31 cases, 26 fulfilled the definition of remission. In 5 patients there was no residual tumor detectable in high-field diagnostic MR imaging, but those patients still showed elevated GH levels and clinical symptoms of acromegaly. There were 8 patients with detectable residual tumor on diagnostic follow-up MR imaging; 1 of those residual tumors was detected with iMR imaging in a patient in whom the remnant was

TABLE 6: Data in patients with first-time surgery versus patients with previous surgery

Parameter	First-Time Op	Pts w/ Previous Op
no. of pts	34	5
median preop tumor vol, in mm^3	1572 [50–13,722]	308 [168–56,549]
pts w/ intraop remnant removal	6 (17.6%)	2 (40%)
pts w/o residual tumor at FU	29 (85.3%)	2 (40%)
pts w/ tumor remnant at FU	5 (14.7%)	3 (60%)
median size of tumor remnant, in mm^3	4 [4–168]	52 [52–4691]
pts w/ intraop/postop complications	0 (0.0%)	1 (20%)
pts in remission	25 (73.5%)	1 (20.0%)

left intentionally because of the impossibility of complete removal due to large tumor size (54 × 50 × 40 mm^3), infiltration of the cavernous sinus, caging of the internal carotid and anterior cerebral arteries, and extensive growth into the hypothalamic region. The median residual tumor volume in those patients was 4 mm^3 (range 4–168 mm^3) in 5 patients after first-time surgery, and 52 mm^3 (range 52–4691 mm^3) for 3 patients with multiple previous surgeries. Interestingly, diagnostic high-field MR imaging did not show residual tumor in 5 of 13 patients who were not in remission.

Discussion

This study shows for the first time a series of 39 consecutive cases in which patients received transsphenoidal iMR imaging–guided surgery for GH-producing pituitary adenoma by applying an ultra-low-field iMR imaging modality (PoleStar N20 unit). Our results show an overall remission rate of 66.7%. In patients without previous surgery the remission rate was even higher (73.5%), and in previously treated patients the remission rate dropped to 20%. These results are at least as good as previously published series in the literature that show a range of overall remission rates between 42% and 82%.[1,2,5–7,11,13,15,17,19,21,25,29,30,33–35] However, in these publications the applied definition of remission differs widely (GH between < 1.0 μg/L and < 5.0 μg/L). Definition of remission in our study was applied according to the international consensus conference. Studies with a comparable definition of remission showed remission rates ranging from 52% to 67%.[5,25,29]

Operations in patients with previous pituitary surgery showed a lower rate of remission (20.0%) than did operations in patients with primary surgery. Such findings are in accordance with the literature, in which remission rates between 20% and 30% are shown.[13,14,24,29]

Among the patients not in remission, there were an additional 5 patients (12.8%) with improvement or remission of clinical symptoms and reduction of GH excess to levels below 2.0 μg/L, even though these patients were not defined as being in remission.

There have been few previous publications in which intraoperative MR imaging was used for tumor resection control in pituitary surgery for acromegaly.[4,14,16,32] Fahlbusch et al.[14] published a series of patients in whom operations were performed with the assistance of 1.5-T iMR imaging studies, and these investigators reported remission in 10 (44%) of 23 patients. Although the results of our study appear to compare well with those reported by Fahlbusch et al., patient characteristics in the 2 small groups may not be fully comparable, and because these considerably influence the surgical outcome, any claim of superiority between these 2 studies would be premature. In a study by Gerlach et al.,[16] only some of the patients analyzed had GH-positive adenomas. The complication rate and neuroradiological tumor remnants were comparably low, but endocrinological assessment was not performed.

Intraoperative imaging studies acquired with the ultra-low-field MR imaging unit PoleStar N20 gave valuable and accurate information regarding tumor remnants after removal. Only in 2 cases was there a false-negative interpretation regarding tumor remnants after the first iMR imaging study for resection control. Detection of a tumor remnant led to an increase of 5.1% in remission rate, because there were 2 patients in remission in whom residual tumor that was found on iMR imaging could be completely resected. Despite this 5.1% increase in the remission rate, we could only identify residual tumor with iMR imaging in 1 of 8 patients with tumor remnants on the diagnostic follow-up MR imaging. Interestingly, the diagnostic high-field MR imaging was unable to visualize residual tumor in 5 of 13 patients who were not endocrinologically in remission. This indicates that even under optimal conditions, as in a diagnostic MR imaging environment, in 5 (12.8%) of 39 patients in the whole study group, visualization of residual tumor could not be achieved, pointing to a systematic limitation of MR imaging for resection control.

Although the iMR imaging system was thought to be useful and led to improved remission rates, the following limitations have to be considered. As in cases with additional tumor removal after iMR imaging studies following resection of the adenoma, there was a higher rate of false-negative results regarding tumor remnants. In these 7 of 8 cases with small adenoma remnants on postoperative diagnostic MR imaging, a high rate (50%) of cavernous sinus tumor infiltration was present. This illustrates the limited visualization of tumor remnants in the cavernous sinus, as mentioned in previous studies.[24] Because remission rates in patients with recurring disease were only 20%, it has to be stated that iMR imaging in this difficult population was not as useful as in patients with first-time pituitary surgery. This may be partially caused by the insufficient differentiation of scar and recurrent adenoma tissue. High-field iMR imaging systems and imaging sequences with higher resolution of details may lead to a better definition of these structures; however, an improved patient outcome with the use of high-field iMR imaging has not yet been demonstrated. Whether the costs related to iMR imaging systems used in pituitary surgery are compensated by improved outcome has to be shown by future investigations.

The surgical procedures described were safe. There was only 1 patient who developed signs of persistent CSF rhinorrhea and needed lumbar drainage for 4 days. Comparison with previously published studies showed rates of severe complications in up to 8% of cases and CSF rhinorrhea in approximately 2% of cases.[1,14,29] One patient developed transient diabetes insipidus and needed temporary treatment with desmopressin. This type of surgery appears to be quite safe for the remaining healthy pituitary cells; in fact, patients did not develop pituitary failure (even gonadotropin and sex hormone deficiency was rare), as confirmed in the follow-up evaluation of these patients. Overall, the complication rate was low and there were no severe complications such as postoperative hemorrhages, meningitis, or injury to cranial nerves.

Since the year 2000, all patients with pituitary adenomas in our department underwent operation with the aid of iMR imaging, and therefore a comparison with patients who underwent operations without iMR imaging was not found to be adequate; this is a limitation of this study.

Conclusions

In this largest study to date of GH-producing pituitary adenomas analyzed using iMR imaging–guided transsphenoidal surgery, the results presented suggest that this method is a highly effective and safe treatment modality, even compared with previously published surgical series in which high-field iMR imaging was used. The overall remission rate of 66.7%, and even 73.5% for patients without previous surgery, and the lack of complications requiring additional surgery underscore this statement. Limitations of iMR imaging are the detection of small remnants in the cavernous sinus and persisting disease that could not be observed, even on diagnostic high-field follow-up MR images. Further analysis points to a systematic limitation of iMR imaging with regard to remission rates beyond 80%, because even high-field MR imaging under ideal conditions could not detect residual tumor in 13% of cases. Detection of tumor remnant with iMR imaging and additional tumor removal led to a 5.1% increase of the remission rate.

Disclosure

The manuscript has not been previously published in whole or in part or submitted elsewhere for review. There was no financial support. The authors report no conflict of interest.

Author contributions to the study and manuscript preparation include the following. Conception and design: Bellut, Hlavica. Acquisition of data: Bellut, Hlavica. Analysis and interpretation of data: all authors. Drafting the article: Bellut. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Bellut. Study supervision: Bernays, Schmid.

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Manuscript submitted June 15, 2010.
Accepted July 16, 2010.
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Neurosurg Focus 29 (4):E10, 2010

Olfactory improvement in acromegaly after transnasal transsphenoidal surgery

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Object. The direct transnasal transsphenoidal approach to the sellar region has become a widely adopted surgical procedure among neurosurgeons and ear, nose, and throat specialists. Nasal complications and their incidence have been investigated, but a systematic testing of olfactory disturbance has not previously been performed. Considering that the sense of smell is deeply anchored and interwoven within the CNS, and that its impairment implies a considerable loss in quality of life, surgical practice should aim at its preservation.

Methods In this retrospective study, pre- and postoperative olfactory performance, nasal airway passage, septal perforation, and epistaxis were assessed in 96 patients who underwent direct transnasal transsphenoidal microsurgery at the authors' department between January 2007 and August 2009. Olfactory performance was assessed using the Sniffin' Sticks test and/or the Zürcher Geruchstest.

Results. After surgery, 47 (49%) of 96 patients improved, 34 (35%) of 96 deteriorated, and 15 (16%) of 96 presented with unchanged olfactory performance. With respect to the underlying pathological entity, the authors noticed a remarkable difference between patients with acromegaly (23 cases) and all other patients (73 cases). Fifteen (65%) of 23 patients with acromegaly improved (others 44%), only 3 (13%) of 23 deteriorated (others 42%), and 5 (22%) of 23 remained unchanged (others 14%) in their ability to distinguish odors. This illustrates a significant shift toward improved postoperative olfactory performance (cross-tabulation, Fisher exact test; $p = 0.028$) in patients with acromegaly.

In nasal breathing, 77 (80%) of 96 patients noticed no change, 11 (12%) of 96 improved, and 8 (8%) of 96 worsened postoperatively. Of the 11 patients with improved breathing, 6 (55%) had acromegaly. Improved nasal airway patency was more frequent in patients with acromegaly (cross-tabulation, Fisher exact test; $p = 0.002$).

Conclusions. The data provide the first significant evidence for improvement in olfactory performance in patients with acromegaly after transsphenoidal surgery (TSS) of growth hormone–producing adenomas. Furthermore, postoperative olfactory disturbance in patients treated with transnasal TSS is more frequent than previously reported. Nevertheless, recurrent transnasal TSS can be performed successfully, even multiple times, and does not involve a higher risk of nasal complications. *(DOI: 10.3171/2010.7.FOCUS10162)*

Key Words • **nasal complication** • **transnasal approach** • **transsphenoidal surgery** • **olfaction** • **acromegaly** • **growth hormone**

The transsphenoidal approach to the sella turcica is the most popular technique for the resection of pituitary adenomas and other tumors of the sellar region. Throughout its implementation, various access routes have been developed, including the sublabial transseptal, transantral, transethmoidal, and especially with the improvement of endoscopic methods, the direct transnasal access has become a routine standard in pituitary surgery. Since the year 2000, the direct transnasal approach to the sphenoid sinus, as first described by Griffith and Veerapen[5] in 1987, has been applied for TSS at our department. Nasal complications caused by this approach have previously been described, but olfactory disturbance has never been investigated in a systematic fashion. The consideration that the sense of smell is deeply anchored and interwoven within the CNS, and that the coding of its function requires 1% of our genome,[2] yields ample incentive for its preservation. These circumstances have motivated us to explore olfactory complications in this widely established surgical approach systematically, to allow more precise counseling of patients prior to their consent to an operation.

A further goal of the study was to test our hypothesis that olfactory performance might improve due to surgery, similar to improvement in median nerve neuropathy after treatment of acromegaly.[7]

Abbreviations used in this paper: GH = growth hormone; TSS = transsphenoidal surgery.

Methods

Patient Inclusion Criteria

A retrospective study was performed in all patients who underwent transnasal TSS at our department between January 2007 and August 2009. A total of 145 operations, excluding revision operations, were performed in 141 patients by the senior author (R.L.B.). At our department, olfactory testing is performed as part of the clinical evaluation in patients who are scheduled to have TSS. All patients who received preoperative olfactory testing were included in the evaluation. These criteria led to a final group of 96 patients who answered questions concerning nasal obstruction, underwent examination of the nasal septum, and were retested in regard to olfactory function at follow-up evaluation.

Preoperative Assessment

All 96 patients underwent preoperative testing of olfactory performance in our department or at our local ear, nose, and throat department. Testing was done with the Sniffin' Sticks olfactory test (Burghart Medizintechnik) or Zürcher Geruchstest (www.novimed.ch). In olfactory testing, both sides were investigated simultaneously. Correct recognition of more than 85% of presented odors was defined as normal, between 85% and 50% as hyposmic, and below 50% as anosmic. The nasal septum was examined at the beginning of each operation by the senior author.

Surgical Technique

Microsurgery was performed in the PoleStar N20 apparatus (0.15 T, www.medtronic.com) by means of a direct transnasal transsphenoidal approach. Following orotracheal induction of anesthesia, the patient was placed in a supine position with the head reclined and fixed in the head holder. The nasal cavities were packed for 3–5 minutes with gauze soaked in a mixture of 30 ml 2% tetracaine HCl and 2 mg adrenaline. Nostrils and surrounding skin were then disinfected with iodine solution. After draping, a self-retaining nasal speculum (www.aesculap.com) was placed in the nasal cavity, typically the narrower one, and the anterior sphenoid wall was visualized with the aid of the operating microscope. The posterior part of the septal bone was then fractured toward the opposite side by leverage with the speculum, and the mucosa was incised in an inverted T shape with a disc knife. The first speculum was withdrawn, and a Buchfelder pituitary speculum (www.dewimed.de) was inserted and fixed in position. After that, the anterior sphenoid wall was removed with punches or a chisel to gain access to the sphenoid sinus. Finally, the sellar pathological entity was removed, without postoperative packing of the nasal cavities.

Postoperative Treatment and Follow-Up

Following the operation, a CT scan was obtained to rule out postoperative complications, and patients were observed daily for fluid and electrolyte balance, epistaxis, nasal dripping, and visual acuity. Acromegaly was considered cured if the GH serum level dropped below 1 μg/L, as defined in the acromegaly treatment consensus workshop.[1,10] Patients with epistaxis were clinically examined if the bleeding was immediately pronounced or if it did not subside within 1 to 2 days of surgery. Postoperative nasal crusting and/or clotting was gently resolved using an isotonic, sterile, saltwater nose spray (Triomer spray, Vifor AG) 3–4 times daily.

After discharge, patients typically received clinical follow-up and underwent MR imaging 3 months postoperatively, and thereafter in yearly intervals. At follow-up, the patients' subjective perception of postoperative nasal breathing ability was assessed in comparison with before surgery. Furthermore, nasal septum defects were evaluated using rhinoscopy, and olfactory performance was tested only with the Zürcher Geruchstest by the senior author.

Statistical Analysis

At each olfactory testing session, the number of correctly assigned odors was transformed into an olfactory performance rate, with a range of 0%–100%. Statistical testing was performed using the PASW Statistics 18 program. For cross-tabulation, we used the Fisher exact test because of small cell counts. Because our data cannot be assumed to be normally distributed, we applied nonparametric testing: the Mann-Whitney test for comparisons between groups and the paired Wilcoxon signed-ranks test for before and after comparisons within groups. All tests were 2-sided, and the significance level was set at 0.05.

Results

Patient Demographic Data

In the 32-month period, 96 patients who underwent 98 direct transnasal transsphenoidal operations were included in this study. The age range was 11.9–86.7 years (mean 53.1 years). There were 62 male and 34 female patients. Two participants had repeated surgery within these 32 months: a 19-year-old woman with recurrence of a GH-producing macroadenoma, and a 50-year-old man with recurrent Rathke cyst. The cohort included 72 macroadenomas, 11 microadenomas, 9 Rathke cysts, and 1 each of meningioma, craniopharyngioma, arachnoid cyst, and oncocytoma. Among the adenomas were 41 hormone-inactive and 42 hormone-active tumors. Of the 96 patients, 23 (24%) had acromegaly; 18 of them were considered cured according to the definition of the acromegaly consensus workshop,[1,10] 4 had normal serum GH levels (but > 1 μg/L), and 1 displayed an elevated level of 6.2 μg/L at follow-up. Overall there were 17 recurrent tumors (18%), 16 of which had been previously treated transsphenoidally (Table 1) and 1 transcranially at another center. Follow-up duration ranged from 3 to 34 months (mean 10.3 months).

Olfactory Performance

Preoperatively, 39 (41%) of 96 patients displayed normal smelling capability, 53 (55%) had hyposmia, and 4 (4%) were anosmic. Postoperatively, 60 (62%) of 96 patients had normal olfactory performance, 30 (31%) were hyposmic, and 6 (6%) had anosmia. Comparing pre- and

TABLE 1: Overview of prior treatments in 17 patients with recurrent disease*

No. of Cases	Type of Recurrent Disease	No. & Type of Prior Treatments
7	inactive macroadenoma	TSS (1)
3	active macroadenoma	TSS (1)
1	inactive macroadenoma	TSS (2), TCS (1), RT (1)
1	inactive macroadenoma	TSS (5), RS (1)
1	active macroadenoma	TSS (1), RS (1)
1	inactive macroadenoma	TSS (3)
1	Rathke cyst	TSS (2)
1	Rathke cyst	TSS (1)
1	inactive macroadenoma	TCS (1)

* Numbers in parentheses represent the number of treatments. Abbreviations: RS = radiosurgery (Gamma Knife, linear accelerator); RT = radiotherapy; TCS = transcranial surgery.

postoperative performance of each patient, we found 15 (16%) of 96 to have experienced no change in their smelling capability (unchanged group), 47 (49%) were able to discriminate more odors (improved group), and 34 (35%) had deteriorated in their ability to distinguish the tested substances (deteriorated group).

Comparing the groups with improved, deteriorated, and unchanged olfaction divided according to the underlying disease, we noticed a remarkable difference between the 23 patients with acromegaly and the 73 others. Among the patients with acromegaly, 15 (65%) of 23 improved, 3 (13%) deteriorated, and 5 (22%) remained unchanged. The values differ remarkably from the patients without acromegaly, of whom 32 (44%) of 73 improved, 31 (42%) deteriorated, and 10 (14%) remained unchanged. The numbers are illustrated in Fig. 1. Based on these numbers, we constructed a table for the categories "olfaction improved/unchanged/deteriorated" and "acromegalic/nonacromegalic," and found a significant difference for the effect of surgery between the 2 patient groups (Fisher exact test; $p = 0.028$). This difference between the groups was confirmed by a nonparametric comparison (Mann-Whitney test; $p = 0.025$). We then compared olfactory performance rates pre- and postoperatively within each group (paired Wilcoxon test). A significant improvement was only found in the acromegalic group ($p = 0.009$), and not in the nonacromegalic group ($p = 0.9$). This is reflected in the median change of olfactory performance in the 2 groups: acromegalic (8%, range from –16% to 33%), and nonacromegalic (0%, range from –67% to 63%). This reflects a change of noticeable magnitude pointing toward its clinical relevance.

Nasal Airway Patency

Unaffected, normal nasal respiration was reported in 77 (80%) of 96 cases. Better nasal air passage was reported in 11 (12%) of 96 cases, and 8 (8%) of 96 patients expressed reduced patency after the operation. Two of these 8 experienced an overall reduced ability to breathe through their nose, whereas 3 each were able to state the side of dominant obstruction. In the 11 cases with better postoperative air passage, 6 patients (55%) had GH-producing adenomas and 1 patient had a correction of a nasal septal deviation in combination with the TSS.

Surgery affected the airway patency of patients with and without acromegaly differently. Of the patients with acromegaly, 3 (13%) of 23 deteriorated, 13 (57%) remained unchanged, and 7 (30%) improved. Of the nonacromegalic patients, 5 (7%) of 73 deteriorated, 64 (88%) remained unchanged, and 4 (6%) improved. The difference between patient groups was significant (Fisher exact test; $p = 0.002$).

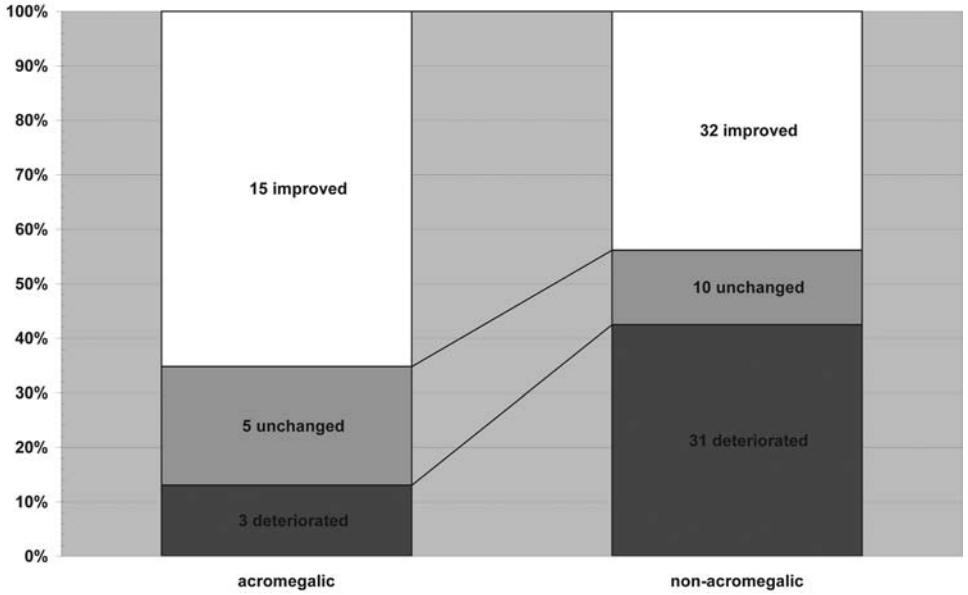

Fig. 1. Bar graph displaying olfactory performance after surgery in patients with compared with those without acromegaly. The percentages of patients with improved, unchanged, or deteriorated performance differed significantly between the groups with and without acromegaly (Fisher exact test; $p = 0.028$). Within groups, olfactory performance improved significantly in patients with acromegaly (paired Wilcoxon test; $p = 0.009$), but not in patients without the disease.

Septal Perforation

Among the 96 patients, we found 2 perforations at the time of surgery: one was in a patient with known cocaine abuse, and the other was in a patient who had undergone 3 prior TSSs at other centers. The other 94 patients did not develop any perforations within the follow-up time.

Epistaxis Requiring Coagulation

We encountered severe or persistent epistaxis in 3 (3%) of 96 patients, who required transnasal surgical revision with coagulation of the sphenopalatine artery. All 3 had undergone TSS for the first time.

Discussion

Olfactory Performance

A remarkable difference was found between patients with and without acromegaly in regard to olfactory performance. In patients with acromegaly, 65% improved in olfactory performance, versus 44% of those without acromegaly, and only 13% of patients with acromegaly deteriorated, versus 42% of those without the disease (Fig. 1). We propose 2 mechanisms by which this improvement may occur. First, an entrapment mechanism in the olfactory system, analogous to median nerve neuropathy,[7] may be reduced after successful treatment of acromegaly, leading to improved nerve function. Second, excessive GH production in patients with acromegaly is associated with hypertrophy of the nasal mucosa,[11] which consecutively congests the region below the cribriform plate. Reduced GH production after surgery may reverse this effect, thus enabling an improved interaction of aromatic molecules with the primary sensory neurons. This hypothesis is supported by the fact that 18 patients with acromegaly were cured, 4 had normal GH serum levels, and only 1 presented with persistent elevation of GH levels.

There is a limitation of our study in that we used the Sniffin' Sticks olfactory test to assess the patients preoperatively and the Zürcher Geruchstest for postoperative follow-up. The change was motivated by the better robustness of the latter test in our follow-up setting. To compare between test results, we had to calculate percentages from the test results instead of using the scored number values. As a consequence, we confined the results to only 3 broad groups: normosmic, hyposmic, and anosmic, without trying to distinguish more subtle nuances in olfactory performance.

Comparison of our data on olfactory complications with existing literature is difficult, because olfactory performance has hardly ever been systematically observed in patients who have undergone TSS. Higgins et al.[6] mention a 2%–12% incidence of anosmia and hyposmia in patients treated with the transseptal approach. Koren et al.[8] found hyposmia and anosmia in 2 (10%) of 20 patients who had undergone transnasal endoscopic surgery, and Tan and Jones[12] report on 1 patient (4%) of 25 with hyposmia. Our results, with a 35% prevalence of postoperative olfactory deterioration, are based on the largest series to date. It must be considered that this high prevalence also accounts for subtle deterioration within the normosmic range, and only 6 patients were actually anosmic.

Nasal Airway Patency and Other Complications

Fairley et al.[4] have demonstrated a strong correlation between the subjective sensation of nasal patency and the objective nasal inspiratory peak flow rate. Considering this, we conducted a survey for postoperative reduced nasal airway patency, and found it in 8% of patients by questioning them. These results were similar to those of Tan and Jones,[12] who analyzed peak nasal inspiratory flow rates and found 3 (12%) of 25 patients with reduced nasal air passage. Griffith and Veerapen,[5] the pioneers of the direct transnasal approach, observed a 3% diminishment of postoperative nasal breathing capability in their cohort of 100 patients. Again, in the analysis of this particular nasal complication, we registered a more than proportional percentage of patients with acromegaly (55%) among those who improved in nasal respiration. This further fortifies our assumption of decreasing mucosal hypertrophy after normalization of GH production as one of the factors leading to improvement of nasal function in these patients. Furthermore, we postulate that the choice in the side of direct transnasal access may be beneficial for patients who present with septal deviation. If the speculum is placed on the side that has greater obstruction due to the septal deviation, the amount of deviation may in part be corrected as a side effect of the direct transnasal approach.

No new perforations of the nasal septum as a result of the direct transnasal approach were observed. This finding is comparable with prior studies in which the direct transnasal microsurgical resection of pituitary adenomas has been analyzed.[3,12] In contrast to this, several authors applying an endoscopic approach reported a 5%–10% septal perforation rate.[6,8] As mentioned by others, we suspect that this may be due to the increased mechanical manipulation within the nasal cavities during endoscopic pituitary surgery.

With a rate of approximately 3% for epistaxis requiring revision surgery, this complication should not be underestimated. In all cases of epistaxis, hemorrhage occurred from branches of the sphenopalatine artery. Management consisted of monopolar cauterization of the bleeding artery in the sphenopalatine foramen, which in all cases was conducted successfully. Published rates of epistaxis range from 1% to 4%.[9,12]

Prior TSS performed via varying approaches does not present a contraindication for repeat direct transnasal TSS in cases of recurrent disease. In all of our 16 cases with prior TSS, in some of which the patients have undergone multiple operations (Table 1), the procedure was always accomplished successfully without a higher occurrence of nasal complications.

Conclusions

Our data provide the first significant evidence for improvement of olfactory performance in patients with acromegaly after TSS of GH-producing adenomas. Furthermore, postoperative olfactory disturbance in transnasal TSS is more frequent than previously reported, when also accounting for subtle deterioration within the normosmic range. Nevertheless, recurrent transnasal TSS can be per-

formed successfully, even multiple times, and does not involve a higher risk of nasal complications.

Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Bernays, Holzmann. Acquisition of data: Bernays, Actor, Prömmel, Holzmann. Analysis and interpretation of data: Bernays, Actor, Sarnthein. Drafting the article: Bernays, Actor, Sarnthein. Critically revising the article: Bernays, Actor, Sarnthein, Holzmann. Reviewed final version of the manuscript and approved it for submission: Bernays, Actor, Sarnthein. Statistical analysis: Actor, Sarnthein. Study supervision: Bernays.

Acknowledgment

The authors thank Sarah R. Haile, Ph.D., for her expert assistance with the statistical analysis.

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Manuscript submitted June 15, 2010.
Accepted July 16, 2010.

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Neurosurg Focus 29 (4):E11, 2010

The role of stereotactic radiosurgery in the multimodal management of growth hormone–secreting pituitary adenomas

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Growth hormone (GH)–secreting pituitary adenomas represent a common source of GH excess in patients with acromegaly. Whereas surgical extirpation of the culprit lesion is considered first-line treatment, as many as 19% of patients develop recurrent symptoms due to regrowth of previously resected adenomatous tissue or to continued growth of the surgically inaccessible tumor. Although medical therapies that suppress GH production can be effective in the management of primary and recurrent acromegaly, these therapies are not curative, and lifelong treatment is required for hormonal control. Stereotactic radiosurgery has emerged as an effective adjunctive treatment modality, and is an appealing alternative to conventional fractionated radiation therapy. The authors reviewed the growing body of literature concerning the role of radiosurgical procedures in the treatment armamentarium of acromegaly, and identified more than 1350 patients across 45 case series. In this review, the authors report that radiosurgery offers true hormonal normalization in 17% to 82% of patients and tumor growth control in 37% to 100% of cases across all series, while minimizing adverse complications. As a result, stereotactic radiosurgery represents a safe and effective treatment option in the multimodal management of primary or recurrent acromegaly secondary to GH-secreting pituitary adenomas. *(DOI: 10.3171/2010.7.FOCUS10159)*

Key Words • acromegaly • growth hormone • insulin-like growth factor–I • pituitary adenoma • radiosurgery

Acromegaly consists of a constellation of clinical signs and symptoms caused by an excess production of GH. The onset of this disease can be quite insidious, and common clinical manifestations include acral overgrowth, soft tissue hypertrophy, metabolic derangements, and cardiovascular complications.[3,7] While a host of pathological entities can cause GH overproduction, more than 90% of patients with acromegaly harbor a GH-secreting pituitary adenoma.[4,9] Although these adenomas arise from the benign proliferation of somatotroph cells within the anterior pituitary gland, the pituitary's confined location within the sella turcica and close approximation to important neurovascular structures render masses in this region problematic. Therefore, aside from complications secondary to GH excess, patients may also experience headache, visual loss, cranial nerve deficits, and symptoms of additional pituitary hormone dysregulation.[18]

Surgical extirpation of the culprit lesion is considered first-line treatment and has the distinct advantage of instantaneously lowering GH levels by directly removing the source of hormone production.[28] Recent studies estimate postoperative endocrinological remission rates to be 68% to 95%, irrespective of tumor volume.[28,34] Despite this clinical efficacy, not only is surgery alone not curative in a select cohort of patients, but recurrent acromegaly following initial postoperative hormonal remission is reported to occur in as many as 19% of cases.[28] Although regrowth of previously resected tumor has been documented,[16] these recurrences most likely represent continued growth of nonresectable tumor tissue, either due to parasellar invasion or involvement of neighboring neurovascular structures.[18,31,37] Stereotactic radiosurgery has emerged as a noninvasive adjuvant treatment modal-

Abbreviations used in this paper: GH = growth hormone; GKS = Gamma Knife surgery; IGF = insulin-like growth factor; LINAC = linear accelerator; SRS = stereotactic radiosurgery.

ity for such recurrent or surgically inaccessible lesions. Unlike conventional fractionated radiotherapy, SRS delivers focused radiation to a precisely defined target in a single session and minimizes radiation exposure to adjacent normal structures.[3,29,50] Over the past two decades, numerous case series have described the efficacy of SRS in patients harboring GH-secreting pituitary adenomas. In this report, we review the results from this robust body of literature, and highlight postradiosurgical rates of endocrinological remission and tumor growth control as well as assess the potential advantages and limitations of SRS in the multimodal management of acromegaly.

Methods

Data Acquisition

A PubMed search (National Library of Medicine) was performed to identify all articles pertaining to the use of SRS for the treatment of acromegaly. Surgical series describing endocrinological and radiographic outcomes were analyzed in detail and reference lists were reviewed for additional articles not identified in the original PubMed search. Pertinent clinical characteristics extracted from each report include the stereotactic radiosurgical unit; marginal radiation dose; rate of pituitary suppressive medication used during SRS; tumor size and prevalence of cavernous sinus invasion; rates of endocrinological remission and tumor growth control; and SRS-associated complications. Case series utilizing GKS, LINAC-based SRS, and CyberKnife radiosurgical systems are included in our analysis. Given a variety of confounding factors, however, no effort was made to directly compare the efficacies of these methods of SRS.

Radiosurgical Techniques

Unlike conventional radiotherapy, in which patients receive a target dose of radiation to the entire brain fractionated over numerous sessions, radiosurgery aims to deliver a high dose of radiation to a precise intracranial region during a single session.[27] The ability to focus ionizing radiation on discrete brain lesions while sparing critical adjacent neurovascular structures may improve local tumor control as well as reduce the adverse effects associated with traditional radiation therapies.[51] The Gamma Knife utilizes cross-firing beams from 201 cobalt-60 sources to deliver ionizing radiation (gamma rays) to an intracranial target. The most commonly used radiosurgical unit for pituitary lesions, this system allows for a high degree of 3D conformity between the radiation field and the target of interest and offers better preservation of surrounding normal structures than conventional radiotherapy.[18,19] Similar to the Gamma Knife, LINAC-based systems deliver beams of photon radiation in multiple arcs to a defined intracranial structure,[50] and allow neurosurgeons to target lesions with a high degree of fidelity and to minimize the extent of collateral damage to surrounding neurovascular elements.

Both the Gamma Knife and traditional LINAC-based systems require the use of a stereotactic frame for rigid immobilization of the head during the radiosurgical procedure. The CyberKnife is a newly developed LINAC-based system that uses image guidance software to adjust in real-time the precise location of radiation therapy and, thus, does not require the use of a stereotactic frame.[1] Irrespective of the radiosurgical unit employed, dose selection and treatment parameters vary depending on the tumor location and size, relationship of the adenoma to the optic apparatus and other eloquent structures, dose and timing of any pretreatment conventional radiotherapy, and other patient-specific characteristics.

Results

Tables 1 and 2 summarize data obtained from case series in which stereotactic radiosurgical procedures were employed in the multimodal management of GH-secreting pituitary adenomas. Across all series, more than 1350 patients underwent SRS using either Gamma Knife- or LINAC-based systems for the treatment of primary or recurrent acromegaly. The mean duration of endocrinological and radiographic follow-up ranged from greater than 6 months to 100 months. The average tumor volume was between 0.9 cm^3 and 11.3 cm^3 and, where reported, 21% to 100% of patients harbored lesions that extended into the cavernous sinus. The mean marginal radiation dose employed across all series ranged from 14.3 to 34.4 Gy. Approximately 71% of patients throughout the series had undergone transsphenoidal or transcranial neurosurgical resection of their pituitary adenoma prior to radiosurgery, while 11% had received antecedent conventional fractionated radiotherapy. Although reported in only half of the case series, approximately 75% of patients had discontinued all suppressive medications for more than 6 to 8 weeks prior to radiosurgery. While the definition of true endocrinological remission was quite variable among the series, approximately 47% of patients fulfilled the given criteria for hormonal remission, and an additional 32% achieved endocrinological normalization after radiosurgery with adjunctive medical therapy. Compared with preradiosurgical volumes, on average more than 97% of tumors decreased or remained the same in size at the time of the latest follow-up.

Endocrinological Remission and Control

Whereas the precise criteria for characterizing endocrinological remission following SRS were inconsistent across the case series, the most widely accepted definition is a random GH level less than 2 ng/ml or a GH level less than 1 ng/ml following an oral glucose tolerance test in addition to a normal IGF-I level when controlled for age and sex.[35] Importantly, these measurements are recorded while the patient is not taking pituitary suppressive medications. If the above criteria are met after radiosurgery with the aid of adjunctive medical therapy, the patient is considered to have achieved endocrinological control.[16] Using the aforementioned strict criteria for hormonal remission, the range of endocrinological normalization was 17% to 82%, and an additional 4% to 47% of patients achieved hormonal control following radiosurgery.[2,4,5,14,16,21,33,45–47,53,54,57,58] For instance, Pollock et al.[45] observed an endocrinological remission rate of 67% and Ikeda et al.[14] observed normalized hormonal levels in 82% of patients following GKS. Using LINAC-based SRS, Voges et al.[58] reported a true remission rate of 37.5%

TABLE 1: Summary of previously reported case series involving SRS in patients with acromegaly (Part I)*

Authors & Year	SRS Unit	No. of Patients	Mean FU (mos)	Interventions Prior to SRS (%)	Off Medication During SRS (%)	Mean Marginal Radiation Dose (Gy)	Cavernous Sinus Invasion (%)
Hayashi et al., 2010	GK	25	36†	surg (100)	NA	21.8†	100
Iwai et al., 2010	GK	26	84‡	surg (85)	85	20.2	35
Castinetti et al., 2009[4]	GK	43	100	surg (70)	53	NA	21
Cho et al., 2009	CK	6	35	surg (83)	NA	NA	NA
Swords et al., 2009	GK	10	38.5	CRT (100); surg (80)	40	NA	NA
Wan et al., 2009	GK	103	67†	surg (14)†	100	21.4	NA
Jagannathan et al., 2008	GK	95	57	CRT (5); surg (100)	71	22	35
Losa et al., 2008	GK	83	69‡	CRT (1); surg (100)	76	25 (goal)	NA
Pollock et al., 2008	GK	27	47‡	CRT (7); surg (93)	100	20‡	NA
Tinnel et al., 2008	GK	9	35‡	CRT (11); surg (75)	56	NA	NA
Pollock et al., 2007	GK	46	63‡	CRT (13); surg (93)	59	20‡	85
Roberts et al., 2007	CK	9	25	surg (89)	67	21	NA
Vik-Mo et al., 2007	GK	61	66	surg (92)	NA	26.5	NA
Jezková et al., 2006	GK	96	54	CRT (11.5); surg (74)	100	32	NA
Voges et al., 2006	LINAC	64	54	CRT (7)†; surg (53)†	NA	16.5	89†
Castinetti et al., 2005	GK	82	49.5	CRT (2); surg (77)	49	25.7	89
Kajiwara et al., 2005	CK	2	35†	CRT (10)†; surg (48)†	NA	14.3†	NA
Kobayashi et al., 2005	GK	67	63	CRT (3); surg (73)	37	18.9	NA
Attanasio et al., 2003	GK	30	46‡	CRT (13); surg (90)	60	20‡	NA
Choi et al., 2003	GK	9	42.5†	surg (32)†	NA	28.5†	NA
Jane et al., 2003	GK	64	>18	surg (100)	100	15†	NA
Petrovich et al., 2003	GK	6	41	CRT (10)†; surg (95)†	NA	15†	96†
Swords et al., 2003	LINAC	13	25‡	CRT (100); surg (77)	23	10 (mode)	67†
Feigl et al., 2002	GK	9	55†	surg (100)	NA	15†	NA
Pollock et al., 2002	GK	26	36†‡	CRT (21)†; surg (86)†	69	20.1†	70†
Ikeda et al., 2001	GK	17	56	surg (100)	100	25	100
Fukuoka et al., 2001	GK	9	42	surg (89)	NA	20	100
Izawa et al., 2000	GK	29	>6	surg (37)†	NA	22.5†	29
Shin et al., 2000	GK	6	43	surg (67)	100	34.4	100
Zhang et al., 2000	GK	68	34	CRT (4); surg (14)	100	31.3	NA
Hayashi et al., 1999	GK	22	16	surg (49)†	NA	22.5	24
Inoue et al., 1999	GK	12	>24	surg (100)	100	20.9	100
Kim et al., 1999[23]	GK	2	12†‡	none	100	22†	NA
Kim et al., 1999[24]	GK	11	27†	surg (55)	NA	28.7†	NA
Laws & Vance, 1999	GK	56	NA	NA	NA	NA	NA
Mokry et al., 1999	GK	10	46	CRT (4)†; surg (96)†	NA	16	NA
Landolt et al., 1998	GK	16	>17	CRT (44); surg (100)	69	25	NA
Lim et al., 1998	GK	16	25.5†	CRT (2)†; surg (51)†	NA	25.4†	22†
Martínez et al., 1998	GK	7	36†	surg (57)	NA	24.7	57
Mitsumori et al., 1998	LINAC	1	47	CRT (22)†	NA	NA	61†
Morange-Ramos et al., 1998	GK	15	20†	CRT (7); surg (87)	NA	28.7	76†
Pan et al., 1998	GK	16	29†	CRT (4)†; surg (16)†	NA	28.6	NA
Witt et al., 1998	GK	20	32	NA	NA	19	NA
Yoon et al., 1998	LINAC	2	49†	surg (96)†	NA	NA	NA
Park et al., 1996	GK	7	15†	surg (14)	NA	27.1†	NA

* CK = CyberKnife; CRT = conventional radiotherapy; FU = follow-up; GK = Gamma Knife; NA = not available; surg = transsphenoidal or transcranial surgery.

† Values represent data pertaining to both somatotroph and nonsomatotroph pituitary tumors.

‡ Median value.

TABLE 2: Summary of previously reported case series involving SRS in patients with acromegaly (Part II)*

Authors & Year	SRS Unit	No. of Patients	Mean Tumor Vol (cm^3)	Tumor Growth Control (%)	Criteria for Endocrin Remission§	Endocrin Remission (%)	Endocrin Control (%)¶	Adverse Effects (%)
Hayashi et al., 2010	GK	25	NA	100	NA	NA	40**	none
Iwai et al., 2010	GK	26	2.3	96	GH <2 or GH <1 after OGTT & IGF-I = N	38	4	HA (4); HP (8)
Castinetti et al., 2009[4]	GK	43	1.2	100	GH <2 or GH <1 after OGTT & IGF-I = N	42	NA	CNP (7)†; HP (21)†; TN (2)†
Cho et al., 2009	CK	6	2.6†	92†	GH <5 mIU/L	33	NA	VC (8)†
Swords et al., 2009	GK	10	NA	100	GH <5 mIU/L & IGF-I = N	10	20	HP (12)†
Wan et al., 2009	GK	103	2.3–21.5	95	NA	NA	37**	BN (2); HP (2)†
Jagannathan et al., 2008	GK	95	2.7	98	IGF-I = N	53	NA	HP (34); TLE (1); VC (4)
Losa et al., 2008	GK	83	NA	98	GH <2.5 & IGF-I = N	60	21	HA (6); HP (9)
Pollock et al., 2008	GK	27	NA	100	GH <2 & IGF-I = N	67	NA	HP (16)†
Tinnel et al., 2008	GK	9	NA	100	IGF-I = N	44	NA	CNP (11); HP (22)
Pollock et al., 2007	GK	46	3.3‡	100	GH <2 & IGF-I = N	50	NA	BN (2); HP (33); CAS (2)
Roberts et al., 2007	CK	9	2.5	100	IGF-I = N	44	12	HP (33)
Vik-Mo et al., 2007	GK	61	1.2	100	GH <2.6 mIU/L after OGTT & IGF-I = N	17	NA	HP (23)
Jezková et al., 2006	GK	96	2.2	100	GH <1 after OGTT & IGF-I = N	44	NA	HP (27)
Voges et al., 2006	LINAC	64	3.0	97	GH <2 & IGF-I = N	37.5	47	BT (3); HP (47)†; TLE (3)†; VC (1)†
Castinetti et al., 2005	GK	82	NA	NA	GH <2 & IGF-I = N	17	23	HP (17); TN (1); VC (1)
Kajiwara et al., 2005	CK	2	11.3†	95†	NA	NA	NA	none
Kobayashi et al., 2005	GK	67	4.4	100	GH <2	17	NA	HP (15); VC (11)
Attanasio et al., 2003	GK	30	NA	100	GH <2.5 & IGF-I = N	23	17	HA (3); HP (7)
Choi et al., 2003	GK	9	1.4†	100	GH <5 mIU/L	NA	50**	none
Jane et al., 2003	GK	64	NA	NA	IGF-I = N	36	NA	HP (28)
Petrovich et al., 2003	GK	6	3.7†	100	NA	NA	100**	HP (4)†; VC (4)†
Swords et al., 2003	LINAC	13	NA	100	GH <5 mIU/L & IGF-I = N	42	8	none
Feigl et al., 2002	GK	9	3.8†	94†	NA	NA	NA	HP (28)
Pollock et al., 2002	GK	26	4.9†	100	GH <2 & IGF-I = N	42	20	BN (5)†; HP (16)†
Ikeda et al., 2001	GK	17	NA	100	GH <1 after OGTT or IGF-I = N	82	NA	none
Fukuoka et al., 2001	GK	9	4.9	100	GH <5 & IGF-I = N	40	NA	none
Izawa et al., 2000	GK	29	7.1†	100	NA	NA	41**	BN (1)†; VC (1)†
Shin et al., 2000	GK	6	1.1	100	GH <10 mIU/L & IGF-I <450	67	NA	CNP (6)
Zhang et al., 2000	GK	68	3.0	100	NA	96	NA	HP (4); VC (1)
Hayashi et al., 1999	GK	22	7.3†	100	NA	41	NA	HP (5); VC (5)
Inoue et al., 1999	GK	12	NA	94†	NA	58	NA	NA
Kim et al., 1999[23]	GK	2	NA	100	NA	0	NA	NA
Kim et al., 1999[24]	GK	11	0.9†	>68	GH <5	45.5	NA	none
Laws & Vance, 1999	GK	56	NA	NA	IGF-I = N	25	NA	NA
Mokry et al., 1999	GK	10	2.9	100	GH <7 & IGF-I <380	NA	40	HP (30)
Landolt et al., 1998	GK	16	1.9	>55	GH <10 mIU/L & IGF-I <380	70	NA	none
Lim et al., 1998	GK	16	NA	92.5†	GH <2	38	NA	HA (36)†; HP (2)†; VC (2)†
Martínez et al., 1998	GK	7	4.3	100	IGF-I = N	71	NA	CNP (3)†
Mitsumori et al., 1998	LINAC	1	1.9†	100	NA	100	NA	HP (23)†; TLE (11)†

(continued)

TABLE 2: Summary of previously reported case series involving SRS in patients with acromegaly (Part II)* *(continued)*

Authors & Year	SRS Unit	No. of Patients	Mean Tumor Vol (cm^3)	Tumor Growth Control (%)	Criteria for Endocrin Remission§	Endocrin Remission (%)	Endocrin Control (%)¶	Adverse Effects (%)
Morange-Ramos et al., 1998	GK	15	1.5	>37†	GH <5 & IGF-I = N	20	NA	HP (16)†; TN (7)
Pan et al., 1998	GK	16	1.0	100	NA	100	NA	none
Witt et al., 1998	GK	20	NA	94	IGF-I = N	20	NA	NA
Yoon et al., 1998	LINAC	2	NA	100	GH <5	100	NA	HP (29)
Park et al., 1996	GK	7	NA	100	GH <5	57	NA	none

* BN = brain necrosis; CAS = carotid artery stenosis; CNP = cranial nerve palsy; Endocrin = Endocrinological; HA = headache; HP = hypopituitarism; N = normal value when controlled for age and sex; OGTT = oral glucose tolerance test; TLE = temporal lobe epilepsy; TN = trigeminal neuralgia; VC = visual complications.

† Values represent data pertaining to both somatotroph and nonsomatotroph pituitary tumors.

‡ Median value.

§ GH in ng/ml or mIU/L (as specified); IGF-I in ng/ml.

¶ Endocrinological control indicates postradiosurgical hormonal normalization with adjuvant medical therapy.

** Percentages indicate overall rates of hormonal normalization irrespective of postradiosurgical medical therapy.

and an additional endocrinological control rate of 47% in their series of 64 patients with acromegaly. When more lenient definitions were employed, the range of hormonal remission rates was 0 to 100% while rates of endocrinological control ranged from 8% to 100% at the time of the latest follow-up.[7–10,12,13,15,17,18,20,22–25,27,30,32,36,38–42,44,48,52,55,59–62] Using only a normalized IGF-I level as the criterion for hormonal remission, Jagannathan et al.[18] reported an endocrinological normalization rate of 53% at a mean follow-up time of 57 months. Zhang et al.[62] observed biochemical remission in 96% of their 68 patients, although the criteria for remission are not given. Not all series, however, documented such impressive rates of endocrinological remission at the time of last follow-up. As examples, Kobayashi et al.[25] and Castinetti et al.[5] observed hormonal normalization in only 17% of patients when they were not receiving medical therapy. Such disparities likely reflect important differences in patient populations, adenoma characteristics, preradiosurgical hormonal control, and treatment regimens.

Although disagreement existed across the case series, several studies identified factors that independently predicted postradiosurgical endocrinological outcomes. Choi et al.[8] found that a greater maximum radiation dose was associated with a higher rate of hormonal remission. Kim et al.[24] reported a similar finding, and also discovered that patients with larger tumor volumes were more likely to achieve biochemical remission than those with smaller masses. Interestingly, while the maximum radiation dose significantly predicted hormonal remission in these studies, Kim et al.,[24] Losa et al.,[33] Pollock et al.,[47] and Zhang et al.[62] found that the marginal radiation dose was not a significant prognostic factor. In addition, in the studies of Castinetti et al.[5] and Jezková et al.,[21] preradiosurgical GH and IGF-I levels were found to predict posttreatment outcomes. Not surprisingly, those patients with near-normal GH or IGF-I levels were more likely to achieve hormonal remission than patients with markedly abnormal baseline values. However, Landolt et al.[26] and Pollock et al.,[46,47] identified arguably the most meaningful prognostic indicator of postradiosurgical hormonal remission. In both series, the concomitant use of pituitary suppressive medications during radiosurgery was shown to reduce the overall rate of and increase the time to hormonal remission. Finally, despite a mean tumor growth control rate of 97% across all series, no study identified a significant correlation between change in adenoma size and eventual hormonal normalization.

Although the mean time to hormonal remission following adjuvant radiosurgery was not consistently reported across the case series in our analysis, several studies did record actuarial rates of endocrinological normalization. In the study by Jezková et al.,[21] while only 15% of patients achieved hormonal normalization 12 months after SRS, 29%, 44%, and 57% of patients were found to be in remission at 36, 60, and 96 months, respectively. Moreover, Vik-Mo et al.[57] reported normal IGF-I levels in 45%, 58%, and 86% of patients at 36, 60, and 120 months following radiosurgery, respectively. Finally, although Jagannathan et al.[18] observed an absolute remission rate of 53% with a mean time to remission of 30 months, a more detailed analysis of the data indicates that 29%, 42%, and 53% of patients achieved normalized IGF-I levels at 24, 48, and greater than 85 months after radiosurgery, respectively.

Tumor Growth Control

The rate of tumor growth control, defined as reduction or stabilization of tumor volume, ranged from more than 37% to 100% across all series, with an average rate of control of 97%. Jagannathan et al.[18] reported that 92% of patients with adequate radiographic follow-up demonstrated a decrease in tumor size following GKS and that an additional 6% showed no change in tumor volume. Voges et al.[58] treated 64 patients with acromegaly with LINAC-based SRS and reported that 23% experienced a reduction in tumor volume while 73% had tumors that did not change significantly in size. To date, the largest series evaluating the use of the CyberKnife in the treatment armamentarium of acromegaly is by Roberts et al.[48]

In this study, 9 patients received CyberKnife SRS and none demonstrated tumor enlargement at the time of last follow-up. Despite these impressive statistics, the rate of tumor growth control did not correlate with rates of endocrinological remission.[2,16,21,57]

Adverse Effects

The overall rate of serious complications following radiosurgery was quite low across all series. New-onset anterior pituitary hormone deficiency was the most common adverse effect, and was noted in 0 to 47% of cases.[2,4,5,9,13,16,18,20,21,25,32,33,38–40,44–48,54,55,57–59,61,62] Feigl et al.[9] reported a 28% incidence of hypopituitarism following radiosurgery, and noted that the degree of hormonal dysfunction was related to the radiation dose received by the pituitary stalk. However, the true incidence of SRS-induced hypopituitarism is difficult to assess accurately, as many patients have undergone prior resection or conventional fractionated radiation therapy, both of which independently increase the likelihood of developing anterior pituitary hormone dysfunction. For instance, in the study by Jagannathan et al.,[18] of the 4 patients who developed visual complications, 3 had received prior fractionated radiation therapy.

Despite the proximity of the optic apparatus to the pituitary gland, only 10 case series[5,7,13,17,18,25,32,44,58,62] in our analysis reported postradiosurgical visual complications, with Kobayashi et al.[25] demonstrating the highest incidence at 11%. The low rate of visual complications following SRS likely stems from each group's attempt to limit the dose received by the optic apparatus to 8–10 Gy. Moreover, Tinnel et al.[55] reported new-onset cranial nerve palsies in 11% of patients, although cranial neuropathies were only observed in 3 other studies.[4,36,52] Headache, trigeminal neuralgia, temporal lobe epilepsy, brain necrosis, and carotid artery stenosis were other documented complications of SRS, although these were noted relatively infrequently across all series. Although none of the case studies were adequately powered to identify parameters that predict postradiosurgical complication rates, several groups did note that adverse effects were more commonly observed in patients who had received prior fractionated radiation therapy.[18,47]

Discussion

Without proper control of systemic growth levels, patients with acromegaly will follow a course of insidious yet progressive decline. The use of pituitary suppressive medications, such as somatostatin agonists or GH receptor antagonists, may minimize some of the metabolic sequelae of GH excess, but many patients are either only partially controlled with these therapies or become resistant after extended treatment periods.[37] In addition, medical therapy is not curative and, therefore, lifelong treatment is required for adequate hormonal control. Current estimates demonstrate that 75% to 90% of patients with GH overproduction harbor a GH-secreting pituitary adenoma, and surgical removal remains the first-line treatment modality.[49] Not only does resection remove the source of GH excess, but it also relieves any compression or mass effect the tumor may be exerting on surrounding neurovascular structures.[28] Surgical extirpation is effective in inducing hormonal remission in more than 68% to 95% of patients with GH-secreting adenomas, yet a select cohort of patients develop recurrent acromegaly due either to regrowth of previously resected adenomatous tissue or to continued growth of surgically inaccessible tumor.[28,34] Prior to the development and modernization of current radiosurgical systems, fractionated radiation therapy was used in the treatment algorithm for patients with acromegaly refractory to medical and surgical interventions. Although early reports document endocrinological remission following radiotherapy in more than 60% of cases, these studies frequently employed definitions of remission that were more forgiving than current standards.[27] Mitsumori et al.[38] compared the efficacy of SRS and fractionated radiotherapy in the adjuvant treatment of hormone-secreting pituitary adenomas, and discovered that the overall incidence of endocrinological normalization was roughly equal between the 2 treatment modalities. However, patients who received SRS achieved remission in 8.5 months, whereas those in whom fractionated radiotherapy was administered did not reach hormonal normalization for 18 months. Similarly, Landolt et al.[27] directly compared GKS to traditional fractionated radiation therapy and found that the percentage of hormonal normalization was roughly similar between the 2 groups, but that the time to remission was much shorter in the radiosurgical group (17 months vs 85 months, respectively). In addition to a more rapid normalization of hormone levels, SRS is also associated with a lower rate and narrower spectrum of adverse effects than conventional radiotherapy. In the study by Landolt et al.,[27] 16% of patients receiving fractionated radiotherapy developed new-onset hypopituitarism whereas no complications were observed in the treatment arm that underwent SRS. Though no prospective, randomized, controlled trials have directly compared these two forms of radiation treatment, the relative safety and efficacy of SRS compared with traditional radiotherapy have engendered its use in modern clinical practice.

Although recent case series have adhered to a strict definition of endocrinological remission, earlier studies varied widely in their criteria for hormonal cure, and thus a large range of remission rates was observed (0 to 100%). At present, most groups consider the following conditions sufficient for endocrinological remission: 1) a random GH level < 2 ng/ml, or 2) a GH level < 0.5 ng/ml following an oral glucose challenge in addition to a normal IGF-I level when corrected for age and sex. Importantly, all measurements must be obtained while the patient is not receiving pituitary suppressive medications. However, Peacey and Shalet[43] demonstrated that GH feedback regulation was disrupted following radiation therapy, and therefore the interpretation of GH levels following radiosurgical procedures can be problematic. Moreover, given the diurnal and pulsatile secretion pattern of GH, it is often difficult to obtain accurate and true levels. On the other hand, IGF-I has a long half-life and stable concentration within the systemic circulation.[37] Because GH exerts most of its action through IGF-I, many neurosurgeons and endocrinologists have found single IGF-I measurements to faithfully represent GH activity. In fact, of the studies in our analysis in which a normal IGF-I level was the only criterion for hor-

monal cure, the rates of endocrinological remission ranged from 20% to 71%.[18,20,36,48,60] As hormonal remission rates following radiosurgery were noted in 17% to 82% of patients in studies in which the more stringent criteria were applied,[2,4,5,14,16,21,33,45–47,53,54,57,58] it appears that the definition of endocrinological remission is of variable consequence.

More important in the postradiosurgical assessment of the patient with acromegaly is the overall length of follow-up. Both Jezková et al.[21] and Jagannathan et al.[18] observed remission rates less than 30% when patients were evaluated 24 months after SRS. However, these rates rose to more than 50% when follow-up was performed for more than 85 months. In addition, Vik-Mo et al.[57] saw an endocrinological remission rate of 86% at 120 months compared with a 45% cure rate at 36 months of follow-up. As a result, to thoroughly assess the true efficacy of SRS in the management of acromegaly, patients should ideally receive routine endocrinological evaluations extending 84 to 120 months beyond the radiosurgical procedure. Lengthy and detailed follow-up is also necessary to diagnose cases of recurrent acromegaly. Jagannathan et al.[18] reported on 3 patients who developed recurrent symptoms of GH excess at 36, 56, and 114 months after SRS. Therefore, as the latency between radiosurgery and hormonal cure or recurrence can be quite long, lengthy endocrinological and radiographic follow-up is necessary to determine the ultimate efficacy of SRS in acromegaly.

The use of somatostatin agonists and GH receptor antagonists in the adjuvant treatment of acromegaly is common practice.[35,37] However, studies by Landolt et al.[26] and Pollock et al.[46,47] demonstrated that patients who concomitantly receive pituitary suppressive medications during radiosurgery experience lower rates of endocrinological normalization than those who terminate medical therapy more than 6 weeks prior to and 6 weeks after SRS. Although the precise mechanism governing this phenomenon is unknown, the current belief is that the suppressive medications place the tumor cells in a quiescent state in which their metabolic and proliferative potential is greatly diminished. By inhibiting cell cycling, these medical therapies reduce the sensitivity of somatotroph cells to the effects of ionizing radiation during DNA synthesis.[47] However, as no large-scale, prospective, randomized controlled trials have evaluated this question, it is difficult to draw definitive conclusions from small observations. In fact, both Iwai et al.[16] and Castinetti et al.[4] observed that pituitary suppressive medication use did not correlate with eventual hormonal outcome, and these differences in observation may be due in part to confounding factors present within each series. For instance, when the concurrent use of pituitary suppressive therapies during radiosurgery is not randomized, patients who require medical therapy for hormonal or symptomatic control are less likely to terminate the medication for a protracted period while those with near-normal endocrine levels or milder symptoms will better tolerate the hiatus in treatment. Therefore, the difference in remission rates observed by Landolt et al. and Pollock et al. may simply reflect a more aggressive and extensive disease phenotype rather than a true effect of medical therapy. Nevertheless, the practice of discontinuing medical therapy during the radiosurgical procedure has gained clinical acceptance, and certain groups have adopted this strategy in light of these data.[16] Irrespective of this controversy, pituitary suppressive medications are a critical component of the multimodal management algorithm for patients with acromegaly. For patients in whom radiosurgery is not completely curative, additional medical therapy can offer hormonal normalization in roughly 32% of patients, according to the series in our analysis.[2,5,8,12,16,17,33,39,44,47,48,53,54,58,59]

In addition to rates of hormonal cure of 17% to 82% following SRS, the mean rate of tumor growth control was more than 97% across the patient series (Table 2). Just as several studies demonstrated that endocrinological normalization increases with time, Mokry et al.[39] reported that tumor volumes progressively decline following SRS. Nevertheless, the stabilization or reduction in adenoma size is not significantly associated with hormonal remission. As a result, except in cases in which the adenoma is compressing critical structures, tumor growth control is an unreliable measure of the success of SRS for the treatment of GH-secreting pituitary lesions. In the future, it will be interesting to determine whether an association between adenoma size and hormonal cure becomes significant as series with larger populations and longer follow-up are reported.

Although surgery remains the first-line treatment for GH-secreting adenomas, resection of tumors that invade the parasellar region is fraught with difficulty.[28] Because numerous important neurovascular structures traverse the cavernous sinus, SRS offers a noninvasive means of accessing this region in a potentially safe manner. However, exposing the cavernous sinus to a high degree of ionizing radiation places the structures found within it at risk for injury. Nevertheless, in our analysis, new-onset cranial neuropathies and carotid artery stenosis were infrequently observed following SRS. Thus, unlike the optic apparatus, which is especially sensitive to radiation dosing, the structures traversing the cavernous sinus appear more resistant to injury.[50,56] Kobayashi et al.[25] reported postradiosurgical visual complications in 11% of the 67 patients with acromegaly in their study, yet new-onset optic neuropathies were only noted in a total of 10 case series in our review of the literature. To minimize damage to the optic apparatus, many groups attempt to limit the dose it receives to 8–10 Gy.[11] In addition, inherent in the dose-planning algorithm is an estimation of the distance between the target tissue and the optic structures. While a distance of at least 5 mm is desired, Petrovich et al.[6,44,50] demonstrated that distances of 1 to 2 mm are acceptable with highly conformal radiation profiles. Furthermore, postradiosurgical anterior hormone dysfunction was observed in 26 of the 45 case series in our analysis. The incidence of hypopituitarism ranged from 2% to 47% when reported, and the majority of this hypopituitarism was adequately controlled with supplemental medical therapy. Estimating the true incidence of hypopituitarism following radiosurgery, however, is difficult. Because many patients have received prior surgery or conventional radiotherapy, it is likely that new-onset anterior hormone dysregulation results from an accumulation of insults rendered through numerous treatment modalities.[50] Overall, complications following SRS for the treatment of acromegaly are uncommon,[35] and this low rate of adverse

effects reflects the reliability with which stereotactic radiosurgical procedures can deliver ionizing radiation that is highly conformal to the target tissue.

When evaluating the efficacy and potential limitations of SRS, it is important to consider the duration of endocrinological and radiographic follow-up. Unlike surgery, SRS requires a protracted period of time before normalization of hormone levels is recognized. A similar degree of follow-up and observation is necessary to gauge the overall safety of radiosurgical procedures. Jagannathan et al.[18] reported anterior hormone deficiencies in 34% of their 95 patients with acromegaly following SRS for failed transsphenoidal operations. A detailed analysis of these cases of new-onset hypopituitarism, however, reveals that the incidence was only 5% at 12 months after radiosurgery and that more than 49 months of follow-up were necessary to identify the 32 individuals with adverse effects. On the whole, despite a range of infrequent adverse effects, SRS is an efficacious component of the multimodal treatment paradigm for acromegaly. Although dose selection and other treatment parameters vary depending on an array of tumor- and patient-specific characteristics, it is our hope that future studies will more clearly define the optimal treatment strategy for acromegaly and identify the cohort of patients who will maximally benefit from SRS.

Conclusions

The goal of SRS in the management of GH-secreting pituitary lesions is to reduce hormone overproduction and control tumor growth while preserving normal brain tissue and minimizing adverse effects. In this regard, our analysis of the available literature concerning the use of SRS in acromegaly reveals that radiosurgical procedures induce endocrinological remission in 17% to 82% of patients and leads to effective tumor growth control in 97% of cases when data are analyzed across all series. In addition, because SRS is capable of precisely conforming the radiation field to the tumor target, the overall rate of adverse effects is remarkably low among the series in our analysis. Overall, SRS represents a safe and effective treatment option for patients with primary or recurrent acromegaly.

Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Weiss, Stapleton. Acquisition of data: Stapleton. Analysis and interpretation of data: Stapleton. Drafting the article: Stapleton. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors.

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Manuscript submitted June 14, 2010.
Accepted July 14, 2010.
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Neurosurg Focus 29 (4):E12, 2010

Radiation treatment strategies for acromegaly

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The high morbidity and mortality associated with acromegaly can be addressed with multiple treatment modalities, including surgery, medicines, and radiation therapy. Radiation was initially delivered through conventional fractionated radiotherapy, which targets a wide area over many treatment sessions and has been shown to induce remission in 50%–60% of patients with acromegaly. However, conventional fractionated radiotherapy takes several years to achieve remission in patients with acromegaly and carries a risk of hypopituitarism that may limit its use. Stereotactic radiosurgery, of which there are several forms, including Gamma Knife surgery, CyberKnife therapy, and proton beam therapy, offers slightly attenuated efficacy but achieves remission in less time and provides more precise targeting of the adenoma with better control of the dose of radiation received by adjacent structures such as the pituitary stalk, pituitary gland, optic chiasm, and cranial nerves in the cavernous sinus. Of the forms of stereotactic radiosurgery, Gamma Knife surgery is the most widely used and, because of its long-term follow-up in clinical studies, is the most likely to compete with medical therapy for first-line adjuvant use after resection. In this review, the authors outline the major modes of radiation therapies in clinical use today, and they critically assess the feasibility of these modalities for acromegaly treatment. Acromegaly is a multisystem disorder that demands highly specialized treatment protocols including neurosurgical and endocrinological intervention. As more efficient forms of pituitary radiation develop, acromegaly treatment options may continue to change with radiation therapies playing a more prominent role. *(DOI: 10.3171/2010.7.FOCUS10124)*

Key Words • **growth hormone** • **pituitary adenoma** • **radiotherapy** • **radiosurgery** • **Gamma Knife surgery** • **CyberKnife therapy**

Transsphenoidal microsurgery to resect the causative GH-secreting pituitary adenoma remains the initial treatment of choice in the majority of patients with acromegaly.[10,25,48,52,53,74,90] However, the optimal management of the 10%–50% of patients who do not enter remission after transsphenoidal surgery[13,52] and the 20% of patients who experience recurrence of acromegaly after transsphenoidal surgery[13] remains less clear. Radiation represents an evolving treatment modality for acromegaly that warrants consideration as an alternative to medical therapy for tumors refractory to transsphenoidal surgery.

The conceptual groundwork for focused irradiation of GH-secreting pituitary adenomas while avoiding damage to surrounding neural structures was established more than 50 years ago.[2,56,97] Since that time, substantial advances in radiation technology have yielded increasingly precise pituitary adenoma–targeting capability and consequently an expanded set of treatment options for acromegaly to supplement resection and hormonal suppression with medical management. A complex array of factors dictate treatment decisions for acromegaly in the modern era, including adenoma size, degree of secretory hyperactivity, invasion of surrounding structures, and therapeutic side effects and their particular impact in the patient in question. For these reasons, contemporary treatment of patients with acromegaly now routinely involves multiple disciplines, including neurosurgery, endocrinology, and radiation oncology.[1,3,27,34,47,62,64,65,76,78] Indeed, in cases of acromegaly, all 3 approaches (surgery, medication, and radiation) can be beneficial and can play a role in management. Thus, an expert panel, the Acromegaly Consensus Group, formed in 2000, publishes guidelines for acromegaly management, most recently in 2009. The recommendations are that tumors deemed completely resectable undergo surgery, with somatostatin analogs used in cases in which remission after surgery is not achieved. Tumors deemed incompletely resectable are treated with somatostatin analogs. Cases in which remission is not achieved with the use of somatostatin analogs are treated with pegvisomant if there is

Abbreviations used in this paper: CFR = conventional fractionated radiotherapy; GH = growth hormone; GKS = Gamma Knife surgery; IGF-I = insulin-like growth factor–I.

no mass effect on MR imaging, because the tumor growth that can occur with pegvisomant would be tolerated, or with radiation if there is mass effect on MR imaging.[63] However, because these recommendations are not based on randomized clinical trials, further studies will likely be needed to definitively determine the role of radiation therapy in achieving the best long-term outcome for patients with acromegaly. Here, we review the results to date with radiation as a treatment modality for acromegaly, and we outline future directions that might get us closer to a definitive understanding of the role of radiation in acromegaly management.

Methods

An online search for journal articles relevant to the topic was conducted using the PubMed Database by entering combinations of the MeSH terms "acromegaly," "radiosurgery," "radiation," "radiotherapy," "fractionated," "Gamma Knife," "Cyberknife," and "proton beam." Articles were limited to the English language. Captured articles were indexed by content using an electronic citation manager. Cited references within articles were also searched for relevancy to the topic. Articles describing independent retrospective studies of CFR and radiosurgery for acromegaly were detailed in table format (Tables 1 and 2).

Results

Conventional Fractionated Radiotherapy

Conventional fractionated radiotherapy is a direct descendant of the radiography devices first used by Béclère and Gramagna in 1909 to irradiate pituitary tumors in patients with acromegaly.[29] Today, CFR has been modified to deliver megavoltage doses of radiation in fractions separated over time to increasingly smaller intracranial target volumes. In the case of pituitary adenomas, a standard dose of 160–180 cGy 4–5 times per week over 5–6 weeks for a total dose of 45–50 Gy is typically performed (Table 1).[69] Using strict remission definitions that began to be adapted in the mid-1990s of GH level below 2 ng/ml and/or normalized IGF-I levels, most studies from the period 1997–2007 have reported remission rates of 35%–75% with CFR (Table 1). These remission rates typically take 10 years to achieve. The main factors identified in these studies that was predictive of achieving remission were the initial GH and IGF-I levels, as patients with higher levels have been shown to take longer to achieve remission and have lower remission rates.[13] Radiotherapy is typically followed by a maximal decrease in GH during the first 2 years, with the mean GH decreasing to 50%–70% of its initial value during this time, followed by a progressive slow decrease over the ensuing 10–20 years.[13]

Conventional fractionated radiotherapy treatment of acromegaly has been associated with high rates of hypopituitarism, ranging from 50% to 80% (Table 1).[50,51,66,83,96] The development of hypopituitarism after CFR has a similar time course as the development of remission, typically occurring 10 years after treatment (Table 1).[50,51,66,83,96] The overall incidence of new pituitary deficits after CFR is greater when pituitary function was already impaired prior to CFR.[7,9] Visual deficits after CFR occur in 5% of patients with acromegaly 7–12 months after treatment,[38] with many patients who suffer visual deficits having suprasellar tumor needing radiation treatment, suggesting that aggressive tumor debulking before CFR, using surgery to remove suprasellar tumor, will be vital to reduce the rate of visual deficits after CFR. Other toxicities, such as radiation necrosis and radiation-induced cerebral tumors occur in less than 1% of CFR-treated patients, with a mean latency of 7–24 years.[67] Vascular injury has been reported with a 1.7- to 2.8-fold increased risk for patients treated with CFR for pituitary adenomas, with the risk directly proportional to the total CFR dose and higher in patients treated previously with surgery and in patients with hypopituitarism.[24]

The pituitary dysfunction rate and time to remission has improved with the most recent study, published in 2007, in which a remission rate of 38% was achieved in a mean time of 6 years and an associated hypopituitarism rate of 47%.[38] However, the radiosurgical techniques described below still are associated with a much shorter time to remission and a lower rate of hypopituitarism, causing some to question the usefulness of CFR in the contemporary management of acromegaly.[5,68,87] Conventional fractionated radiotherapy could still prove useful in treating particularly large, aggressive GH-secreting adenomas with significant residual tumor after surgery due to invasion of bilateral cavernous sinuses or extension into the temporal lobe that cannot be safely treated with radiosurgery because adjacent elegant structures would be affected by the high-dose precise targeting of radiosurgery.[13,38]

Introduction to Stereotactic Radiosurgery

In contrast to CFR, which focuses single beams of high-energy radiation onto a small treatment field, radiosurgery, conceived in the 1950s,[55] delivers multiple low-energy beams toward a target with improved stereotactic accuracy and a suprathreshold integral dose. The principal advantage of radiosurgery is that it reduces the dose of radiation received by transirradiated tissue close to the target because the multiple low-energy beams converge at the target to create a dosimetry map in which the target receives a dose high enough to inactivate or kill tissue in the target, but a sharp falloff of radioactivity near the target lowers the dose received by adjacent structures compared with CFR. Stereotactic radiosurgery accomplishes this precise targeting in a single or few fractions, and the radiation can be delivered as photons using devices such as the Gamma Knife or CyberKnife or as charged particles using proton-beam radiosurgery.

In the 1990s, neurosurgeons began to use stereotactic radiosurgery to treat pituitary adenomas to improve on the remission rate, time to remission, and hypopituitarism rate associated with CFR.[19,28,32,39,43,44,57,61,71,72,77,82,89] The beam trajectories were calculated to spare critical structures near the pituitary adenoma, such as the optic chiasm.

Gamma Knife Surgery. Gamma Knife surgery is a

TABLE 1: Results of published series studying conventional fractionated radiotherapy in the treatment of acromegaly*

Authors & Year	No. of Patients	FU Time (yrs)	Mean Total Dose in Gy (range)	Mean No. of Fractions (range)	Remission Criteria	Remission Rate (%)	Mean Time to Remission (yrs)	New Posttreatment Hormone Deficiency		Induced Tumors
								% Patients	Mean Time to Deficit (yrs)	
Barkan et al., 1997	38	mean 6.8	46 (45–50)	24	normal IGF-I	5	5	NE	NE	NE
Powell et al., 2000	47	mean 5.2	47 (45–54)	26 (25–30)	normal IGF-I	60	10	32	NE	0
Biermasz et al., 2000	0	mean 11.3	40 (25–50)	19	normal IGF-I	74	10	50	10	0
Epaminonda et al., 2001	67	median 10	54 (40–75)	33 (30–35)	GH <2.5 ng/ml & normal IGF-I	65	15	60	NE	2 meningiomas, 1 pinealoma 9–22 yrs after CFR
Barrande et al., 2000	128	mean 11.5	52	29	GH <2.5 ng/ml & normal IGF-I	53	10	80	10	0
Cozzi et al., 2001	49	median 14	45	22	GH <2.5 ng/ml & normal IGF-I	10	10	8	10	2 meningiomas 27–30 yrs after CFR
Minniti et al., 2005	74	median 12	45	25	GH <1.0 ng/ml & normal IGF-I	47	10	80	10	0
Jenkins et al., 2006	884	median 7	45 (10–55)	25	GH <2.5 ng/ml or normal IGF-I	60	10	60	10	0
Jallad et al., 2007	89	mean 5.9	50 (32.4–60)							

* NE = not evaluated.

TABLE 2: Results of series reported in 2007–2009 studying radiosurgery for the treatment of acromegaly*

Authors & Year	No. of Patients	FU Time (yrs)	Modality (targeted field of treatment)	Dose	Remission Criteria	Remission Rate (%)	Mean Time to Remission (mos)	New Posttreatment Hormone Deficiency	
								% Patients	Time to Deficit (yrs)
Roberts et al., 2007	9	mean 2.1†	CyberKnife therapy (NR)	21 Gy‡	normal IGF-I	44	12	33	NR
Petit et al., 2007	22	median 6.3	PBRS (sella)	median 20 CGE	normal IGF-I	59	42	38	median 3–4.7†,§
Pollock et al., 2007	48	median 5.3†	GKS (tumor margins)	20 Gy¶	normal IGF-I & GH <2 ng/ml	50	36	33	median 2.7†
Vik-Mo et al., 2007	53	mean 5.5	GKS (tumor margins)	25 Gy‡	normal IGF-I	17	not stated	13	NR
Jagannathan et al., 2008	95	mean 4.8†	GKS (various)	22 Gy‡	normal IGF-I	53	29.8	34 (1.6)	mean 1.6†
Losa et al., 2008	83	median 5.8†	GKS (tumor margins)	25 Gy‡	normal IGF-I & GH <2.5 ng/ml	60	60	10	3.3%–4.9% cumulative risk at 5 yrs
Imran et al., 2009	12	median 2.4†	LINAC-based (tumor margins)	NE	normal IGF-I	33	NR	8	2 (in 1 patient)†
Swords et al., 2009	10	median 3.0†,**	GKS (tumor margins)	NE	normal IGF-I	80	NR	NR	NR
Cho et al., 2009	6	median 3.0†,**	CyberKnife therapy (tumor margins)	1983 cGy††	GH <5 mIU/L	33	15	0	
Ronchi et al., 2009	35	median 9.5†	GKS (tumor margins)	20 Gy¶	GH <2.5 ng/ml, normal IGF-I, & postglucose GH nadir <1 ng/ml	46	120	50	median 8.3†
Castinetti et al., 2009	43	mean 8.5 remission†; mean 8.2 uncured†	GKS (tumor margins)	24 Gy‡‡	GH <2 ng/ml &/or postglucose GH <1 ng/ml & normal IGF-I	42	50	NR for acro cohort	NR for acro cohort
Kobayashi, 2009	71	mean 5.3†	GKS (NR)	18.9 Gy‡	GH <1 ng/ml	4.8	NR	14.6	NR

* acro = acromegaly; CGE = cobalt Gray equivalents; NR = not reported; PBRS = proton-beam radiosurgery.
† Conversion from months.
‡ Mean margin dose.
§ Depending on the hormone deficit.
¶ Median margin dose.
** Calculated median from raw data to nearest tenth.
†† Mean total dose.
‡‡ Mean isodose 50.

neurosurgical technique using a source of ^{60}Cobalt to deliver narrow beams in a single session with stereotactic precision and accuracy to destroy or inactivate a target with minimal damage to the surrounding brain. In acromegaly, mean doses of 20 to 25 Gy are delivered to the tumor margin, higher than the 10–20 Gy mean margin doses used for GKS of endocrine inactive adenomas, because the goal when using radiosurgery to treat acromegaly or other endocrine active adenomas is to completely disrupt hormonal hypersecretion, while the goal with GKS for endocrine inactive adenomas is to prevent adenoma growth. Gamma Knife surgery is the most extensively studied radiosurgery method in the treatment of acromegaly (representative case shown in Fig. 1). A landmark 1998 study compared GKS with CFR for acromegaly at a single institution and found that stereotactic radiosurgery had a mean time to normalization of GH and IGF-I of 1.4 years, far less than the mean time to normalization of 7.1 years seen with CFR ($p < 0.0001$).[50] In addition, the rate of new pituitary deficits was 16% in the CFR-treated group, while no patient treated with GKS developed a new pituitary deficit.[50] While this study did not specify the remission rates achieved in the 2 groups, around the time of this 1998 study, 6 other studies of GKS for acromegaly reported a wide range of remission rates of 31%–58%. These rates are slightly below rates seen in CFR, but they increased somewhat in radiosurgery studies published in the latter portion of the next decade (Table 2). While it does still appear that the published remission rates seen with CFR (Table 1) may be higher than the acromegaly remission rates seen with GKS (Table 2), it should be emphasized that the CFR series in the literature tend to be slightly older studies that preceded the recent increasing use of medical treatments for acromegaly, while the GKS studies tend to be more recent studies occurring at a time when patients receiving radiation are those with partial or total resistance to medical treatments. All of these follow-up studies have consistently confirmed a faster remission and lower rate of hypopituitarism with GKS (Table 2) than with CFR (Table 1).[4,16,30,35–37,41,46,58,60,81,85,91–93,95,98] Gamma Knife surgery is typically followed by a maximal decrease of GH secretion during the 1st year, followed by progressive slow decrease over the next 5 years.[13] Achieving timely remission of acromegaly is vital because, like Cushing disease,[21] the mortality remains elevated in patients with acromegaly even after hormonal normalization,[22] possibly due to irreversible physiological effects of elevated GH. And achieving timely remission with reduced risk of hypopituitarism is also important because of studies showing increased long-term mortality associated with hypopituitarism.[94]

Several groups have identified the following 4 factors predictive of achieving remission in patients undergo-

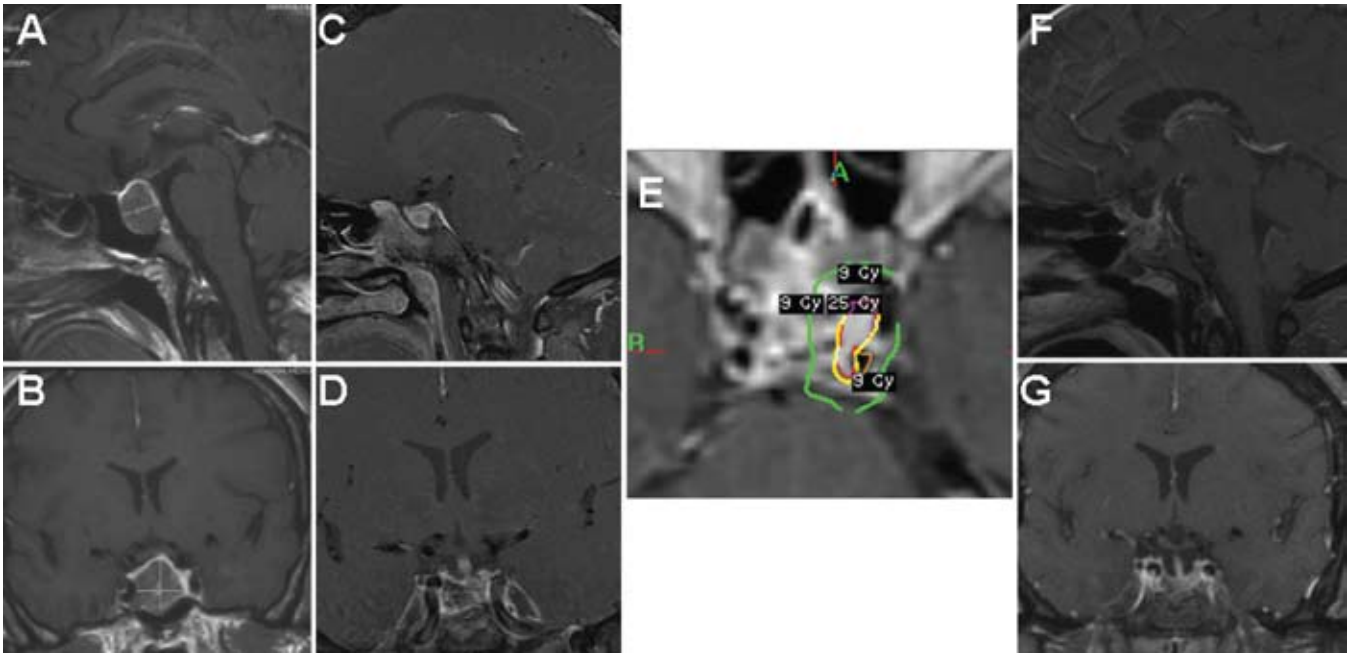

Fig. 1. Case example. A 55-year-old woman presented with acromegaly (GH level 36 ng/ml [reference level < 11 ng/ml] and IGF-I = 1200 μg/L [reference range 81–225 μg/L]) and a 15 × 22 × 18–mm adenoma with left cavernous sinus invasion, seen on T1-weighted Gd-enhanced sagittal **(A)** and coronal **(B)** images. The patient underwent transsphenoidal surgery for the adenoma 2 weeks after the MR images were obtained. Six weeks after surgery, postoperative MR imaging revealed residual tumor in the left cavernous sinus, seen again on T1-weighted Gd-enhanced sagittal **(C)** and coronal **(D)** images. Six weeks after surgery, her postsurgical GH and IGF-I levels were 2 ng/ml and 344 μg/L, respectively. The latter value, along with MR imaging showing residual adenoma, was indicative of persistent postoperative acromegaly. Four months after transsphenoidal surgery, the patient underwent GKS to target residual adenoma in the left cavernous sinus, prescribed to a dose of 25 Gy to the 54% isodose line **(E)**. Twenty months after radiosurgery and 2 years after diagnosis, the IGF-I level normalized to 200 μg/L, the GH level remained normalized to 1 ng/ml, and T1-weighted Gd-enhanced sagittal **(F)** and coronal **(G)** images showed no residual enhancing tissue, consistent with remission of acromegaly.

ing GKS for acromegaly: 1) discontinuation of antiacromegaly medications at the time of radiosurgery, namely dopamine agonists, somatostatin analogs, and/or the GH antagonist pegvisomant; 2) lower pretreatment GH and IGF-I levels; 3) higher total integral radiation dose; and 4) higher maximal dose to the adenoma.[15]

Several groups have found that patients who are off all acromegaly medications at the time of radiosurgery achieve greater biochemical remission,[81,95] with the most comprehensive study reporting a hazard ratio of 4.2 in patients who had not been on medications 1 month prior to radiosurgery.[81] Antiacromegaly medications could inhibit radiosurgery efficacy for 3 possible reasons as follows: 1) patients unable to wean off antiacromegaly medications prior to radiosurgery may have tumors more resistant to treatment, regardless of modality; 2) medical therapy for acromegaly reduces metabolic activity in pituitary adenoma cells, making these cells less proliferative and therefore less responsive to radiation therapy, which causes DNA damage in rapidly replicating cells at the time of treatment;[49] and/or 3) the somatostatin analogs, for example, octreotide, contain disulfide bonds that are reduced to expose free thiols, which help to scavenge DNA-disrupting oxygen-free radicals that arise from ionizing radiation and cause the DNA damage that precedes radiation-induced cell death. Although these explanations are indirectly substantiated by recent data, they remain speculative at this point, and other studies have found no effect of antiacromegaly medications on remission, such as a 2005 study from a French group that failed to find any correlation between the probability of remission and the discontinuation of antiacromegaly medications for at least 3 months at the time of radiosurgery.[13]

Several other groups have found that lower pretreatment IGF-I levels are predictive of likelihood of remission, while adenoma size is not.[58,81] A 2007 study demonstrated IGF-I levels less than 2.25 times the upper limit of normal (hazard ratio 2.9) as predictive of remission in a multivariate analysis.[81] Another group found that initial GH and IGF-I levels while off somatostatin analogs were significantly higher in patients who did not achieve remission than in patients with biochemical remission,[13] which suggests that, even if being off antiacromegaly medications at the time of radiosurgery does not improve the chances of remission, another benefit of being off medications at the time of GKS is that the pretreatment hormone levels provide a better understanding of the likelihood of achieving remission with radiosurgery.[85]

A study of 42 patients with endocrine active adenomas identified 2 other factors predicting remission in a multivariate analysis, higher total integral dose ($p = 0.005$), and maximum dosage ($p = 0.001$).[19] The integral dose represents the total energy absorbed by the adenoma during radiosurgery in gram rad units (1 g rad unit represents 100 ergs/g), while the maximum dosage represents the highest dose any part of the adenoma receives in Gray units.

As with CFR, hypopituitarism is the primary adverse effect associated with GKS, but, as stated above, its occurrence seems to be less frequent with GKS than with CFR. The risk of hypopituitarism in patients with acromegaly undergoing GKS seems to be higher in 1) those who have undergone previous transsphenoidal surgery; 2) those who have undergone previous CFR; 3) the degree of target definition, as lack of an enhancing abnormality on MR imaging causes the hypopituitarism risk with GKS to be as high as it is with CFR; and 4) the dose to the pituitary stalk. In identifying factors predicting the development of hypopituitarism in patients with pituitary adenomapatients who are undergoing radiosurgery, a German group retrospectively reviewed 92 cases (of which 9 had acromegaly) and found that the pituitary stalk in patients who went on to lose pituitary function received 7.7 Gy, compared with 5.5 Gy in those without subsequent loss of pituitary function ($p = 0.03$),[26] suggesting that the pituitary stalk may be even more radiosensitive than the overlying optic chiasm, where doses are typically kept below 10 Gy.[81]

Optic neuropathy is the second most frequent adverse event seen with GKS for patients with acromegaly, but it occurs far less often than hypopituitarism, occurring in less than 1% of patients with acromegaly treated with GKS. Other rare side effects that have been reported with CFR, such as radiation necrosis, vascular injury, and the development of secondary tumors, appear to be even less common with radiosurgery than with CFR, but CFR has been studied with longer-term follow-up than radiosurgery, and these adverse effects take 10–25 years to develop. A recent review reported 13 cases of radiation necrosis in 1567 patients with pituitary adenomas treated with radiosurgery, but half of the patients who developed radiation necrosis had received prior CFR, making the etiology of the necrosis difficult to definitively determine.[11]

As the number of studies showing the efficacy of GKS in treating acromegaly continues to grow, it will be important to account for differences in remission criteria, the frequency with which antiacromegaly medications are used, and variations in laboratory assays. For example, a 2009 study of GKS by Ronchi et al.[85] found a 10-year time to remission, which is significantly slower than the times to remission reported with other series (Table 2). But these results reflect the fact that Ronchi et al. reported remission rates in patients who were off somatostatin analog therapy at the time of radiosurgery using a strict 3 criteria must be met definition of remission (normal oral glucose tolerance test, "safe" GH levels, and normal IGF-I level), whereas other studies with faster times to remission included patients on medical therapy at the time of treatment and used only 1 or 2 criteria for remission. Furthermore, rates of hypopituitarism can be underestimated in the absence of adequately sensitive assays.[85] In the future, it is hoped that conflicting results with regard to time to remission, remission rates, factors predicting remission, and factors predicting adverse effects like hypopituitarism may be addressed through large multicenter trials with central review, in which patients are ideally randomized according to variables of interest, such as those on or off acromegaly medications for specific durations of time at the time of treatment.

CyberKnife Therapy

The CyberKnife system is a frameless, image-guided, robotic radiosurgical device that delivers linear accelera-

tor (LINAC)–based x-ray radiation in one or a few sessions with accuracy comparable to frame-based methods such as the Gamma Knife. To date, however, few studies have been published on the efficacy of CyberKnife treatment of GH-secreting pituitary adenomas. The Stanford University group reported the largest series of 9 patients with acromegaly treated with CyberKnife from 1998 to 2005. The group achieved remission in 44% of patients, with a 1-year mean time to remission and a 33% rate of new hormone deficiency.[84] Two other reports noted similar efficacy using the CyberKnife, although a larger series is needed to confirm these results.[17,42] The CyberKnife has several potential advantages over the Gamma Knife in that it can treat intracranial and extracranial tumor sites. One particularly significant advance with regard to treatment of acromegaly is the potential to reduce rates of hypopituitarism even further by using dose hypofractions rather than single fraction–based therapy.[31]

Proton-Beam Radiosurgery

Proton-beam radiosurgery takes advantage of the superior dose distribution of protons versus photons, resulting from the peak in the energy distribution of protons (that is, the Bragg-peak) before they come to rest at the treatment depth. This method of irradiation was widely used for treatment of acromegaly in the 1960s and 1970s.[33,45,56] Its popularity, however, waned as more advanced technologies, such as GKS, were optimized for less frequent side effects.[6,59,83] Still, interest in this modality remains, and the treatment continues to be studied at the 7 proton beam centers in the US. A 2007 study of proton-beam radiosurgery in treating acromegaly found a 59% remission rate, among the highest reported for acromegaly radiosurgery, and a 33% rate of hypopituitarism,[79] suggesting the benefit of the superior dose distribution in the region of the target must be weighed against a greater dose being delivered to the normal gland or pituitary stalk as well.

Comparison of Radiation With Medical Management

Medical management of acromegaly has a mean time to achieve remission of 6 months with octreotide[73] and 9 months with pegvisomant.[12] These numbers are less than the 30- to 60-month time to remission reported in most studies of radiosurgery. However, the cost of medical management is $20,000–$25,000 US dollars per year for short-acting octreotide,[66] $29,000–$35,000 per year for long-acting formulations like Sandostatin LAR,[8] and $40,000–$65,000 per year for pegvisomant,[70] far more than the $8,000–$16,000 cost of a single radiosurgery treatment.[18,54,88] Thus, as radiosurgical techniques continue to improve, thereby lowering the morbidity and increasing the efficacy of radiosurgery for acromegaly, clinicians caring for patients with acromegaly will need to consider the cost effectiveness of a single radiosurgery treatment followed by medical management that can be discontinued if remission is achieved, compared with not doing radiosurgery and being committed to the cost of lifelong medical management, as most,[80] but not all,[86] studies have suggested the need for lifelong continuation of medicines in medically treated acromegaly.

Conclusions

These results from studies of multiple modalities of radiosurgical treatment of acromegaly will require verification in larger series conducted over a longer period of time. Future experimental directions designed to improve the remission rates with radiosurgery for acromegaly could include use of somatostatin receptor scintigraphy to localize adenoma cells[75] and better define a target for radiosurgery. Another goal of future studies will be to document the long-term recurrence rates in patients with acromegaly who achieve remission after radiosurgery. Overall, GKS, present in 109 centers in the US and 30 centers in Europe, is so far the most extensively studied modality with several reports involving 10-year patient follow-up data. Large single-fraction and high-precision doses of radiation with steep falloff are features of radiosurgery that make it an attractive option for adjuvant therapy for refractory acromegaly after transsphenoidal surgery. Its use may be optimally effective in patients who have discontinued their antiacromegaly medication at the time of treatment, have low basal GH and IGF-I levels, and receive higher total integral radiation doses and higher maximal doses. Future multicenter clinical trials that are currently under development such as the Phase II Radiation Therapy Oncology Group (RTOG) trial 0930 will study radiosurgery for the treatment of persistent acromegaly after transsphenoidal surgery and will be poised to confirm the findings to date from smaller studies and to address the other as yet unanswered questions described in this review.

Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Aghi. Acquisition of data: Rowland. Analysis and interpretation of data: both authors. Drafting the article: Rowland. Critically revising the article: both authors. Reviewed final version of the manuscript and approved it for submission: Aghi. Study supervision: Aghi.

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Manuscript submitted May 11, 2010.
Accepted July 6, 2010.
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Neurosurg Focus 29 (4):E13, 2010

A systematic analysis of disease control in acromegaly treated with radiosurgery

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Object. Stereotactic radiosurgery (SRS) has emerged as an adjuvant radiation-based therapy for pituitary adenomas. Here, the authors present a systematic analysis of SRS for growth hormone–secreting adenomas to characterize the efficacy of SRS in the treatment of acromegaly.

Methods. A comprehensive search of the English language literature revealed 970 patients with new, recurrent, or persistent acromegaly that had been treated using SRS along with assessable and quantifiable outcome data. Articles published between June 1998 and September 2009 were included in the analysis. Patient outcome data were aggregated and investigated based on tumor size, radiosurgery dose, and clinical outcomes both with and without medication.

Results. The overall disease control rate without medication was 48%–53%, and the overall disease control rate with or without medication was 73%. The overall mean duration of the reported follow-up was 48.5 ± 25.8 months. The mean overall tumor volume in this analysis was 2.11 ± 1.16 cm^3. The Pearson product-moment correlation coefficient for tumor volume and cure rate was not significant ($r = 0.0668$, $p = 0.8546$).

Conclusions. Data from this analysis suggest that tumor size may not be a significant prognostic factor in disease control after radiosurgery for acromegaly. The overall disease control rate was approximately 48% without suppressive medications after radiosurgery for acromegaly. With the advancement of increasingly sophisticated stereotactic planning and tumor targeting, the precision of radiosurgery may continue to improve in the treatment of acromegaly.
(DOI: 10.3171/2010.7.FOCUS10170)

Key Words • stereotactic radiosurgery • acromegaly • growth hormone • pituitary adenoma • insulin-like growth factor–I

Acromegaly is an endocrine disorder characterized by the excess production of GH, generally by hypersecreting pituitary adenomas, resulting in progressive somatic disfigurement and increased morbidity and death due to the systemic effects of organ overgrowth.[9] The control of GH and its primary mediator IGF-I has been associated with a reduction in the mortality risk.[11,20,21,29,32]

Historically, the primary treatment for GH-producing pituitary adenomas has been resection and/or medical management. The reported rates of biochemical cure following surgical removal has varied based on tumor size and the definition of a cure, but is generally considered to range from 75%–95% for microadenomas and 40%–68% for macroadenomas. Note that the latter lesion type affects the majority of patients.[5,6,9,14,15,25,31,35,44] Remission rates achieved using purely medical therapies have improved over the past decade, with several studies reporting biochemical control in approximately 70% of patients. But current medical therapies, such as somatostatin analogs and GH antagonists, must be taken lifelong and are costly.[5,6,9,14,15,25,31,35,44]

Radiation treatment has typically been used when surgery is not an option or has left residual tumor and/or when medical therapy has failed.[3,7,12,17,36,43] Stereotactic radiosurgery has largely supplanted traditional external beam radiation therapy for pituitary adenomas. Through the use of stereotactic precision, beams of radiation are delivered specifically to the target tissue, thereby avoiding surrounding normal neuronal tissue.[2,13,50] The efficacy of SRS as well as surgery for the treatment of GH-secreting pituitary tumors is debated largely because of inconsistent methods of analysis and endocrine criteria throughout the past decade of studies. Furthermore, the criteria defining "remission" and "cure" have evolved and become more stringent over time. Earlier studies assessing only serum GH levels are now considered wholly inadequate. A recent consensus from the Acromegaly Consensus Group regarding the criteria for cure in acromegaly has further

Abbreviations used in this paper: GH = growth hormone; IGF-I = insulin-like growth factor–I; SRS = stereotactic radiosurgery.

tightened the level of endocrine remission, requiring a normal age-adjusted IGF-I level plus GH levels dropping below 1 ng/ml with the oral glucose tolerance test.[18] Pure outcome analyses of sole surgical, medical, or radiation treatment for acromegaly are important but do not necessarily reflect current clinical management protocols, since more than one are often used. From the patient's perspective, what is desired is endocrinological control.

Here, we summarize the most recent data regarding the SRS treatment of GH-secreting adenomas to characterize the efficacy of SRS in the treatment of acromegaly. In addition to compiling data pertaining to disease remission, our goal was to assess the rate of disease control in patients continuing medical therapy after SRS.

Methods

Article Selection

A Boolean PubMed search was conducted using the key words "stereotactic radiosurgery," "acromegaly," "pituitary adenomas," and "growth hormone adenomas," alone and in combination. This query revealed 26 primary reports describing over 970 patients with new, recurrent, or persistent acromegaly who had received SRS as either primary or adjuvant therapy. Articles published between June 1998 and September 2009 were included in our analysis. Inclusion criteria for the articles were as follows: 1) the treatment of GH-secreting pituitary adenomas using SRS, 2) adequate follow-up data for clinical outcome aggregation and analysis, 3) definitions of "biochemical cure" or "disease remission following treatment," and 4) reported median or mean time of follow-up. Patient outcome data were then aggregated and evaluated based on tumor size, radiosurgery dose, and clinical outcomes both with and without continued medical therapy.

Data Extraction

Patient outcomes from individual and aggregated cases were extracted from each paper and analyzed for clinical characteristics. Those cases without follow-up or clinical treatment data were excluded. All other pituitary tumor variants, such as craniopharyngiomas, Rathke cysts, and other adenomas, were not included in this analysis. Data were then analyzed as a whole and stratified based on tumor size, radiosurgery dose, and endocrine control rate both with and without continued medical therapy. "Disease control" meant "meeting the criteria for biochemical remission in patients off medical therapy" and "normalization of age-adjusted IGF-I levels in patients on continued medical therapy." Tumor volume was assessed in mean tumor volume of centimeters cubed. The clinical outcome of endocrine cure reported in each study was also analyzed.

Statistical Analysis

The raw statistical data and patient information were aggregated and tabulated using Microsoft Excel (Microsoft Corp.). All results were statistically analyzed using a Fisher exact test, a Pearson correlation coefficient, or a t-test when appropriate (GraphPad Software). Tests for significance were 2-sided with a p value of 0.05 considered statistically significant. Continuous data variables are presented as the means ± SDs unless otherwise noted.

Results

Results of Systematic Analysis

Twenty-six studies totaling 970 patients who received SRS for GH-producing pituitary adenomas met the inclusion criteria (Table 1).[1,7,8,10,16,19,22,23,25–28,30,33,34,37–42,45,47–49,51] The mean reported patient age was 45.2 ± 3.78 years. The overall mean duration of reported follow-up was 48.5 ± 25.8 months, and the overall median duration of reported follow-up was a similar 46.6 ± 20.4 months. The mean time to remission was 28.2 ± 13.7 months. The overall mean tumor volume was 2.11 ± 1.16 cm^3.

Analysis of Endocrine Parameters and SRS

Twenty-four of the 26 studies included in the analysis reported remission rates in patients off medical therapy at the time of assessment. Of these 951 patients, 472 (49.6%) achieved biochemical remission following SRS based on study-dependent endocrine criteria.[1,7,8,10,16,19,22,23,25–27,30,37–42,45,47–49,51] When considering only those studies that used GH < 2.5 ng/ml or oral glucose tolerance test, GH < 1 ng/ml and normal IGF-I compared with age- and sex-matched controls as their criteria for biochemical remission, 44.5% of patients achieved disease control following SRS without medication. Utilizing a more stringent criteria of age-matched IGF-I normalization levels in series of 10 patients or more, our analysis revealed a similar 52.5% disease control rate in 506 patients with acromegaly treated using SRS. This subset of patients had a similar overall mean age of 44.9 ± 2.35 years.

Ten studies provided endocrinological control rates with patients continuing medical therapy. Hormone normalization was achieved in 60.3% of patients when including those still on pharmacological therapies following SRS treatment.[1,8,23,30,37,40–42,47,48] Pharmacological interventions before and/or after radiosurgery included both the short- and long-acting somatostatin agonists subcutaneous octreotide and octreotide-LAR or lanreotide, respectively,[30,42] the dopamine agonist cabergoline,[8,40] or the GH receptor antagonist pegvisomant.[30,42,48] Biochemical remission was defined as meeting study-specific endocrinological criteria for cure only while on 1 or more of the above-mentioned medications. However, separate criteria, namely IGF-I levels, were used to measure treatment outcomes in patients on pegvisomant, as GH levels are unreliably assayed while on this drug.[30,42,48] The majority of patients involved in this analysis were refractory to medical treatment prior to undergoing radiosurgery. Although they could not meet biochemical remission criteria on medications prior to SRS, 14.2%–16.7% of medically refractory patients had normalized GH and IGF-I levels on the same doses of medication following radiosurgery.[1,30,48]

Discussion

On account of the increased morbidity and mortality

TABLE 1: Studies including patients who received SRS for GH-producing pituitary adenomas*

Authors & Year	No. of Patients w/ Acromegaly	Mean Age (yrs)	Criteria for Endocrinological Remission	Cure Rate		Mean Tumor Vol (cm^3)	Median Dose to Tumor Margin (Gy)	FU Time (mos)	
				w/o Meds	w/ Meds			Median	Mean
Castinetti et al., 2009†	43	42.7	GH <2 ng/ml &/or OGTT GH <1 ng/ml & normal IGF-I	42					50
Ronchi et al., 2009	35	45	GH <2.5 ng/ml, normal IGF-I, & OGTT GH <1 ng/ml	46	50		20	114	103
Swords et al., 2009†	10	51	GH <1.8 ng/ml & normal IGF-I‡§	29	43		10	36	38.5
Pollock et al., 2008†	27	46	GH <2 mg/ml & normal IGF-I	67			20	46.9	
Jagannathan et al., 2008	95	43	normal IGF-I	53	67		22	49	57
Losa et al., 2008	83	42.6	GH <2.5 ng/ml & normal IGF-I	60	84	1.1	21.5	69	
Vik-Mo et al., 2007	53	47	GH <1 ng/ml & normal IGF-I or OGTT GH <1 ng/ml	17		1.23	26.5		66
Roberts et al., 2007	9	43.3	normal IGF-I	44	56	2.46	21¶		25.4
Pollock et al., 2007	46	45	GH <2 ng/ml & normal IGF-I	50		3.3	20	63	
Jezková et al., 2006	96	48.8	GH <1 ng/ml in OGTT & normal IGF-I	57.1		1.4	35	54	53.7
Castinetti et al., 2005	82	53	GH <2 ng/ml & normal IGF-I	17	40		26		49.5
Gutt et al., 2005	44	43	normal IGF-I	48		1.5	18	22.8	
Attanasio et al., 2003	30	46	GH <2.5 ng/ml & normal IGF-I	23	40	1.43	20	46	42.8
Choi et al., 2003†	12	NR	GH <1.8 ng/ml	50		†	†	†	†
Swords et al., 2003†	12	47.4	GH <1.7 ng/ml & normal IGF-I	50	58	†	†	25	
Petrovich et al., 2003†	6	NR	GH <5.0 ng/ml	100	100	†	†		
Pollock et al., 2002†	26	NR	GH <2 ng/ml & normal IGF-I	42	62	†	†	†	†
Ikeda et al., 2001	90	47	cure: OGTT GH <2 ng/ml & normal IGF-I; remission: normal IGF-I**	57			25		58.8
Fukuoka et al., 2001	9	35.7	GH <5 ng/ml & normal IGF-I	50		4.9	20	36	42
Landolt et al., 2000	31	47.4	GH <5 ng/ml & normal IGF-I	45		2.6	24.5		19.2
Shin et al., 2000	6	51	GH <3.8 ng/ml & IGF-I <450 ng/ml	67		1.1	34.4		42.7
Zhang et al., 2000	68	44.3	GH <12 ng/ml	96			31.3		34
Mokry et al., 1999†	10	46	GH <7 ng/ml & IGF-I <380 IU/ml		40	2.9	16		45.9
Landolt et al., 1998	16	41.3	GH <3.8 ng/ml & IGF-I <50 IU/L	69			25		16.8
Lim et al., 1998†	16	41.6	GH <2 ng/ml	37.50			†		
Morange-Ramos et al., 1998†	15	42	GH 5 ng/ml & normal IGF-I		20	1.5	28	20	

* FU = follow-up; NR = not reported; OGTT = oral glucose tolerance test.
† Growth hormone–secreting adenomas only subset of study; cannot extrapolate certain statistics as they are averaged over all tumors types.
‡ Patients on pegvisomant subtracted from total number of patients in cure analysis as GH could not be reliably analyzed.
§ Includes patients on pegvisomant as well (10 patients).
¶ Dose to tumor bed.
** Extrapolated as only 42 of 60 patients with normal IGF-I had oral glucose tolerance test.

rates associated with elevated GH and IGF-I levels, hormone normalization remains the primary end point in the treatment of patients with acromegaly.[18] To date, disparate cutoffs for biochemical remission and increasingly stringent consensus criteria that define remission have made it difficult to appreciate the true efficacy of SRS in the treatment of GH-secreting pituitary adenomas. In our analysis of studies published within the past decade, the rate of disease remission no longer requiring hormone suppressive therapy by study-specified criteria was 48%–53%. When only the studies with stricter criteria for endocrine remission were included (GH < 2.5 ng/ml and IGF-I of age- and sex-matched controls), the rate of cure decreased only modestly—to 45%. However, the most updated consensus on the criteria for the cure of acromegaly dictates disease remission to be when GH < 1 ng/ml and IGF-I levels are those of age- and sex-normalized controls.[18] Although it is difficult to assess true rates of cure based on these measures, it is reasonable to infer that they would be considerably less than initially appreciated.

Assessing the rates of endocrinological cure is difficult given the paucity of studies with true long-term follow-ups (> 10 years). If the experience from Cushing disease is any indication, in which short-term surgical remission rates of > 75% reported by many authors is contrasted by long-term data that suggests that the recurrence rate exceeds 50% short-term remission rates reported in acromegaly series must be regarded accordingly.[5,6,9,14,15,25,31,35,44] This is especially true for older series using less stringent biochemical outcome criteria. As a result, there will be a significant proportion of surgical patients who either fail to achieve remission or have disease recurrence.

Medical control of acromegaly continues to improve and may continue to contribute as an adjuvant to surgical therapy. For some patients, intolerable side effects preclude continued treatment. In others, medical therapy fails to achieve normalization of IGF-I. Whether this is due to tumor resistance or excessive disease burden remains unclear. With lifelong medical management of acromegaly, the concept of endocrinological "control" is logical and required. The concept of "control" for published surgical and radiation treatment series has largely been absent, with most authors implying that short-term remission would extrapolate to long-term cures.

The control of functional pituitary adenoma growth has been attributable to the normalization of hormone levels in hypersecreting endocrine tumors. The former end point in GH-secreting tumors of the pituitary is readily achieved, as illustrated by a recent review in which 95% of patients across multiple series had either stable tumor sizes or decreased tumor volumes on serial imaging following SRS.[24] With larger tumors, greater extension into critical structures, such as the cavernous sinus and optic chiasm, can limit the efficacy of SRS by prohibiting the margin doses used around these structures,[22] which may be an inherent bias in these SRS treatment studies of acromegaly. Future prospective studies evaluating the physical characteristics of tumors, including their size and invasion of structures, will be needed to better address the importance of these factors on clinical outcome.

There are some obvious limitations in this systematic analysis of SRS treatment of GH-secreting pituitary adenomas.[4,46] The inconsistent criteria used to define disease remission make it difficult to appreciate the actual efficacy of SRS in normalizing GH and IGF-I levels in acromegaly patients with hyperfunctional pituitary adenomas. Moreover, other prognostic and outcome measures, such as side effects, baseline endocrine function, and posttreatment hormone levels, are inconsistently reported. The diverse range of methods and data reported in these various studies limits the number of variables and the regression analysis that can be performed in our study. Whether the patient was on suppressive medications prior to radiosurgery and if that affected clinical outcomes should also be evaluated in future prospective studies. Limited data presentation also made it difficult to analyze specific groups on suppressive medication at the time of radiosurgery compared with groups not on suppressive medication. Lastly, the retrospective nature of our analysis does not permit actuarial or time-dependent analysis for prognostic factors or clinical characteristics, but it does highlight critical correlations that warrant further investigation with large prospective cohort studies. By utilizing an aggregated database, the large number of patients in this analysis permits an encompassing multicenter analysis of SRS for acromegaly and may minimize the inherent error and bias in any one particular study.

Conclusions

In summary, we report the results of a large aggregated analysis of SRS treatment in patients with acromegaly. Utilizing this systematic data permits analysis of this patient population with increased statistical power and expansive international results while minimizing inherent error and institutional bias. The overall disease control rate was approximately 48%–53% for patients no longer taking suppressive medications after radiosurgery for acromegaly. Hormone normalization appears to be improved to 60.3% of patients when including those still on pharmacological therapies following SRS treatment. With the advancement of increasingly sophisticated stereotactic planning and tumor targeting, the precision of radiosurgery may continue to improve in the treatment of acromegaly.

Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Yang, Kim. Acquisition of data: Yang, Kim. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: Yang, Bergsneider. Statistical analysis: Yang, Kim, Bergsneider. Administrative/technical/material support: Kim, Bergsneider. Study supervision: Yang, Bergsneider.

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Manuscript submitted June 16, 2010.
Accepted July 9, 2010.
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Neurosurg Focus 29 (4):E14, 2010

Pharmacological management of acromegaly: a current perspective

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Acromegaly is a chronic disorder of enhanced growth hormone (GH) secretion and elevated insulin-like growth factor–I (IGF-I) levels, the most frequent cause of which is a pituitary adenoma. Persistently elevated GH and IGF-I levels lead to substantial morbidity and mortality. Treatment goals include complete removal of the tumor causing the disease, symptomatic relief, reduction of multisystem complications, and control of local mass effect. While transsphenoidal tumor resection is considered first-line treatment of patients in whom a surgical cure can be expected, pharmacological therapy is playing an increased role in the armamentarium against acromegaly in patients unsuitable for or refusing surgery, after failure of surgical treatment (inadequate resection, cavernous sinus invasion, or transcapsular intraarachnoid invasion), or in select cases as primary treatment. Three broad drug classes are available for the treatment of acromegaly: somatostatin analogs, dopamine agonists, and GH receptor antagonists.

Somatostatin analogs are considered as the first-line pharmacological treatment of acromegaly, although efficacy varies among the different formulations. Octreotide long-acting release (LAR) appears to be more efficacious than lanreotide sustained release (SR). Lanreotide Autogel (ATG) has been shown to result in similar biological control as octreotide LAR, and there may be a benefit in switching from one to the other in some cases of treatment failure. The novel multireceptor somatostatin analog pasireotide, currently in Phase II clinical trials, also shows promise in the treatment of acromegaly. Dopamine agonists have been the earliest and most widely used agents in the treatment of acromegaly but have been found to be less effective than somatostatin analogs. In this class of drugs, cabergoline has shown greater efficacy and tolerability than bromocriptine. Dopamine agonists have the advantage of oral administration, resulting in increased use in select patient groups. Selective GH receptor antagonists, such as pegvisomant, act by blocking the effects of GH, resulting in decreased IGF-I production despite persistent elevation of GH serum levels. Thus far, tumor growth has not been a concern during pegvisomant therapy. However, combination treatment with somatostatin analogs may counteract these effects. The authors discuss the latest guidelines for biochemical cure and highlight the efficacy of combination therapy. In addition, the effects of pharmacological presurgical treatment on surgical outcome are explored. *(DOI: 10.3171/2010.7.FOCUS10168)*

Key Words • **acromegaly** • **octreotide** • **lanreotide** • **pasireotide** • **pegvisomant** • **growth hormone**

Acromegaly is a chronic disorder characterized by elevated GH secretion with a resultant increase in serum IGF-I level. A pituitary adenoma is the most common cause of the disorder. Persistently elevated levels of GH and IGF-I lead to significant morbidity and mortality. Complications of acromegaly include, but are not limited to, acral growth, cardiovascular disease, insulin resistance and diabetes, arthritis, hypertension, and sleep apnea. All of these adverse complications individually and collectively lead to a shortened life span. With GH-secreting tumors being the most common cause of acromegaly, other symptoms related to the tumor itself are often present in patients with these lesions. These symptoms include headaches and visual disturbances due to the mass effect on the optic nerve and chiasm.

Abbreviations used in this paper: ATG = Autogel; GH = growth hormone; GHRH = GH-releasing hormone; IGF = insulin-like growth factor; LAR = long-acting release; SC = subcutaneous; SR = sustained release.

Progressive expansion of GH-secreting tumors can also lead to loss of pituitary function and variable degrees of hypopituitarism. In children, in whom the epiphyseal growth plate is not closed, excessive GH secretion leads to progressive linear growth as the predominant symptom, clinically manifesting as gigantism.

The goals of treatment should include complete tumor removal, alleviation of symptoms, and control of complications.[13] Control of excessive GH secretion can be achieved through surgical removal of the tumor, radiotherapy, and medical treatment.[27] In this review, we examine the pharmacological management of acromegaly, with a focus on the efficacy and side-effect profile of medical therapy.

Pathophysiology of Acromegaly

The molecular genetics of tumorigenesis in acromegaly have been recently elucidated. Development and differentiation of somatotrophs, GH-producing cells in the anterior pituitary, are influenced by a gene named the *Prophet of Pit-1 (PROP1)*, which is responsible for the embryological development of the cells of the Pit-1 (POU1F1) transcription factor lineage. The binding of Pit-1 to the GH promoter in the cell nucleus results in development and growth of somatotrophs and subsequent GH transcription. Growth hormone is a 191–amino acid polypeptide synthesized and secreted in a pulsatile fashion by the anterior pituitary. Growth hormone–releasing hormone (GHRH) stimulates the synthesis and secretion of GH while somatostatin inhibits GH release, with both traveling in the portal vein and acting on somatotroph-specific transcription factors (Fig. 1). The effects of GH are mediated by GH receptors found primarily in the liv-

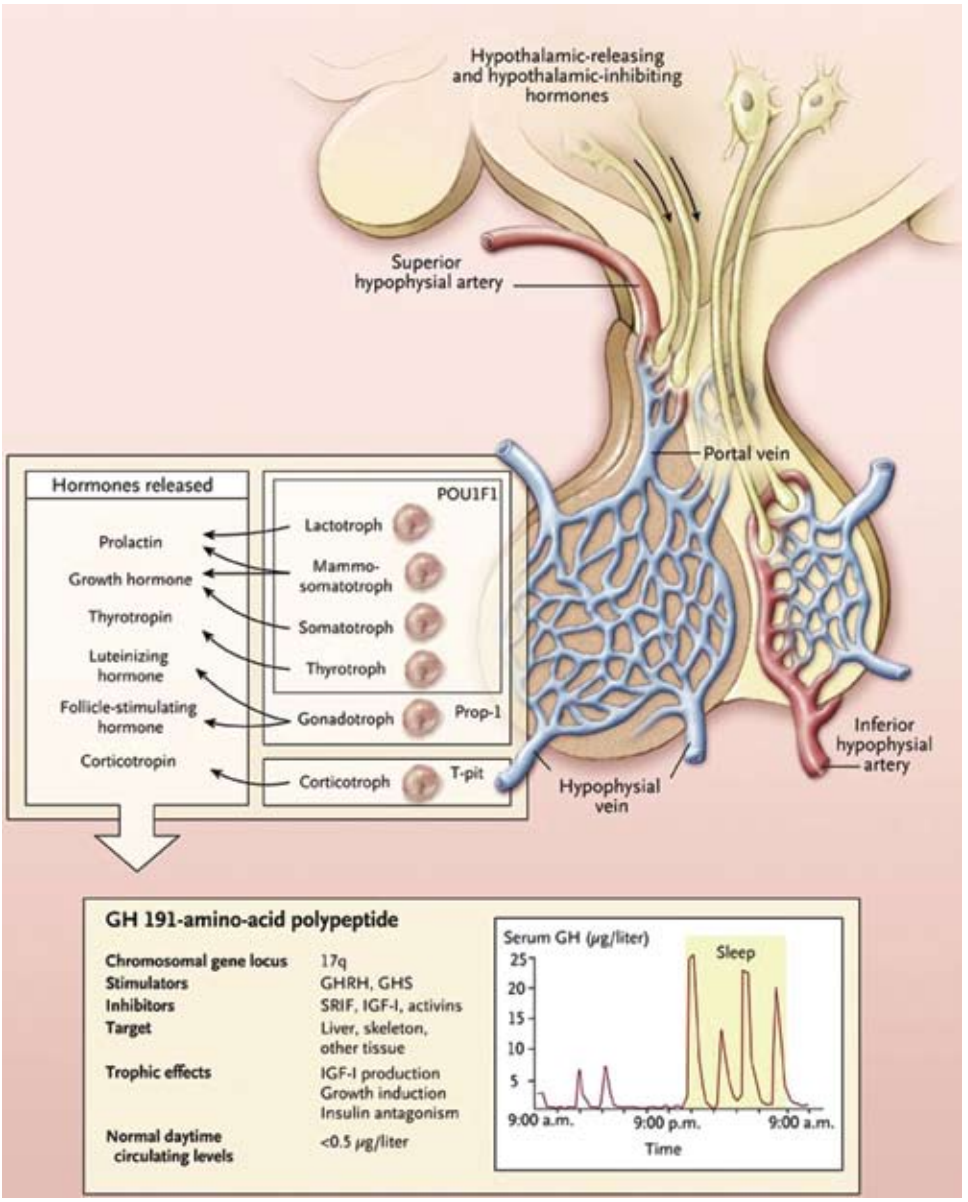

Fig. 1. Hypothalamic-pituitary axis: control of GH secretion. Reproduced with permission from Melmed S: Medical progress: acromegaly. **N Engl J Med 355:**2558–2573, 2006. Copyright © 2006 *Massachusetts Medical Society. All rights reserved.*

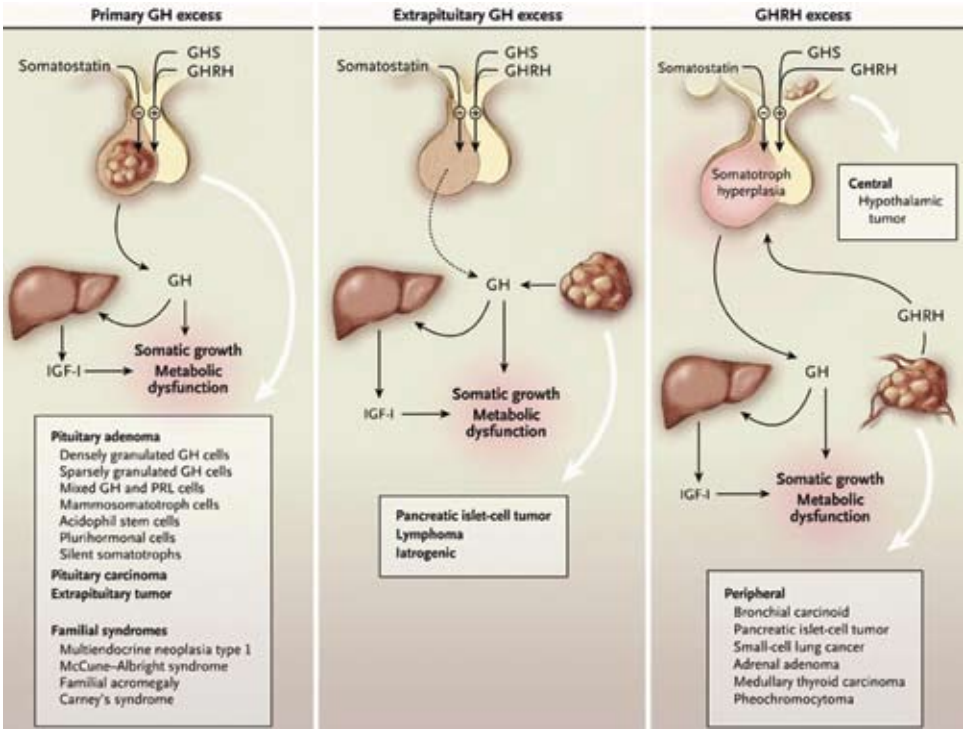

Fig. 2. Causes of acromegaly: excessive GH or GHRH. Reproduced with permission from Melmed S: Medical progress: acromegaly. **N Engl J Med 355:**2558–2573, 2006. Copyright © 2006 *Massachusetts Medical Society. All rights reserved.*

er and cartilage. Activation of the GH receptor results in phosphorylation of the receptor and Janus kinase 2 (JAK2) followed by the binding of signal transducer and activator of transcription (STAT) proteins to the complex. The STAT proteins then become phosphorylated, translocate into the cell nucleus, and initiate transcription of target proteins, such as IGF-I, which induces cell proliferation and inhibits apoptosis. The development of a GH-secreting tumor is the result of variables that affect the development and growth of somatotrophs and their hormone production. Approximately 40% of tumors appear to harbor a mutation in the α-subunit of the G_s protein that results in constitutive activation of cyclic AMP. Overexpression of the pituitary tumor–transforming gene (PTTG) protein and lost expression of the growth arrest and DNA damage-inducible (GADD) 45γ protein, a proapoptotic factor, has been demonstrated in GH-secreting pituitary adenomas. Overproliferation of somatotrophs and the resultant excessive secretion of GH results in acromegaly.[27]

The majority of somatotroph tumors are macroadenomas, but there have been rare instances of pituitary carcinomas. Up to 40% of GH-secreting pituitary adenomas cosecrete other pituitary hormones, especially prolactin and thyrotropin, leading to additional clinical manifestations. Other rare causes of primary GH excess include familial syndromes, such as Carney syndrome, multiple endocrine neoplasia Type I, McCune-Albright syndrome, and familial acromegaly. Extrapituitary causes of excess GH can result from ectopic hypersecretion of GH by pancreatic islet-cell tumors or lymphoma. Finally, GH excess can result from somatotroph hyperplasia due to excess GHRH production by central hypothalamic tumors or peripheral neuroendocrine tumors (Fig. 2).[27]

Biochemical Criteria for Diagnosis of Acromegaly

Acromegaly is diagnosed by finding an elevated IGF-I level compared with the age- and sex-adjusted normal range and a failure to suppress GH in response to an oral glucose tolerance test (OGTT). Unlike normal subjects, patients with acromegaly do not suppress GH secretion to very low levels with a glucose load. A post-OGTT GH level of less than 1.0 μg/L is the most recent cutoff level used to separate individuals without acromegaly from those with the disorder. As newer and more sensitive immunological assays become available, the cutoff points to define acromegaly may need to be adjusted accordingly.[13,18]

Overview of the Management of Acromegaly

Treatment of this disease requires optimal interaction between the management team members. Our focus in this article will be on patients with GH-secreting adenomas because they represent more than 98% of cases of acromegaly. All authorities in the field believe that surgery by an experienced neurosurgeon is the treatment of choice for GH-secreting adenomas. In experienced hands, this treatment leads to disease control in 50% of patients. Some patients, however, might refuse surgery or could be poor candidates for this procedure. In addition, there are a large number of patients in whom surgery is not curative and who would require additional treatment. Available options

include various forms of irradiation and medical therapy. While radiation therapy can be effective, it takes years to show its benefits in controlling GH secretion. Thus, even patients given all forms of radiation therapy would require additional treatments to control GH secretion until radiation effects become apparent. With the availability of newer and more effective agents, the focus on medical therapy has intensified to the point that some researchers and practitioners advocate it to be the primary therapy in most patients. The following section will address available medical therapies and their efficacies, advantages, and disadvantages.

Somatostatin Analogs

First introduced in the 1980s, somatostatin analogs have been widely used in the treatment of acromegaly. The concept is to mimic the physiological inhibitory action of somatostatin on the anterior pituitary gland. Two endogenous, biologically active forms of somatostatin are formed by the cleavage of prosomatostatin: SRIF-14 and SRIF-18.[27] Five different somatostatin receptor subtypes, $sst_{1–5}$, have been characterized. These subtypes are 7–transmembrane domain G-protein–coupled receptors.[38] The importance of delineating the subtypes becomes apparent when one considers the expression profile in normal pituitary gland and pituitary adenomas as well as the receptor selectivity of drugs. Studies have shown that the human pituitary gland primarily expresses the sst_1, sst_2, sst_3, and sst_5 receptors.[30,37] Additionally, GH secretion by human fetal somatotroph cells appears to be regulated by the sst_2 and sst_5 receptors.[47] When pituitary adenomas were investigated, the sst_1, sst_2, sst_3, and sst_5 receptor subtypes were also shown to be expressed. Additionally, most human GH-secreting pituitary tumors primarily express the sst_2 and sst_5 receptors.[50]

Octreotide SC was the first somatostatin analog available for clinical use. Initial dosage is 100 μg injected subcutaneously 3–4 times daily, titratable to a maximum of 1.5 mg/day. The dosing regimen of 3–4 times daily is required to maintain therapeutic serum levels because of the 2-hour half-life. To reduce the inconvenience of multiple injections per day and increase compliance, long-acting formulations have been developed. Octreotide LAR was the first long-acting formulation and is based on octreotide delivered in polymeric microspheres.[19] The starting dosage is 20 mg intramuscular injection every 4 weeks and can be titrated up to 40 mg. Octreotide has been shown to act primarily at the sst_2 receptor subtype.[49] Lanreotide was the second long-acting somatostatin analog developed and is available in 2 formulations: lanreotide SR and lanreotide ATG. Lanreotide ATG is currently the only formulation available in the US. Lanreotide SR consists of lanreotide packaged in a biodegradable polymer microparticle and is given as a 30-mg intramuscular injection every 7–14 days. Lanreotide ATG, on the other hand, consists of lanreotide acetate in an aqueous solution packaged in prefilled syringes for deep SC injection. It is available in 60-, 90-, and 120-mg mixtures. Like octreotide, lanreotide appears to be sst_2-preferential. Pasireotide (SOM230), the newest somatostatin analog, is a novel multireceptor ligand analog with high affinity for the somatostatin receptor subtypes $sst_{1–3}$ and sst_5.[44] Since most GH-secreting pituitary adenomas predominantly express sst_2 and sst_5 receptor subtypes, pasireotide may potentially be more effective than octreotide and lanreotide at suppression of GH secretion.

The reported biochemical efficacy of somatostatin analogs in the treatment of acromegaly varies greatly by study. In an extensive meta-analysis by Freda and colleagues,[17] results from 44 trials were analyzed, comparing the efficacy of octreotide LAR and lanreotide SR. The authors concluded that the efficacy of octreotide LAR is greater than that of lanreotide SR among patients unselected for prior somatostatin analog responsiveness. It was also shown that efficacy was similar when treatments were given as primary or secondary therapy. In their review of somatostatin analog formulations, Murray and Melmed[32] found that octreotide LAR was slightly more effective than lanreotide SR in the biochemical control of acromegaly. Lanreotide ATG is the primary formulation of lanreotide currently used clinically, but there are only a handful of studies comparing the efficacies of octreotide LAR and lanreotide ATG. Results from nonrandomized open-label studies have suggested that lanreotide ATG is at least as effective as octreotide LAR.[2,4,42] A randomized crossover trial by Andries and colleagues[3] further supports the findings of equal efficacy between octreotide LAR and lanreotide ATG. Additionally, their study suggests that some patients who experience treatment failure or adverse effects may benefit from a switch between the 2 drugs. Pasireotide, which is currently in Phase II clinical trials, has demonstrated biochemical control in 27% of patients after 3 months of treatment in a recent study. As the authors of this randomized multicenter trial have reported, the study was not designed or powered to compare the efficacy of pasireotide to octreotide, which was first self-administered for 28 days. However, pasireotide shows promise as a new treatment for acromegaly.[39]

Another important parameter to consider in the medical management of acromegaly is the effect on tumor shrinkage. A number of studies have investigated the antitumor effects of somatostatin analogs, and their data has been examined in various reviews. From a total of 22 studies, Bevan[8] found that 217 (45%) of 478 patients who were treated with octreotide SC had significant tumor shrinkage. It was also noted that tumor shrinkage was seen in 110 (51%) of 217 patients treated primarily with octreotide SC compared with 22 (27%) of 82 patients who received octreotide adjunctively after surgery and/or radiation treatment. Freda and colleagues[17] showed that, of 468 patients treated with octreotide SC, 40.8% had significant decreases in tumor size. In considering studies involving octreotide LAR treatment, tumor size reduction was shown in 103 (57%) of 180 patients. As with octreotide SC, primary treatment with octreotide LAR resulted in a higher percentage of patients with tumor shrinkage than secondary treatment did (80% vs 28%). Studies of lanreotide SR showed decreases in tumor size in 62 (24%) of 263 patients. As with the other drugs, primary therapy with lanreotide SR showed a greater degree of tumor-size reduction than secondary therapy (31% vs 9%). The caveat is that, in a few of the octreotide LAR studies, patients were preselected

for drug responsiveness, which could falsely elevate the response rate. When data were combined from all the studies, 382 (42%) of 920 patients had a decrease in tumor size. Again, primary therapy showed a more pronounced effect on tumor shrinkage than secondary therapy did (52% vs 21%).[8] The meta-analysis by Freda and colleagues[17] supports the general finding that primary treatment results in higher rates of tumor shrinkage than secondary treatment. Melmed and colleagues[29] reported similar findings in a review, noting that significant tumor reduction was found in 36.6% of 424 patients receiving primary somatostatin treatment. Bevan[8] suggested that this observation may be the result of alterations in tumor anatomy, such as fibrosis or scarring, caused by prior surgery or radiotherapy. Overall, among the different somatostatin analogs, octreotide LAR has shown greater rates of tumor size reduction than octreotide SC and lanreotide SR.[8]

The side-effect profile and safety of somatostatin analogs has been well studied. Generally, they are well tolerated and fairly safe. Among the side effects, gastrointestinal symptoms, including nausea, diarrhea, and abdominal pain, are the most commonly reported. Biliary tract abnormalities, such as biliary sludge and cholelithiasis, have also been known to occur. In addition, somatostatin analogs have the potential to impair the secretion of insulin, which is of particular concern in acromegaly, a condition that already has an increased risk of impaired glucose tolerance and diabetes.[6,48]

Dopamine Agonists

Like somatostatin analogs, the dopamine agonists inhibit GH secretion in pituitary tumors but do so by binding to D_2 receptors. Dopamine receptors exist in 5 subtypes with specific distribution in tissue. D_2 receptors are found in the anterior and intermediate lobes of the pituitary.[31] Bromocriptine, a nonselective dopamine agonist, was the first to be widely used since it became available in 1974. Unfortunately, it has been found to be less effective when compared with somatostatin analogs. Additionally, acromegaly—as compared with prolactinomas—requires more frequent and higher doses of bromocriptine for treatment. Cabergoline, a more selective D_2 receptor agonist, has a longer half-life (62–115 hours) and demonstrated better efficacy and tolerability.[1,31] Other dopamine agonists, such as lysuride, pergolide, quinagolide, and terguride, have been studied but were found to be less effective than bromocriptine and cabergoline.

Dopamine agonists, however, have advantages over other pharmacological treatments. They can be taken orally as opposed to requiring injection, and are perhaps less expensive than octreotide. These drugs can be used alone or as an effective adjunct to somatostatin analog therapy. Among all GH-secreting adenomas, dopamine agonists are the most effective in patients with pituitary tumors that cosecrete prolactin or thyrotropin.[1]

Side effects of dopamine agonists include constipation, nausea, postural dizziness, and nasal congestion. The adverse responses can be minimized if the drug is started at a low dose with a slow increase and taken with food. It should be noted that, in patients with Parkinson disease, there is evidence that the high dose of cabergoline used for treatment is associated with valvular heart disease. While cardiac abnormalities have not been demonstrated in patients with pituitary adenomas on cabergoline, monitoring patients receiving higher than regular doses is recommended.[28]

Chimeric Compounds

Dopamine agonists have been reported to suppress GH levels in some patients with acromegaly.[20] Furthermore, the combination of a somatostatin analog and a dopamine agonist has been suggested to work synergistically.[16,24] Rocheville and colleagues[41] subsequently demonstrated that somatostatin and dopamine receptors can form hetero-oligomers with enhanced receptor activity. Several chimeric molecules with both somatostatin and dopamine receptor affinity have been developed. BIM23A387, which has selective binding to sst_2 and D_2 receptors in cultured somatotropic tumor cells, has been shown to have greater GH suppression compared with an individual agonist or a combination.[43] To date, there have been no published clinical studies for BIM23A387. Another chimeric molecule, BIM23A760, has an affinity for sst_2, sst_5, and D_2 receptors. It has demonstrated more potent inhibition of GH secretion than sst_2, sst_5, and D_2 agonists and pasireotide.[21] A variety of other novel chimeric molecules have been investigated and show potential for treatment.[22]

Growth Hormone Receptor Antagonists

Pegvisomant represents the first in a novel class of drugs that act on GH receptors. It is a genetically engineered, pegylated analog of human GH that functions as a selective GH receptor antagonist. Pegvisomant competes with physiological GH for binding, thus preventing receptor dimerization and signaling, resulting in decreased IGF-I production. The mechanism of action blocks the effects of excessive GH instead of inhibiting its secretion and so can function independent of tumor receptor expression or type.[52] Because the drug is pegylated, it has an increased half-life of approximately 6 days and a reduced possibility of antibody formation.[51] Pegvisomant is available in 10-, 15-, and 20-mg SC injections. The initial loading dose is a 40-mg SC injection; it is followed by maintenance dosages of 10 mg daily, adjustable to a maximum maintenance dose of 30 mg daily.

Trainer and colleagues[51] investigated the efficacy of pegvisomant in a 12-week randomized placebo-controlled study of 112 patients with acromegaly. They reported a dose-dependant normalization of serum IGF-I levels, with 89% of patients in the 20-mg daily dose group and improvements in clinical symptoms in all pegvisomant-treated groups. Another study found similar results when analyzing the long-term efficacy of pegvisomant in 160 patients treated for up to 18 months. The investigators report that 87 (97%) of 90 patients treated for at least 12 months attained normal serum IGF-I levels.[51] In a recent study from the German Pegvisomant Observational Study, 76.3% of patients treated with pegvisomant for 24 months had normal IGF-I levels.[45]

Because pegvisomant blocks GH from binding to its receptor instead of suppressing GH secretion by the pituitary tumor, there has been concern for potential tumor

growth as a result of an interruption in GH-mediated negative feedback inhibition on the tumor. A rise followed by a plateau of serum GH levels echoing the reduction in serum IGF-I with no significant change in tumor size has been reported during treatment.[51,52] A recent prospective multicenter study designed to investigate tumor volume during long-term therapy found similar results, with an increase in tumor size (> 25%) in only 3 (4.9%) of 61 patients.[9]

Pegvisomant has been found to be generally well tolerated. One often-reported adverse reaction is elevated levels of alanine transaminase and aspartate transaminase. In patients with elevated liver enzyme levels, some had transient abnormal values that normalized during treatment while others had enzyme levels that returned to normal following discontinuation of pegvisomant.[45,51,52] It has been recommended that liver function tests be performed regularly during treatment. Injection-site lipohypertrophy has also been experienced, though it resolves with more frequent injection-site change.[33,45] Other adverse reactions include hypercholesterolemia, infections, and self-limited injection-site erythema.[45,51,52]

Primary or Secondary Pharmacological Therapy

According to the recent consensus statement on management by the Acromegaly Consensus Group, transsphenoidal surgery is still considered first-line treatment for intrasellar microadenomas, noninvasive macroadenomas, and adenomas resulting in compression symptoms.[28] Reports indicate that surgical excision achieves normalization of serum IGF-I in 75%–95% of patients with microadenomas and 56%–68% of patients with noninvasive macroadenomas.[7,15,26,36,46] Remission rates drop when surgical removal of invasive macroadenomas is considered. Primary pharmacological therapy may be indicated in such patients and in those who are otherwise poor surgical candidates. While studies designed to investigate the use of primary pharmacological therapy are limited, the use of drugs in treatment-naive patients may be efficacious.

In a study comparing octreotide as primary treatment versus octreotide as secondary therapy after surgery or radiation, Newman and colleagues[35] reported equal efficacy with octreotide as primary or secondary therapy. A retrospective study investigating the efficacy of octreotide LAR as primary and adjunctive therapy also found similar efficacy.[5] In an open prospective multicenter trial, Colao and colleagues[12] demonstrated that, in patients with micro- and macroadenomas, primary octreotide LAR treatment controlled hormone excess, reduced tumor volume, and improved symptoms. In another study, Colao and colleagues[14] investigated the effects of octreotide LAR and lanreotide ATG on tumor-size reduction in treatment-naive patients. A reduction in tumor size of at least 25% was observed in 75.5% of patients after 12 months of primary therapy with a somatostatin analog. The authors also found that the best predictor of tumor reduction was the posttreatment serum IGF-I level.

The use of primary pharmacological treatment also has the potential to influence surgical outcome positively. In a prospective randomized trial, Carlsen and colleagues[10] reported that 6-month pretreatment with octreotide improved surgical cure rates in patients with macroadenomas compared with those who had direct surgery without pretreatment (50% vs 16%). However, they observed no benefit of pretreatment and possibly an adverse effect in patients with microadenomas. Yin and colleagues[53] reported similar results in patients treated with octreotide LAR for 3 months prior to transsphenoidal tumor resection. In a retrospective study, Colao and colleagues[11] concluded that 3–6 months of presurgical octreotide treatment improved clinical symptoms and surgical outcomes and decreased hospitalization time postoperatively. Other studies, however, showed no benefit.[25,40] Further investigation is needed to define the role of presurgical pharmacological treatment in acromegaly.

Combination Pharmacological Therapy

Another area of study that shows promise in the management of acromegaly is the use of drug combinations. As discussed earlier, pegvisomant can result in increased serum GH levels. Additionally, there is the concern of tumor growth during therapy. By adding a somatostatin analog to the treatment regimen, one may be able to reduce serum GH levels and reduce tumor size, potentially counteracting the shortcomings of pegvisomant. A recent review by Neggers and van der Lely[34] examined the long-term efficacy and safety of pegvisomant and somatostatin analog combination therapy. They concluded that treatment was effective in normalizing serum IGF-I levels in more than 90% of patients. Additionally, they found that combination therapy resulted in tumor reduction in approximately 20% of patients, which is not seen in pegvisomant monotherapy. The addition of dopamine agonists to somatostatin analog therapy has also been shown to increase the efficacy of treatment in some patients (Table 1).

Cost of Pharmacological Management

Previous studies on economic burden in the management of acromegaly have revealed that the cost of medication represents the greatest contribution (38%) and exceeds the cost of surgery.[23] An accurate comparison of the cost of the various pharmacological agents mentioned above would be extremely difficult due a myriad of reasons: microadenoma versus macroadenoma (the latter costs more than double the cost of the former), variations in the physician's choice of drug management, and economic determinates, such as health care systems and currency value.

Conclusions

Pharmacological management plays a pivotal role in the treatment of acromegaly. Somatostatin analogs, particularly the long-acting formulations, are considered first line in medical therapy and have shown to result in the reduction and normalization of GH and IGF-I levels. In addition, they have been found to reduce pituitary tumor size. Dopamine agonists, while less effective than somatostatin analogs, have certain advantages, including oral administration. When added to somatostatin analog therapy, dopamine agonists may increase efficacy of treatment. Growth

TABLE 1: Pharmacological therapy of acromegaly*

Variable	Somatostatin Analogs	Dopamine Agonists	GH Receptor Antagonists
indications	1st-line therapy in cases w/ low expectation of surgical cure (large extrasellar tumors); postop/lack of biochem control; to achieve partial disease control prior to radiation therapy for acromegaly	patient preference of oral medication & cost factors; patient w/ markedly elevated prolactin w/ GH & IGF-I; combination therapy w/ somatostatin analogs in refractory cases	persistent high IGF-I levels despite max treatment w/ other modalities; included in combination therapies
dosage	octreotide SC: 100 μg SC 3 × daily (max 1.5 mg daily); octreotide LAR: 20 mg IM every 4 wks (max 40 mg); lanreotide SR: 30 mg IM every 7–14 days; lanreotide ATG: 60, 90, & 120 mg deep SC every 4 wks	cabergoline: 1–4 mg orally weekly	pegvisomant: 40 mg SC loading dose, 10 mg daily maintenance dose (max 30 mg daily)
biochem control			
GH < 2.5 mg/L	~70%	<15% (cabergoline)	↑ GH (pegvisomant)
normalization of IGF-I	~70%	<15% (cabergoline)	>90% (pegvisomant)
onset of response	rapid	slow	rapid
tumor mass shrinkage	~ 50%	unchanged	unchanged
adverse effects	biliary tract disease (biliary sludge, cholelithiasis); impaired glucose tolerance & diabetes; GI symptoms (nausea, vomiting, ab pain)	GI symptoms; postural dizziness; nasal congestion; valvular heart disease	↑ LFTs; injection-site lipohypertrophy; hypercholesterolemia

* ab = abdominal; biochem = biochemical; GI = gastrointestinal; IM = intramuscular; LFT = liver function test; ↑ = elevated.

hormone receptor antagonists have also shown promise in the control of acromegaly, particularly when combined with a somatostatin analog. Novel chimeric compounds with both somatostatin and dopamine receptor affinity have demonstrated greater suppression of GH than an agonist alone or in combination. Several somatostatin analogs show equal efficacy whether given as primary or secondary therapy but result in greater tumor size reduction with primary treatment. Further studies are needed to evaluate the effect of presurgical pharmacological treatment on tumor characteristics and operative outcome.

Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Manjila. Acquisition of data: Manjila, Wu. Analysis and interpretation of data: Manjila, Wu. Drafting the article: Manjila, Wu, FR Khan, MM Khan. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Study supervision: Selman, Manjila.

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Manuscript submitted June 15, 2010.
Accepted July 27, 2010.

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Neurosurg Focus 29 (4):E15, 2010

Acromegaly: a review of current medical therapy and new drugs on the horizon

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Acromegaly is a disease that results from a growth hormone (GH)–secreting pituitary tumor. Clinically, the disease is characterized by excessive skeletal growth, soft tissue enlargement with disfigurement, and increased risk of cardiovascular death. The goals of treatment are the removal or reduction of the tumor mass via surgery and normalization of GH secretion. Another treatment goal is the preservation of normal pituitary function if possible.

Transsphenoidal surgery by an experienced neurosurgeon is usually the first line of therapy, especially for small tumors. Surgeon expertise is crucial for outcome, with dedicated pituitary surgeons having better results. However, overall cure rates remain low because patients with these tumors usually present at an incurable stage. Therefore, medical therapy to control excess GH secretion plays a significant role in a large proportion of patients with acromegaly who are not cured by surgery or other forms of therapy, such as radiotherapy, and/or are awaiting the effects of radiotherapy. If surgery is not curative, lifelong monitoring and the control of excess GH is usually necessary by a care team experienced in handling this chronic disease.

In the past decade major progress has occurred in the development of highly specific and selective pharmacological agents that have greatly facilitated more aggressive management of active acromegaly. Treatment approach should be individualized and take into consideration a patient's tumor size and location, symptoms, comorbid conditions, and preferences. Because a surgical cure can be difficult to achieve, all patients, even those with what seems to be a clinically and biochemically inactive disease, should undergo long-term biochemical testing and pituitary MR imaging. *(DOI: 10.3171/2010.7.FOCUS10154)*

Key Words • acromegaly • pituitary tumor • transsphenoidal surgery • growth hormone

Acromegaly was previously considered a rare disease, with a prevalence of 40–70 cases per million persons and an annual incidence of 3–4 new cases per million persons.[59,77] However, recent European studies suggest that clinically significant pituitary adenomas occur in 1 case per 1064 people. With GH-secreting tumors constituting at least 10% of benign pituitary tumors, the calculated incidence could be 77.6 cases per million inhabitants. Furthermore, a provocative German cross-sectional epidemiological study[96] in almost 7000 unselected primary care patients documented a prevalence of biochemical acromegaly of 1043 per million persons. Acromegaly screening in that study was performed by measuring IGF-I, and most cases were further confirmed by additional testing. Thus, acromegalic patients are theoretically more prevalent than previously thought,[39,44] and in our opinion, this is clearly conceivable. Nonetheless, more studies are needed to establish an accurate incidence.

The nonspecific and protean symptomatology of acromegaly often results in late diagnosis, that is, 4 to > 10 years after initial symptom onset. Besides the local mass effect of the pituitary tumor, acromegaly results in multiple metabolic and "structural" dysfunctions.

Surgery, medical therapy, and radiation have specific advantages and disadvantages that should be weighed and tailored very carefully for each patient. Surgery is considered the mainstay of therapy for most, whereas medication is reserved for patients with persistent excess GH secretion uncontrolled by surgery. In selected cases, primary medical therapy is also an option, and radiotherapy remains a third line of treatment.[34,79] Blood tests using serum GH and IGF-I remain the backbone of determining cure or control of the disease. Recently, consensus guidelines regarding the diagnosis and treatment of acromegaly were published.[34,55,79]

Abbreviations used in this paper: DA = dopamine agonist; DR = dopamine receptor; D2R = dopamine receptor 2; GH = growth hormone; GHRA = GH receptor antagonist; IGF-I = insulin-like growth factor–I; LAR = long-acting release; OGTT = oral glucose tolerance test; SSA = somatostatin analog; SSTR = somatostatin receptor subtype.

In this review we focus on the medical treatment of acromegaly, including novel concepts and experimental therapies, and we emphasize our personal experience.

Goals of Therapy

Acromegaly is a severe disease with increased rates of morbidity and mortality if not treated appropriately. Epidemiological studies estimate the excess mortality rate as approximately 2-fold, attributed primarily to cardiovascular, cerebrovascular, and respiratory disease.[31,60] A potential confounding mortality factor in patients appears to be the presence of hypopituitarism, mainly adrenocorticotropic hormone deficiency.[98,99] Adverse mortality outcomes have been linked to both GH and IGF-I levels.[6,60]

Earlier studies suggested that GH levels < 10 ng/ml,[115] and later ≤ 5 ng/ml,[73] were adequate for control. Based on newer data, these values are now associated with mortality rates above those in the normal population. Growth hormone concentrations < 2.5,[12,68,85] < 2,[6,60] or < 1 ng/ml[60] are associated with mortality rates comparable with those in the normal population. Five epidemiological studies investigated IGF-I as a predictor of increased mortality, although not everyone agrees that IGF-I is predictive of death.[6,12,60,68,103] Swearingen et al.,[103] in 1998, were the first to suggest that a normal IGF-I level in patients with acromegaly predicted a normal expected mortality rate.

A comprehensive treatment strategy should alleviate pituitary tumor effects, normalize GH and IGF-I hypersecretion, improve associated comorbidities, and reverse the increase in mortality risk, all while preserving normal pituitary function (Table 1).

Surgery remains the first treatment of choice for patients with acromegaly, given 2 caveats: the need for an experienced surgeon and the tumor's appearance on MR imaging. In the hands of an inexperienced surgeon, the results of surgery can be quite disappointing.[2,54] If an experienced surgeon is not available, medical therapy can be offered to the patient as first-line therapy. If the tumor has invaded the cavernous sinus or for other reasons is not completely resectable, medical therapy can be offered as a first-line treatment or in addition to surgery.

Surgical treatment also offers a significant advantage: a final pathological diagnosis. The pathological distinction between different types of GH-secreting tumors can impact the response to therapy as well as prognosis making; therefore, accurate pathological classification is important. Growth hormone–producing tumors range from well-demarcated slowly growing microadenomas to large, more rapidly growing macroadenomas. They vary in morphology and can be separated into several different types: tumors that secrete only 1 GH (monohormonal somatotroph adenomas), tumors that secrete GH and prolactin (bihormonal mammosomatotroph adenomas), and silent GH-secreting adenomas (express GH in the tumor without GH hypersecretion or acromegaly).[5] Monohormonal somatotroph adenomas represent the majority of these lesions (90%) and can be further classified as densely granulated or sparsely granulated. Densely granulated tumors are composed of well-differentiated somatotrophs with positive staining for GH when using an immunoperoxidase technique and an electron microscope appearance similar to nontumoral cells. They have a better prognosis overall with slower growth rates, are easier to remove, and recur less frequently after surgery. Sparsely granulated tumors consist of less differentiated cells with positive GH staining but electron microscope characteristics different from normal cells. The sparsely granulated type is prevalent in younger patients and appears to grow more rapidly.[5,78]

Pituitary GH-secreting cells have 5 SSTRs: SSTR-1 to SSTR-5, with receptors SSTR-2 and SSTR-5 predominant (90%–95%) in GH-secreting tumors.[20]

TABLE 1: Results of available therapies for treating patients with acromegaly*

Parameter	Surgery†	SSA	GHRA	DA	Radiotherapy
treatment end point of GH <2.5 ng/L (%)	50–80	~65	0‡	<15	~60§
tumor mass	debulked or resected	no growth, shrinkage occurs frequently	unknown, possible enlargement of pituitary tumor	unchanged (no shrinkage)	shrinkage over time
cost	1 time	ongoing	ongoing	ongoing	1 time
hypopituitarism (%)	<10	none	low IGF-I	none	>50
other disadvantages	diabetes insipidus, CSF leak	gallstones, nausea, diarrhea	elevated liver enzymes	high dose required	accelerates cerebrovascular disease
unique feature	experienced pituitary surgeon required	preop use may improve surgical results	best agent to improve glucose control	cabergoline use requires echocardiogram heart valve monitoring	slightly increased incidence of stimulating a new tumor in radiated bed

* Note that no single technique is superior. Adapted from Melmed S: Medical progress: acromegaly. **N Engl J Med 355:**2558–2573, 2006. Surgery, medical therapy, and radiation have specific advantages and disadvantages that should be weighed and tailored very carefully for each acromegalic patient. Percentages represent the proportion of patients who have positive results after each treatment.

† Transsphenoidal surgery.

‡ The GH level increased.

§ At 10 years after treatment.

The density and expression of SSTRs also have potential clinical significance as clinical predictors of response to pharmacotherapy with SSAs.[16,25,41] Somatostatin analog resistance is observed in about one-third of tumors and could be related to density reduction or different receptor expression. In 1 study, for example, both SSTR-1 and SSTR-2 had higher expression levels in patients with normalized GH and IGF-I after treatment with SSAs, and SSTR-3 expression correlated with tumor shrinkage as well.[26] Selecting which SSA to use may, in the future, depend on SSTR analysis of the surgical specimen.

All of the above emphasizes the importance of accurate morphological classification using immunohistochemistry and/or electron microscopy, which in our opinion should be performed on all pituitary pathology specimens.

Medical Therapy

Three drug classes are available to treat acromegaly (Fig. 1), each with unique advantages and disadvantages. In patients with uncontrolled hormonal levels after surgery, SSAs are the treatment option of first choice. Dopamine agonists and GHRAs are generally indicated after SSA failure.

Somatostatin Analogs

Somatostatin acts as an endocrine inhibitor to a number of endocrine cells including GH-secreting pituitary cells, pancreatic beta cells releasing insulin, and a number of gastrointestinal tract hormones. Somatostatin ligands or "analogs" bind with varying affinity to the 5 SSTRs described above[20] and mimic the GH suppressive effects of native somatostatin. A potential added benefit of SSAs is their antiproliferative effect.

Somatostatin analogs represent the mainstay of medical treatment for acromegaly, and most pituitary centers now have 25 years of experience with their use. Three SSAs are approved for use in the US: short-acting octreotide, octreotide LAR (Sandostatin LAR), and Somatuline Depot (lanreotide Autogel; Table 2). Octreotide was first approved for use in the US in 1995, followed by octreotide LAR in 1998 and lanreotide in 2007.

Short-Acting Octreotide

Octreotide is approximately 20 times more potent than native somatostatin and has a half-life of 1.5 hours.[11] It is administered as a subcutaneous injection 3 times a day with an immediate biochemical response, suppressing both basal and stimulated GH secretion for up to 5 hours.[71]

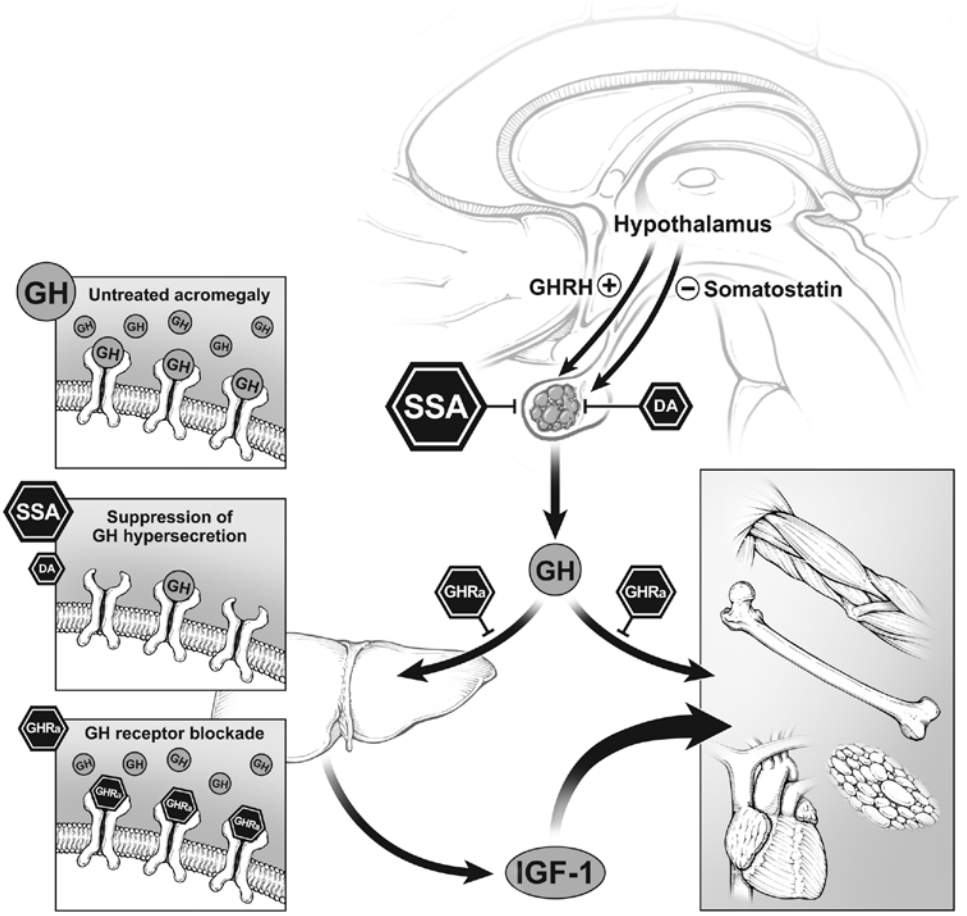

Fig. 1. Illustration showing medical therapy targets in the GH/IGF-I pathway. The SSAs directly inhibit GH secretion and control both GH and IGF-I levels; DAs reduce GH hypersecretion; and GHRAs (GHRas) directly block peripheral GH-dependent release of IGF-I and GH effects, have no direct effects on the pituitary tumor, and cause no decrease in GH levels. GHRH = growth hormone releasing hormone.

TABLE 2: Somatostatin analogs commercially available in the US*

Factor	Octreotide	Octreotide LAR	Lanreotide
use	multiple dose 5-ml vials	requires reconstitution	ready to use, prefilled syringe
dose	efficacy up to 750 μg/day	10, 20, 30 mg; dose vials	60, 90, 120 mg; prefilled syringes
administration	self-administered subcutaneous 3–4 ×/day w/ insulin syringe	administered by health care professional deep IM every 4 wks	self- or partner administration deep subcutaneous every 4 wks
needle	30-gauge	19-gauge	18-gauge
vial size/vol	1000 mg/ml vials	vol: 2.5 ml, all doses (concentration dependent)	vol: 0.3–0.5 ml (volume dependent)
preparation	only preparation available for "test dose" use	may be able to discontinue in some patients after long-term use	most user friendly, long-acting preparation
stability	stable for 14 days at room temp if protected from light	keep refrigerated until 30–60 mins before use	keep refrigerated until 30–60 mins before use

* IM = intramuscular; temp = temperature.

With the development of long-acting SSAs, short-acting octreotide is rarely used, except in the acute octreotide test.[49] We consider acute suppression tests valuable tools for evaluating a patient's tolerance of therapy, but their prognostic value in predicting long-term response, despite initial reports,[67] is limited.

Octreotide LAR

Octreotide LAR is a formulation consisting of octreotide incorporated into microspheres of a slowly dissolving polymer that provides smooth and reliable steady-state kinetics when administered intramuscularly once a month.[102] The injection of 20–30 mg results in peak drug levels at 28 days with integrated GH suppression for up to 49 days.[48] The pharmacodynamics suggest that although GH suppression will be observed after the first dose, maximal suppression is not observed until after the administration of 3 doses.[102] This timeframe should be kept in mind by clinicians when assessing the response to a given dose. Accurate drug administration is imperative, and a dedicated physician-nurse care provider team is essential for long-term care.

The 2 largest studies of octreotide LAR[37,72] compiled 261 patients, with more than one-half pretreated with short-acting octreotide and the remainder naïve to medical treatment; GH suppression to < 2.5 μg/L and normal IGF-I was achieved in 63%–75% of patients.

Lanreotide Autogel

A recent development has been the introduction of a supersaturated aqueous formulation, lanreotide Autogel, in a prefilled syringe that requires deep subcutaneous administration every 28 days. Lanreotide has a linear pharmacokinetic profile over a dose range of 60–120 mg after both single and repeat injections.[19] This new formulation has the potential to increase dosing intervals, and the user-friendly characteristic for the patient to self-administer[15,75] (or a partner to administer) could result in improved compliance.

A randomized placebo-controlled study in an unselected population (99 patients) published in 2010[80] showed that lanreotide Autogel was effective in controlling both GH and IGF-I hypersecretion: 54% of patients had normalized IGF-I and 38% had both normalized IGF-I and a GH level ≤ 2.5 ng/ml. This drug was well tolerated by all patients in the long term.

Similar to other SSAs studied, patients who were not naïve to medical treatment at the beginning of the study were more likely to respond. This study also confirmed an improved response in patients with prior pituitary surgery and less severe acromegaly at baseline.

It is difficult to appreciate the true efficacy of SSAs in achieving biochemical control due to varied study entry criteria and desirable cutoff goals. A 2005 meta-analysis by Freda et al.[49] showed that overall GH and IGF-I were normalized in 49%–56% and 48%–66% of patients, respectively, with the efficacy of octreotide LAR higher than that of a slow-release lanreotide (not used in the US). Note, however, that Freda and colleagues' study was flawed by the inclusion of more than 50% of patients who were preselected with previous octreotide responsiveness.[82] The currently available SSAs octreotide and lanreotide seem equally effective,[3,105] with the majority of patients achieving symptom control and biochemical control being achieved in approximately one-half of unselected patients. Further meta-analysis of prospective randomized trials on the efficacy of each SSA with respect to GH control and tumor shrinkage is warranted.

Somatostatin analogs are generally safe and well tolerated.[78] The most frequent adverse events of SSA treatment are abdominal symptoms (usually improving over time), glucose intolerance, and gallbladder sludge or stones.

Other potential drawbacks of SSA use are its high cost and patient compliance. In an Italian study, however, the cost of caring for patients who did not respond to SSA was much higher[40] than for those who did respond. Recent evidence has suggested that these agents can be used at lower doses or at less frequent intervals with obvious cost and compliance implications. Both octreotide LAR and lanreotide have been successfully used at 6- to 8-week intervals.[92,107]

Predictors of Biochemical Control

The selection of patients for treatment with SSAs has changed over time. A report by Bevan et al.[14] in 2002 suggested that the control of GH and IGF-I was unlikely in patients with a GH level > 20 ng/ml and an IGF-I level > 900 ng/ml. On the other hand, in 2006 Cozzi et al.[38] showed in 110 patients treated with octreotide LAR that the untreated IGF-I concentration, whether very high or low, did not predict response. Furthermore, in a 2010 report by Melmed et al.,[80] patients with less severe acromegaly at baseline had better responses to treatment with lanreotide. No reliable predictive factors relating to a final dose frequency were identified in any studies,[107] and thus stressing the importance of individual tailoring of the dosing regimen for each patient.

Tumor Shrinkage

A number of studies have reported tumor shrinkage in patients with acromegaly treated with SSA therapy, both adjunctively and primarily. This shrinkage can be significant (20%–80% in about one-third of patients) but unpredictable (Fig. 2).[10,33,49,82]

Tumor reenlargement after SSA discontinuation has also been noted in some cases. Several mechanisms have been proposed for the observed reversible tumor shrinkage; however, the exact cellular mechanism remains unclear.[13,32,79]

Primary therapy, as expected, has more impressive shrinkage results.[76] In a prospective study in 99 patients with acromegaly, 75.5% experienced ≥ 25% tumor shrinkage after 12 months, while a significant increase in tumor mass occurred in only 2.1% of the patients. The best predictor of tumor shrinkage was posttreatment IGF-I levels,[27] with patients having the lowest IGF-I level also demonstrating the best tumor shrinkage. A longer prospective study[38] confirmed this observation; the higher the basal GH values and the greater the GH/IGF-I changes, the greater the tumor shrinkage. The authors reported tumor shrinkage of 62% ± 31% (range 0%–100%) in 82.1% of patients.

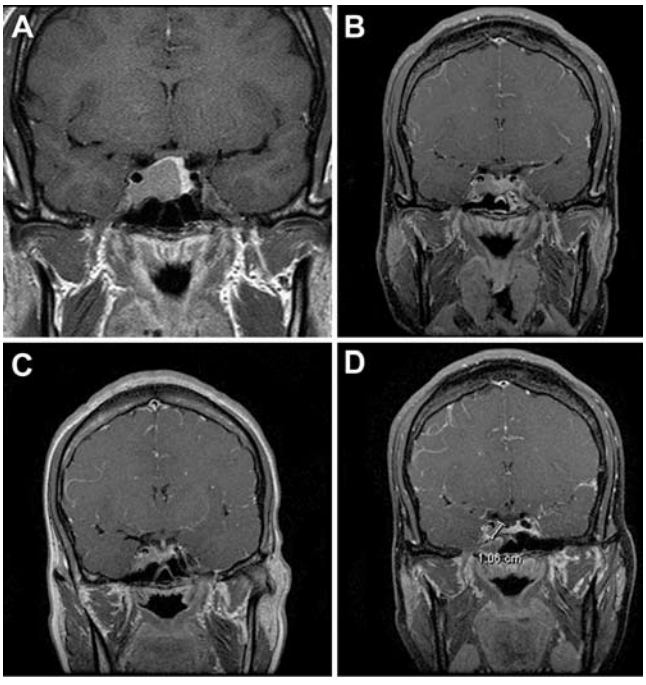

Fig. 2. Coronal post-Gd T1-weighted MR images obtained in a 31-year-old woman with a GH-secreting pituitary adenoma. She underwent partial tumor resection due to cavernous sinus involvement. **A**: Preoperative. **B**: Three months postoperative. **C**: Six months after starting SSA. **D**: One year post-SSA treatment.

Use of SSAs in Primary Therapy

Somatostatin analogs may be equally effective if used as adjuvant or initial therapy.[7,8,84] Most studies examining the efficacy of long-acting SSAs have focused on patients after surgery and radiation treatment. More recently, however, a large cohort of patients has been treated with primary/de novo therapy.[28] For microadenoma cases in which the surgical cure rate can reach 80%–90%, primary SSA therapy should be used only in those patients who refuse to undergo or have contraindications for surgery. At this time, there are no randomized controlled studies that compare primary medical therapy with initial surgery.

A large German study, ACROSTUDY 2008,[87] showed that pituitary surgery in 554 patients normalized GH and IGF-I levels in 54.3% and 67.2% of patients, respectively. This approach was clearly more effective than the 36.3% (normalized GH) and 30.5% (normalized IGF-I) obtained by using primary SSA in 145 patients. In some of the SSA-treated patients, the control rate increased slightly with a longer administration of medical therapy (> 360 days).

In a recently published 5-year primary SSA trial by Colao et al.,[28] differing results were achieved. In all 45 patients on prolonged octreotide LAR therapy (28 patients) and lanreotide therapy (17 patients), successful control of GH and IGF-I was achieved, and hypertension, cardiac function, and lipid abnormalities improved. Interestingly, glucose metabolism was not affected despite biochemical control. Unfortunately, these data represent only those patients who were fully responsive to SSA, as another 31 patients unresponsive to SSA therapy underwent surgery within 1–2 years.

Overall, we conclude that SSAs are a good primary treatment option in carefully selected patients.

Pretreatment With SSAs

It has been suggested that SSA treatment prior to surgery can reduce surgical risks[29] and potentially improve surgical cure results. While symptomatic improvement and reduction in soft tissue swelling have been well documented,[17,74] the effect of SSA pretreatment on surgical outcome remains unclear at present.[89] In the ACROSTUDY 2008, for example,[87] SSA treatment before surgery was shown to improve surgical outcome only marginally.

One of a few well-designed prospective studies by Carlsen et al.[22] suggested that with pituitary macroadenomas, SSA pretreatment improves surgical outcomes; however, the surgical cure rate (23% achieved IGF-I normalization, and just 16% by using a combined criteria, that is, adding a GH nadir during OGTT ≤ 1.0 ng/L) was much lower than the average reported in the literature (between 50% and 70%).[10,33,49,82] Most probably, the rela-

tively low cure rate combined with just the few microadenomas included in the study played a role in the negative effects of pretreatment in pituitary microadenomas. Interestingly, in contrast with other studies,[101] Carlsen et al.[22] noted that SSA pretreatment increased the consistency of the tumor, making the tumor more fibrotic and easier to identify during surgery.

Role of Surgical Debulking

Convincing evidence has emerged showing that the efficacy of medical therapy may be improved if the majority of the tumor is removed (that is, debulked) despite incomplete surgical removal. Tumor debulking is often used with SSA therapy when GH is partially but not completely controlled with treatment. In these cases, tumor debulking may allow SSA therapy to reduce GH and IGF-I levels into the normal age-adjusted range.[27,66,114] The removal of more than 75% of the tumor load in a retrospective study in 86 patients increased the response to SSAs with no additional pituitary function impairment.[27]

It has also been suggested that patients with a high GH concentration and a large tumor could benefit more from debulking surgery.[87] In our opinion, surgical debulking has an important role to play in the treatment algorithm, and we routinely use this approach in our practice.

Dopamine Agonists

For many years, the only drugs available to treat acromegaly were DAs such as, for example, bromocriptine. This class of drug causes the stimulation of GH release in healthy individuals but leads to paradoxical suppression of GH hypersecretion in a proportion of patients with acromegaly. The effectiveness of DAs in the control of GH secretion appears to correlate with the expression of D2Rs within the tumor rather than with the presence of prolactin.[30]

Experience with bromocriptine is well documented;[62,112,113] however, only approximately 10% of patients achieve safe GH and normal age-adjusted IGF-I levels despite using substantially higher doses than those required for the successful treatment of prolactin-secreting tumors. Side effects often limit the ability to even use this higher dose.

Cabergoline is a more potent DA and better tolerated than bromocriptine. A wide range of satisfactory biochemical control with cabergoline alone has been reported.[29,50,61] The highest rate of response, up to 39% of patients,[1] has not been reproduced elsewhere, although clinical improvement[47,61,81] and substantial reductions in GH and IGF-I levels have been observed in the majority of patients studied.

The potential for the long-term use of cabergoline (especially at the higher doses usually required in patients with acromegaly) to cause cardiac valvular damage cannot be ignored.[56] However, cabergoline administration at a dose < 3 mg/week appears safe.[24] Future studies will help to clarify DA-induced cardiac valvular disease. A conservative approach for now would be to use bromocriptine rather than cabergoline or to use low-dose cabergoline in combination with other drugs. If cabergoline is used, a pretreatment echocardiogram should be obtained to determine the anatomical integrity of heart valves; and if one or more valves are deemed incompetent, cabergoline should not be used. Heart valve incompetency has been reported as an adverse effect associated with acromegaly independent of DAs.[86,109]

In summary, the general advantages of DA use are oral administration, relatively low cost, and no associated hypopituitarism; however, overall efficacy is quite limited. We consider DA use effective in a subset of patients with very modest IGF-I elevations. We also recommend DA as a possible first-line therapy in mixed GH/prolactin–secreting tumors or as a combination therapy.

Growth Hormone Receptor Antagonist

The GHRA pegvisomant directly inhibits peripheral GH action by interfering with the functional dimerization of the 2 GH receptor subunits, thus blocking the signal for IGF-I production.[69] In initial clinical trials, lowered or normalized IGF-I was observed in about 90% of patients.[105,110] However, recent data from a large 5-year observational study of pegvisomant use[104] has revealed a much lower IGF-I normalization rate (70% of patients), most probably due to inadequate dosage (more than two-thirds of the patients were taking the lowest dose). The cause of dose titration failure seems unclear; however, it does raise a very interesting point about the importance of both initiating the right treatment and further close monitoring.

In a 1-year, open-label randomized study of 118 patients, pegvisomant and octreotide LAR were equally effective in normalizing IGF-I in the overall population, but pegvisomant was more effective in patients with a higher baseline IGF-I. Treatment-related adverse events were mild to moderate in both groups.[53] In that study, as in previous trials,[105,111] pegvisomant had a more favorable effect on the parameters of glycemic control and thus has even been suggested as first-line medical therapy in patients with glucose metabolism abnormalities.[9]

The adverse events most frequently attributed to pegvisomant are disturbed liver function tests and injection site reactions.[106] Lipodistrophy[18,93] and acute hepatotoxicity[100] have also been reported.

Pegvisomant is unique in that the drug does not lower GH levels—in fact, levels are raised due to feedback mechanics—thus making IGF-I the only available marker for disease activity.

Pegvisomant has no known antiproliferative effects and, despite some concern,[52] has not been associated with tumor growth overall.[57,65] In a very recent 2-year German prospective study[21] that included serial MR images, a tumor volume increase of > 25% during the study was observed in 3 (4.9%) of 61 patients. (Note that approximately two-thirds of the initial group completed that study.) All tumor changes were observed during the first year of enrollment. Interestingly, all 3 patients had prior SSA treatment, revealing a potential rebound effect of stopping this treatment and/or the natural history of aggressively growing pituitary tumors. Longer studies on

naïve patients to those on medical therapy would be necessary to definitely answer this question. We recommend continued long-term surveillance of tumor volume in all patients treated with pegvisomant, particularly in nonirradiated patients.

The selection of patients for GHRA therapy has been further defined.[79] In most cases, pegvisomant should be reserved for SSA nonresponders, patients intolerant of SSAs, and patients whose diabetes is worsened by SSAs or who are considered to be taking combination therapy.

Combination Therapy

Over the years newer therapeutic options have included combination therapies with DAs, SSAs, and the GHRA pegvisomant.

Somatostatin Analogs and DAs

To overcome resistance to 1 agent, the combined use of SSAs and DAs has been extensively studied with various results. The addition of high doses of cabergoline to SSA treatment has been shown to improve the response to GH in patients whose GH levels were not previously controlled with a maximum dose of SSA.[36,97] The beneficial effects of cabergoline in combination with SSAs occur even when pretreatment prolactin levels are normal and/or there is no tumor GH/prolactin coexpression.[63] Randomized prospective controlled studies are needed to confirm the effects of this combined regimen.

Somatostatin Analogs and GHRAs

The addition of weekly pegvisomant to SSA treatment has been shown to control disease in the majority of patients with no significant increase in adverse effects.[43] A combination of long-acting SSAs once monthly and pegvisomant once weekly (up to 80 mg, median 60 mg) in 26 patients with active acromegaly normalized IGF-I in 18 (95%) of 19 patients who completed 42 weeks of treatment.[43] This combination therapy has also been successfully used in patients resistant to SSAs.[83] Long-term safety data are now available for 86 patients (follow-up 29.2 ± 20.2 months; median dose of 60 mg pegvisomant administered weekly), added to data for patients previously treated with SSA for at least 6 months.[83] Transient elevation in liver enzymes was observed in 23 (27%) of 86 patients regardless of the cumulative dose of pegvisomant, but enzymes subsequently became normal after discontinuing the drug. This study also showed tumor shrinkage of > 20% in 19% of patients. The highest percentage of tumor shrinkage was observed in those who received primary medical treatment.[83] The possibility of lower doses of both SSAs and GHRAs[43,106] must be investigated further. The overall effects on the cost of this combination have been debated.

Elevation in liver enzymes is observed more frequently with combination therapy, and long-term safety should be established before definite treatment recommendations are made.

In our opinion, the decision to use monotherapy or combination treatment should depend on individual patient circumstances. Tumor shrinkage with SSAs would be a good reason to continue SSAs, whereas worsening glucose control could tip the balance toward GHRA use.

New Therapies on the Horizon: Drugs in Clinical Trials

The role of SSTRs and DRs as molecular targets for the treatment of pituitary adenomas is well established. More recently, however, work on the expression of SSTR and DR subtypes, their coexpression, and their functional interface via dimerization has opened new perspectives for patients currently unresponsive to or intolerant of clinically available drugs. Research into an additional long-term delivery method (compared with the monthly injection of long-acting octreotide) as well as potential patient compliance and cost improvement is underway.

Multiligand SSA Pasireotide

A relatively high proportion of patients are resistant to octreotide and lanreotide, which could be explained in part by variable tumor expression and/or decreased density of SSTR-2. The multiligand SSA pasireotide (SOM 230) is a novel somatostatin analog (mimetic) with a unique structure. It has a very long plasma half-life, potent in vitro and in vivo inhibitory effects on GH and IGF-I release, a high binding affinity to SSTR-1, -2, -3, and -5, and up to a 40-fold greater affinity for SSTR-5 than octreotide. Therefore, it is a promising therapeutic candidate with several potential advantages over currently used SSAs. The high affinity of pasireotide for both SSTR-5 and SSTR-1 could be important in GH-secreting adenomas resistant to current therapy. Furthermore, binding and functional synergy between SSTR-2 and SSTR-5 could be beneficial even in responsive tumors.

Phase I and II trials on GH-secreting tumors have been encouraging with good biochemical control and "significant" tumor shrinkage,[88,108] making SOM230 a promising candidate. There are, however, potential concerns related to glucose intolerance.[35] The safety and efficacy of pasireotide LAR versus octreotide LAR in patients with active acromegaly is presently being studied in a large, Phase III, randomized, blind multinational study (www.clinicaltrials.gov).

A future role for pasireotide remains to be determined, but its use in the treatment of octreotide-resistant tumors, especially large ones, seems most likely.[58]

Somatostatin-Dopamine Chimeric Ligand

A functional interaction between D2R and SSTR-5 has been reported recently, with the subsequent development of a new chimeric compound containing structural elements of both somatostatin and dopamine, that is, dopastatin. The exact mechanism by which combined somatostatin-dopamine treatment has a synergistic effect on GH suppression is not completely clear, but Saveanu et al.[95] suggested crosstalk of the G-coupled receptors or dimerization on the cell membrane/postmembrane level. Nonclinical pharmacological studies have shown that dopastatin is more potent and more effective than oct-

reotide alone[94] or octreotide in combination with cabergoline[94] in suppressing GH secretion, and thus seems a promising approach for acromegaly treatment. Patients who express both SSRT-2 and D2R should be especially suitable for this treatment. As a note of caution, however, a discrepancy between the presence of a receptor profile SSTR/D2R and the limited efficacy of an agonist drug has been reported.[45,46,91]

After encouraging in vitro results,[64] a study to assess the efficacy and safety of the repeated administration of dopastatin (BIM-23A760) in patients with acromegaly is presently underway in a Phase II multinational clinical trial (www.clinicaltrials.gov).

Extended Delivery of Octreotide Including Octreotide Implants

Another exciting area of research involves changing the delivery system. A Hydron implant delivering octreotide for up to 6 months has been analyzed recently. Two Phase I/II clinical studies have evaluated the pharmacokinetics, efficacy, safety, and drug release characteristics of this octreotide implant in 45 patients with a full or partial response to octreotide. The implant maintained GH at < 5 ng/ml in 94% of patients and achieved normal IGF-I in 60% of patients as compared with octreotide LAR (83% and 51% of patients, respectively). There were no serious or severe adverse events, and all patients completed the study.[70] These results suggest a possible improvement over currently used daily and monthly formulations of octreotide. The implant delivery system is being studied in Phase III multinational clinical trials (www.clinicaltrials.gov).

Overall, it remains to be determined where all of these new therapies will ultimately fit into the treatment paradigm.

Monitoring Therapy

Cutoff Numbers

It is important to note that despite major advances in test methodology and accuracy, the normal value, or target, for the treatment of the GH axis is still controversial. The present trend of lowering the cutoff seems to correlate with disease outcome,[60] and clinicians should be aware of the limitations of each test.[4,90]

The general consensus is to lower the IGF-I concentration to within the reference range for the patient's age and sex and to lower the random serum GH concentration to < 1 or 0.4 ng/ml after a glucose load (OGTT).[79]

Insulin-like growth factor 1 provides a measure of integrated GH secretion, and IGF-I concentrations are closely correlated to GH, although discrepancies remain. It is still unclear which is more important to follow over time: GH or IGF-I.

Therefore, we recommend IGF-I as an excellent end point to assess therapeutic efficacy for both the patient and the physician. Of course, it is critical to use an established IGF-I assay with age- and sex-dependent normal ranges while using the same laboratory every time.

Postoperatively, it may take several months for IGF-I levels to fall into the normal range despite a cure.[42] However, the OGTT can be performed earlier in the postoperative period and can be relied on as early as 1 week after surgery to confirm GH secretion status.[42] Postoperatively, we routinely obtain both IGF-I levels and OGTT results. In cases of discordant results, we rely on GH values (random or GH profile).

Oral glucose tolerance test utility in diabetic patients or in those treated with SSAs has been questioned more recently.[23] As mentioned earlier, there is no use in obtaining GH measurements for patients on pegvisomant.

Frequency of Monitoring

Monitoring frequency should be clearly individualized depending on the initial tumor size, activity of the disease, and type of treatment. Regardless of the therapy used, patients with clinically and biochemically inactive disease should undergo long-term follow-up, biochemical testing, and pituitary MR imaging. Preoperative long-acting SSA treatment may influence the timing of postoperative evaluation.

At a minimum, random serum GH and IGF-I levels should be measured on an annual basis for all acromegalic patients after surgery, since recurrences have been reported 10–20 years after an apparent cure.[51]

Monitoring a patient's tumor size with serial MR imaging during drug therapy with an SSA, a DA, or a GHRA is also mandatory.

Persistent subtle elevations in GH levels in the presence of normalized IGF-I levels may predict recurrence,[50] despite the remission of coexisting illnesses and normalized IGF-I levels.

Monitoring endogenous pituitary reserve, cardiovascular function (including echocardiographic evaluation), pulmonary status, blood sugar control, and rheumatological complications is also essential to patient care.

For pegvisomant therapy, liver function tests should be performed monthly for the first 6 months and every 6 months thereafter, since elevated hepatic aminotransferase levels have been reported. Magnetic resonance imaging should be performed every 6 months for the 1st year and annually thereafter to detect possible continued tumor growth.

Conclusions

Acromegaly is a severe, often chronic disease with increased morbidity and mortality rates if not treated appropriately. It remains a challenging condition to manage, particularly if the disease persists after an initial transsphenoidal surgery. The treatment of patients with persistently active acromegaly has been facilitated over the past decade by the advent of highly specific and selective pharmacological agents, which are sometimes used in combination. It is anticipated that newer somatostatin receptor ligands or chimeric molecules could help control GH hypersecretion in patients refractory to current therapies, and clinical trials are underway. A better delivery system may improve patient compliance. The neurosurgeon should be prepared to discuss the possible need for adjuvant treatment, including medical therapy and/or radiation therapy. Acromegalic patients are best cared for

at a specialized center by a multidisciplinary neuroendocrine team comprised of neurosurgeons, endocrinologists, radiation oncologists, neuroophthalmologists, and otolaryngologists. No single treatment algorithm applies to all patients. Treatment should be individualized with long-term follow-up. Monitoring both biochemical control (IGF-I and GH levels close to normal) and tumor size is essential. The clinician must think in terms of therapy for today with an expectant eye toward tomorrow.

Disclosure

Dr. Fleseriu has received consultant fees from Novartis Pharmaceuticals, Tercica, Inc., and Endo Pharmaceuticals, and is a principal investigator in clinical trials sponsored by Novartis Pharmaceuticals and Ipsen Pharma. Dr. Cook has received consultant fees from Novartis Pharmaceuticals, Tercica, Inc., and Endo Pharmaceuticals, and is a principal investigator in clinical trials sponsored by Ipsen Pharma, Endo Pharmaceuticals, and Pfizer, Inc.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Fleseriu. Analysis and interpretation of data: Fleseriu, Cook. Drafting the article: Fleseriu. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors

Acknowledgments

The authors thank Shirley McCartney, Ph.D., for editorial assistance and Andy Rekito, M.S., for illustrative assistance.

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Manuscript submitted June 10, 2010.
Accepted July 16, 2010.
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Neurosurg Focus 29 (4):E16, 2010

Editorial

Unresolved issues: radiosurgery versus radiation therapy; medical suppression of growth hormone production during radiosurgery; and endoscopic surgery versus microscopic surgery

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This issue of *Neurosurgical Focus* contains important reviews of several aspects of acromegaly. Three themes are emphasized in at least 3 contributions: the attributes of radiosurgery compared with conventional fractionated radiation therapy for patients with residual tumor after surgery; the use of medical therapy to suppress tumor production of growth hormone (GH) during radiosurgery; and the "pure" endoscopic approach for surgery. The authors of these reports already emphasize much of what I have to say here. However, certain arguments, arguments that have been recently proposed and widely avowed, albeit without solid validation by scientific or clinical studies, justify further discussion here.

Radiosurgery Versus Fractionated Radiation Therapy

The most compelling arguments for the selection of radiosurgery over fractionated radiation therapy are that the former is more convenient because of its single-session treatment than a course of radiation treatments over 4–5 weeks and because it reduces GH earlier. In addition, many authors propose that the risk of loss of pituitary function is smaller with radiosurgery than with fractionated therapy. There is, however, no compelling evidence to support this. Loss of pituitary function after either therapy is usually limited to 1 or 2 pituitary functions, rather than panhypopituitarism, and it occurs over several years, accumulating for 10–15 years after treatment, as summarized in the current issue in reports by Stapleton et al.[8] and Yang et al.[9] Because with radiosurgery we have access to very few studies with follow-up durations beyond 5 years (see the tables in the reports by Rowland et al.,[7] Stapleton et al.,[8] and Yang et al.[9]), the true incidence of adverse effects on pituitary function over time cannot be known until the data to measure it are available. For instance, in the only radiosurgery series with a minimum median follow-up of 10 years,[6] 46% of patients with acromegaly who underwent radiosurgery had endocrine remission at 10 years and 50% developed new anterior pituitary insufficiencies, the majority of which appeared more than 5 years after treatment. This incidence of hypopituitarism is similar to that reported in many studies of radiation therapy with follow-up of similar duration.

Other factors that influence a perception of radiosurgery's increased utility of and lower risk of loss of pituitary function include comparison of the results of the 2 modalities in different eras. The summary of radiation therapy experience is almost always from period before the general use of radiosurgery. The imaging modalities used to detect the tumor and define its anatomy in the pre-radiosurgery era were less sensitive (before MR imaging), and modern surgery is more effective at removing tumor. Considering the 2 treatment eras and the smaller tumor size and more minimally damaged pituitary before delivery of radiosurgery, differences in tumor size at diagnosis or after surgery could affect the success of treatment and influence the incidence of impaired pituitary function that cannot be accurately compared between 2 groups. For instance, in the frequently cited study comparing radiosurgery and conventional radiation therapy by Landolt et al.,[5] radiation therapy was administered between March 1973 and January 1992, whereas the radiosurgery was performed from 1994 to 1996. Furthermore, the total dose of fractionated therapy was only 4000 cGy, a dose below the generally recommended minimum dose of 4500 cGy. Moreover, the average pretreatment GH level, the main predictor of response to radiosurgery or radiation therapy, was 67% higher in the radiation therapy group, perhaps explaining some of the difference in the percentage of patients in whom endocrine remission was achieved as well as the mean time to response in the 2 groups, as patients with higher levels are less likely to reach normal levels, and if the levels do normalize, they do so over a longer interval. In the absence of a prospective randomized trial the same selection biases would also contaminate contemporary case series because tumors selected for fractionated therapy today are likely to be lesions that are either too large for radiosurgery or are immediately contiguous to the optic system (fractionated therapy is selected since it is necessary to include the optic nerves or chiasm in the treatment field and the risk of normal tissue toxicity is reduced by fractionation).

Also, discussion of the side effects associated with conventional fractionated therapy almost always includes studies that used delivery techniques that did not incorporate modern radiation techniques. In the last decade it has

become routine to precisely target pituitary tumors while simultaneously avoiding normal brain through the use of conformal techniques such as intensity modulated radiation therapy (IMRT). IMRT is based on multileaf collimation in which leafs move in and out of the radiation beam to modulate the intensity of the beam, thereby allowing the radiation dose to target the sella and avoid normal brain. In contrast, prior to conformal techniques two opposing temporal fields were often used, resulting in the temporal lobes receiving a similar radiation dose as the pituitary tumor.

A limitation of radiosurgery is that the field of treatment is often the region of visible tumor on MR imaging. Yet MR imaging is very insensitive for detecting microscopic tumor infiltration of the cavernous sinus or other structures adjacent to the pituitary. Because of the limited knowledge of what will occur 3–5 years after radiosurgery, the recurrence rate after what appears initially to be successful treatment, because of clones of resistant tumor, or due to progression of microscopic tumor outside the field of treatment, cannot now be known.

These arguments should not be perceived as refutations against the routine use of radiosurgery in most patients who need additional therapy after surgery (either because of incomplete endocrine control with medical therapy or because of the extraordinary expense that currently accompanies a lifetime of medical therapy with somatostatin analogues or GH receptor blockade). The convenience of having a single-session therapy and the potential of an early hormonal response are reasons enough for radiosurgery to be the first choice in most patients. However, there is no reason to add superfluous arguments, such as a reduced incidence of hypopituitarism compared with modern radiation therapy, when the data do not yet exist for us to reach those conclusions. There are also circumstances in which the use of modern techniques to deliver conformal fractionated radiation is the best choice, such as when, after surgery, residual or recurrent tumor abuts (within 2 mm) the optic nerves or chiasm or when the field that requires treatment is larger than what can be safely treated with radiosurgery.

Influence of Medication on Response to Radiosurgery

Many of the aforementioned issues also apply to the concept that medical therapy to suppress GH secretion during treatment reduces the efficacy of radiosurgery. There are only a handful of studies that address this issue. Some investigators suggest that the somatostatin analogs, if used during radiosurgery, reduce tumor response, whereas others find no correlation between the use of medical therapy during radiosurgery and the likelihood, degree, or pace of the endocrine response.

It is possible that considerable patient selection bias in the use of medication during the irradiation has been present. For instance, Landolt et al. reported that in patients treated with octreotide during radiosurgery, normal levels of GH and insulin-like growth factor–I took longer to develop than in patients without medical therapy. However, compared with patients receiving medical treatment, the group of patients without medical therapy during radiosurgery had lower average levels of GH (see Fig. 1, Landolt et al.[4]), which is the only consistent predictor of response to radiosurgery. The authors of other studies have reported no difference in response related to medical therapy during radiosurgery, as discussed by Rowland and Aghi[7] and Stapleton et al.[8] in this issue of *Focus*. Whether or not medical therapy during radiation exposure influences tumor response—one benefit of briefly withdrawing medical suppression of GH-producing tumors, as summarized by Rowland and Aghi[7]—it also provides a beginning baseline of GH and insulin-like growth factor–I without the confounding influences of hormonal suppression, for later comparisons; furthermore, unlike prolactin-producing tumors, brief withdrawal of medical therapy is unlikely to result in a rapid rebound of tumor size.

Endoscopic Surgery Versus Conventional Approaches Using the Operating Microscope

The potential advantages of using the surgical endoscope for pituitary surgery have been detailed for the past 20 years. In the past 15 years the advantages of the "pure" endoscopic technique compared to surgery with the operating microscope have been championed by its enthusiasts. Despite this claim, none of the 3 surgical series reported in the current issue, nor those reported elsewhere, demonstrates superior outcomes to conventional techniques by experienced surgeons. In fact, one group (Hofstetter et al.[3]) experienced with endoscopy describes a 46% remission rate, a 50% incidence of intraoperative CSF leakage, and 2 (8%) of 24 patients were left with panhypopituitarism after endoscopic surgery. Although several of the reports describe commendable results, there is no evidence that they are superior to other approaches. As stated by Gondim et al.[2] who use the pure endoscopic approach, "Although presenting better illumination and visualization of the lesions, no report has definitively proved the superiority of endoscopy over microsurgery in pituitary surgery…" and by Campbell et al.,[1] "While endoscopic approaches provide many theoretical benefits over standard microscopic techniques, recent publications have not consistently shown improvement in resection and complication rates in the endoscopic group."

Let us examine the advantages and disadvantages of the endoscopic and microscopic approaches. The principal advantage of the endoscope is that it can be used to provide a view lateral to the direct line-of-sight view of the operating microscope. This is particularly valuable for removing large tumors that extend laterally, beyond the direct view of the operating microscope, including large suprasellar tumors with lateral extension.

The disadvantages of the endoscope are as follows: 1) it provides monocular vision, whereas one has true binocular 3D vision with the microscope, permitting more precise microscopic dissection; 2) despite that endoscopic pituitary surgery was initially advertised as being less invasive, as practiced now it is the most invasive. The pure endoscopic procedures remove the posterior one-third of the midline structures of the nose (some surgeons include removal of a turbinate), whereas the microscopic approaches leave the midline, including the nasal mucosa, intact (there appear to

be no side effects from resection of the posterior segment of the midline nasal structures, but this cannot be accurately described as being "less invasive").

Finally, what is the basis of the emphasis on the "pure" endoscopic approach? If the surgeon needs to see laterally beyond where he can directly see with the operating microscope, he can do so with an endoscope-assisted approach, either by simply using the corridor of the nasal speculum, or, if more room is required, by removing the nasal speculum, replacing the nasal mucosa to the midline, and using a binasal endoscopic approach. In fact, the endoscope-assisted approach permits combining the advantages of the operating microscope and the endoscope in many patients. To take advantage of some of the features of the operating microscope, one of our coeditors, Dr. Laws, recently reported reverting to the microscope in 18% of 148 consecutive "pure" endoscopic cases, including 5 patients with acromegaly, and patients with Cushing's disease, repeated pituitary surgery, or those with an extended transsphenoidal approach.[10]

As neurosurgeons we are still exploring the ideal circumstances for using the endoscope compared with the microscope. At our institution we use both; Dr. John Jane Jr. uses the endoscope primarily, I use the operating microscope primarily, and in some circumstances we combine the two. It is clear from our experience that larger suprasellar tumors and tumors extending laterally beyond the direct view of the operating microscope are often best addressed with the endoscope, whether endoscopic surgery alone or endoscope assisted, whereas the very small tumors, those occurring with some frequency in Cushing's disease, may be best addressed with the operating microscope. Tumors between these extremes—most pituitary tumors requiring surgery—can be addressed via either approach with the expectation of success in most patients. In fact, the absence of improved outcomes when comparing series that uniquely used the endoscopic approach or the operating microscope may simply reflect the fact that the optimal approach was not selected for individual patients, but one approach or the other was used for all patients. Selection of patients for surgery with the endoscope whose circumstances are best managed by that approach, using the microscope for situations that are best suited for it, and either approach that the surgeon is most experienced with, and most adept at, for the tumors that fall between these extremes, may yield optimal overall outcomes. Of course, before that strategy can be implemented we must define which tumors are better managed with which approach.

We are still learning how to best use various new tools recently brought by advances in technology, including the most advanced techniques of radiosurgery and fractionated irradiation, surgery with the endoscope and the microscope, intraoperative MRI, etc. It is premature for claims of superiority to be made for one approach over another until the facts are in. *(DOI: 10.3171/2010.8.FOCUS10215)*

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