

Pituitary Tumors

By Michael H. Brisman, M.D., F.A.C.S.

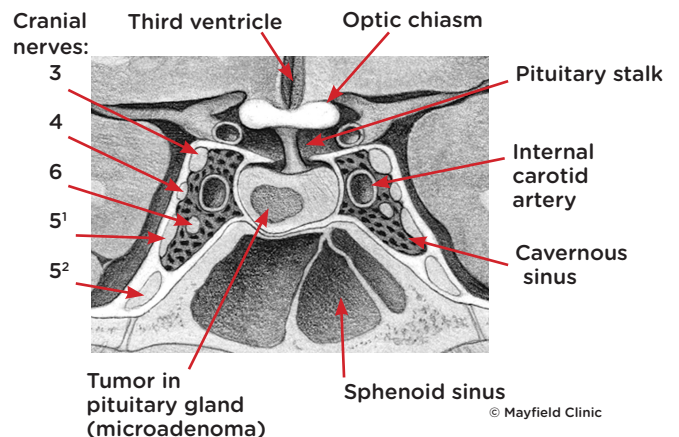
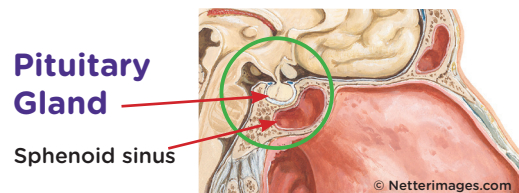
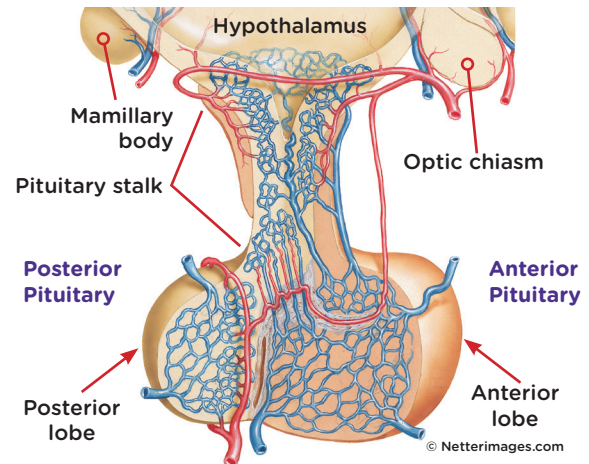
An Overview

The pituitary gland, also known as **the master gland**, directs the activity of numerous other glands and organs in the body. The hypothalamus acts, from a short distance, on the pituitary gland. The pituitary gland in turn, releases hormones that travel through the blood stream and act on distant glands (which themselves produce hormones), and distant organs, thus regulating various functions including metabolism, growth, and fertility [Table 1 – see page 2].

Pituitary tumors that occur are almost always benign **adenomas**. Small adenomas are quite common, and may be found incidentally at autopsy in as many as 20-25% of people. Symptomatic pituitary tumors are much less common, and represent about 15% of clinically symptomatic primary brain tumors.

Anatomy Around the Pituitary Gland

The pituitary gland sits in a cup-shaped segment of bone in the anterior skull base call the **sella turcica** (see image on page 5) which means the **turkish saddle**. The pituitary gland is attached to the hypothalamus by the **pituitary stalk**. The hypothalamus releases hormones into a venous plexus that causes the release or inhibition of hormones produced in the **anterior** pituitary gland. The hypothalamus synapses directly on the **posterior pituitary gland**, where other hormones are stored and released. Above the pituitary gland is the optic chiasm, the joining of the two optic nerves (cranial nerves 2). On either side of the pituitary gland are the right and left **cavernous sinuses**, small pathways of veins through which run cranial nerves 3, 4, 5 (the first and second branches), 6, and the cavernous portion of the **carotid artery**. Underneath the sella is a bone called the **clivus** (see image on page 5), and in front of the sella is the **sphenoid sinus** (an aerated bony space behind the nose which is lined by mucosa).



Classification of Pituitary Tumors

Pituitary tumors are generally classified into those that do not secrete hormones (**non-secretory**), and those that do secrete hormones (**secretory**). The three major categories of “secretory” pituitary adenomas are (1) **Prolactinomas**, (tumors that secrete an excess of prolaction), (2) Growth Hormone producing tumors which cause **Acromegaly** (or **Gigantism** in children), and (3) ACTH producing tumors which cause **Cushing’s Disease**.

Rarer secretory pituitary adenomas include tumors that produce an excess of Follicle Stimulating Hormone or Lutenizing Hormone, which usually behave like non-secretory adenomas, and tumors that produce an excess of Thyroid Stimulating Hormone, which can lead to excess thyroid hormone production.

Extremely rare is the malignant pituitary tumor, known as the **pituitary carcinoma**.

Pituitary adenomas are also further classified by their size. Tumors under 1 cm are considered **microadenomas**, tumors 1 cm or greater are considered **macroadenomas**.

TABLE 1

ANTERIOR PITUITARY LOBE

Hypothalamus → **Pituitary Gland** → **Organ** → **Function**

Releasing Factors

CRH	ACTH	Adrenals > Cortisol*	metabolism
CRH	TSH	Thyroid >> T3, T4*	metabolism
GnRH	FSH } LH }	Ovaries >> Estradiol, Progesterone Testes >> Testosterone	fertility fertility
GRF	GH	Liver, other tissues >> IGF-1	growth

Inhibiting Factors

Somatostatin	GH	Liver, other tissues >> IGF-1	growth
PIF (Dopamine)	PRL	Breasts, Gonads	lactation

POSTERIOR PITUITARY LOBE

Hypothalamus → **Pituitary Gland** → **Organ** → **Function**

ADH (Vasopressin)	ADH* (stored in posterior pituitary gland)	Kidney	water resorption
Oxytocin	Oxytocin (stored in posterior pituitary gland)	Uterus	labor contractions

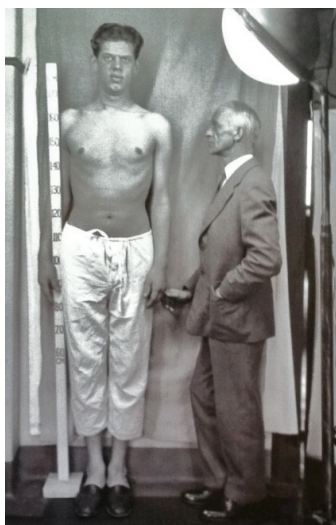
*Hormones needed by adults

CRH – corticotropin releasing hormone; GnRH – gonadotropin releasing hormone; GRF – growth hormone releasing factor; PIF – prolactin inhibiting factor; ADH – antidiuretic hormone; ACTH – adrenocorticotrophic hormone; TSH – thyroid stimulating hormone; FSH – follicle stimulating hormone; LH – lutenizing hormone; GH – growth hormone; PRL – prolactin; T3, T4 – thyroid hormones; IGF-1 – insulin like growth factor 1

Presentation of Pituitary Tumors

Pituitary tumors usually present gradually with symptoms related to mass effect or hormonal irregularity. Mass effect will usually cause frontal headaches or visual problems (most commonly loss of peripheral vision in either eye, a **bitemporal hemianopsia**, from compression of the optic chiasm). If a tumor causes an excess secretion of prolactin in a woman, she may experience loss of menstrual periods (**amenorrhea**) and milky drainage from the breasts (**galactorrhea**). If a tumor causes an excess secretion of growth hormone, an adult will develop Acromegaly (a child would develop Gigantism). If a tumor causes an excess secretion of ACTH, the person will develop Cushing's Disease.

Acromegaly is the syndrome that adults develop when there is excess secretion of growth hormone (GH). Over time, the face, hands, and feet become quite enlarged, as do various organs. Diabetes Mellitus can occur. If untreated, patients have reduced life expectancies from complications of various organ enlargements. The most reliable test for acromegaly is the blood IGF-1 level, which is almost always elevated in acromegaly. Exposure to excess growth hormone in childhood would cause abnormal growth of the arms and legs as well, leading to **Gigantism**. While acromegaly is almost always caused by a pituitary tumor, it can very rarely be caused by other tumors producing excess growth hormone releasing factor (GRF).



Harvey Cushing posing with a patient with Gigantism.

© Cushing/Whitney Medical Library

Cushing's Disease

occurs when a pituitary tumor produces an excess of ACTH, resulting in an excess of cortisol production in the body.

Cushing's Syndrome (hypercortisolism)

is the condition when the body has too much cortisol for any reason. Cushing's Syndrome can be caused by rare non-pituitary tumors that produce an excess of

ACTH, rare adrenal tumors that produce an excess amount of cortisol, or, most commonly, by taking steroid supplements. The end result of an excessive amount of cortisol in the body is a constellation of symptoms including obesity, hypertension, diabetes mellitus, a round shaped face with red cheeks, and easy bruisability. If untreated, patients have a reduced life expectancy from complications of prolonged exposure to excess cortisol.

Pituitary Apoplexy occurs when a pituitary tumor presents suddenly with a stroke or bleed within the tumor. In this case, there is sudden expansion of the tumor volume which can cause bad headaches, visual loss, trouble with movement of the eyes or eyelids (due to compression of nerves in the cavernous sinus), hormonal insufficiency, metabolic derangements, lethargy, or even death. Patients with pituitary apoplexy are hospitalized, receive hormonal replacement, and often require emergency surgery to remove or decompress the pituitary tumor.

Evaluation/Work-up for Pituitary Tumors

If a person is suspected of having a pituitary tumor, either because of headaches, vision problems, or hormonal abnormalities, a work-up should ensue. The major components of this work-up include an MRI of the brain, (with and without intravenous gadolinium, with a focus on the pituitary gland), various hormonal (endocrine) blood tests, and ophthalmologic examination. Blood tests that are used include the following: prolactin level, growth hormone level and IGF-1 level, morning cortisol, ACTH level, TSH, T3, and T4 levels, FSH, LH, and testosterone levels, and a basic blood count and chemistry. Pituitary hormone levels may be too high or too low and blood tests may determine what type of pituitary tumor a person has.

A special consideration in patients with macroadenomas or other large masses in the region of the pituitary gland is a phenomenon known as the **stalk effect**. The hypothalamus normally releases dopamine through the pituitary stalk to inhibit the release of prolactin from the pituitary gland. If there is a significant mass compressing the pituitary stalk, this inhibition is disrupted, leading to excess production of prolactin, up to as much as 200 ng/ml. Levels above this, however, are usually only seen in prolactin secreting tumors.

A head CT may be helpful if a craniopharyngioma is being considered, as the CT is particularly good at demonstrating calcifications, which are commonly found in craniopharyngiomas. CT scan is also useful if there is consideration for an acute hemorrhage into a pituitary tumor, as CT scans are also very good at demonstrating fresh bleeds.

For patients in whom Acromegaly is suspected, the diagnosis can also be confirmed with a **glucose suppression test**. GH blood levels which are normally suppressed after an oral glucose load, are not suppressed in acromegalics.

For patients in whom Cushing's Disease is clinically suspected, additional tests are performed including a 24 hour urine free cortisol measurement, and a **dexamethasone suppression test** [patients with Cushing's Disease will not suppress their blood cortisol levels after a low dose (1mg) of dexamethasone taken orally the night before, but will suppress their blood cortisol levels after a high dose (8mg) of dexamethasone taken orally the night before]. A salivary cortisol test may also be performed. If Cushing's Disease is suspected and the brain MRI is normal, an additional test may be performed, a **petrosal sinus sampling** (a test which assesses ACTH levels in the veins that drain the pituitary gland), to try to confirm and localize the tumor.

Ophthalmologic examination is performed in cases of visual compromise or optic nerve compression on brain imaging studies. This examination will usually include a test for acuity as well as visual field testing.

Pituitary Tumors due to Familial Syndromes

Almost all pituitary tumors are considered to be "sporadic" (spontaneous occurrences). However, there are some rare inherited or **familial** conditions that can involve pituitary tumors, the most common of which is **Multiple Endocrine Neoplasia type 1** (MEN 1). In MEN 1, people get tumors that involve multiple endocrine glands, the most common of which are the parathyroid glands, the pituitary gland, and the pancreas. MEN 1 patients can also get tumors of the thyroid gland and adrenal gland.

Differential Diagnosis of Pituitary Tumors

Other abnormalities can occur in the same region as pituitary tumors. These include Rathke's cysts, craniopharyngiomas, meningiomas, hypophysitis (lymphocytic and granulomatous), and aneurysms. These can usually be distinguished with MRI and CT imaging as well as clinical history.

Pituitary Carcinoma

Malignant tumors of the pituitary gland are fortunately, extremely rare. Malignant pituitary tumors, or pituitary carcinomas, are characterized by rapid growth and metastasis. Treatment is difficult, but will usually involve transsphenoidal surgery, followed by radiation and consideration for chemotherapy.

Pregnancy and Pituitary Tumors

The ability to become pregnant requires normal levels of pituitary hormones. The major problem in becoming pregnant in the case of pituitary tumors are the high prolactin levels that are usually seen in prolactinomas. The high prolactin levels usually cause irregular menses and prevent becoming pregnant. With medication (bromocriptine), prolactin levels normalize and women can again become pregnant normally.

During pregnancy, prolactin levels rise, and there can be growth of prolactinomas. In the case of a macroprolactinoma, this can threaten visual function if left untreated. Fortunately, bromocriptine will prevent the growth of these tumors, and studies have shown that bromocriptine is safe to take during pregnancy.

Women who lose significant amounts of blood and develop low blood pressure during delivery are at risk of developing a stroke of the pituitary gland with resultant hormone insufficiency. This condition is called **Sheehan's syndrome**. It does not involve any pituitary tumor. Treatment is with hormone replacement.

Women late in their pregnancy and in the early post-partum period can develop an autoimmune inflammatory condition of the pituitary gland called **lymphocytic hypophysitis**, a condition that can mimic a pituitary adenoma. Patients can develop headache, and vision problems and the MRI and CT are often suggestive of a pituitary adenoma. However, the presentation towards

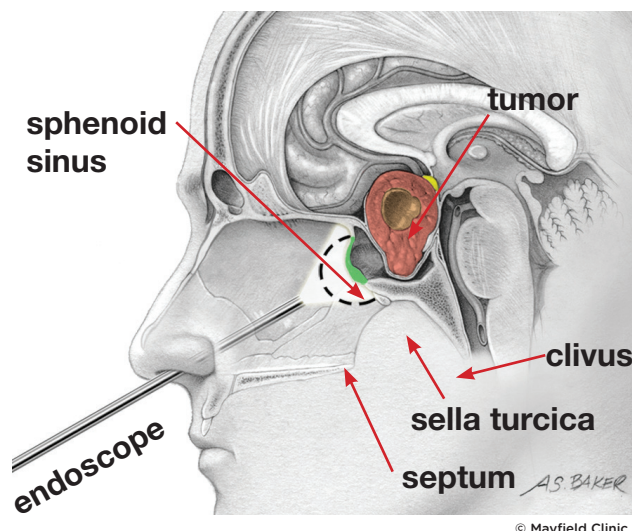
the end of a pregnancy along with lower than expected pituitary hormone levels suggests the diagnosis of lymphocytic hypophysitis. This condition is usually successfully treated with steroids and spontaneously resolves.

Surgery for Pituitary Tumors

Surgery is generally considered the first line of a treatment for non-secretory macroadenomas, Acromegaly, and Cushing's Disease. This procedure involves approaching the tumor from the nasal passages that are directly in front of the tumor (the sphenoid sinus), i.e., **a transsphenoidal approach**. The incision for this approach can be either through the upper gum or inside the nostril. Visualization is performed either with a microscope or an endoscope. I am currently performing more of these operations with the endoscope, though I am quite happy with the visualization achieved with both the endoscope and the surgical microscope, and am very comfortable using both techniques.

At the back end of the sphenoid sinus is the front of the sella turcica, the bone in front of the pituitary gland. This bone is usually thinned in cases of larger pituitary tumors. A small opening is made in this bone, and then an "X" shaped incision is made in the "dura", the parchment-like cover over the brain. At this point, the tumor usually comes into view. Pituitary tumors are usually very soft, with a consistency similar to oatmeal. The tumor is gradually removed with small ring-shaped curettes. A covering is then placed over the dura and some packing is left in the nose.

Sometimes, cerebrospinal fluid (CSF), the clear fluid that bathes the brain and spinal cord, can be encountered during this operation. If this occurs, I



Transnasal transsphenoidal endoscopic surgery.

will, at the time of surgery, usually place a spinal drain (a drain in the low back that gradually drains off CSF) for a few days to divert CSF from the pituitary region to allow it to scar in and heal.

Factors that may make complete surgical removal of the tumor more difficult include (1) firm tumor consistency, which occurs in about 5% of cases; (2) tumor growth off to the side, particularly into the cavernous sinus; and (3) very large tumor size.

In rare instances, a standard frontal **craniotomy** (surgical opening of the skull) may be required to remove a pituitary tumor. This would usually occur in cases of tumors that were very large, particularly if they were firm or grew far off to one side or the other.

Risks of surgery are very low, but can include bleeding, infection, hormonal insufficiency that might require replacement therapy with medicines, visual compromise, and other uncertainties.

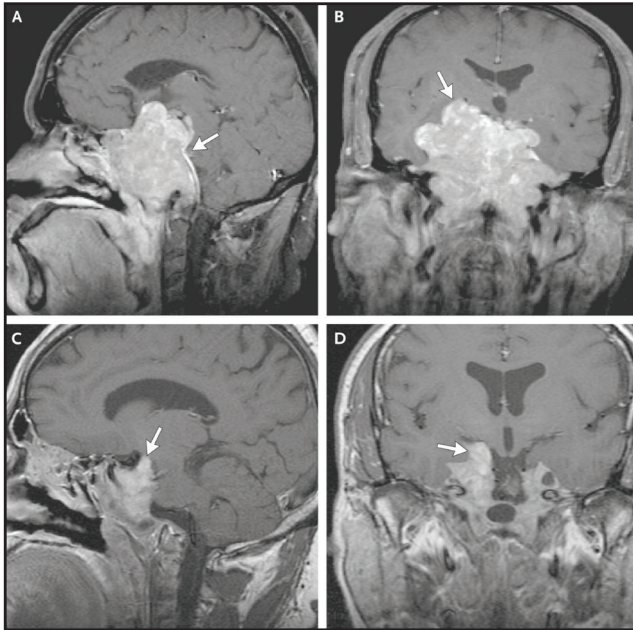
Radiation for Pituitary Tumors

For pituitary tumors that require surgical treatment (non-secretory macroadenomas, Acromegaly cases, and Cushing's cases), radiation is usually the second line treatment when tumor remains after surgery (or the first line treatment in a patient who could not undergo surgery for whatever reason). I will usually perform this treatment with **stereotactic radiosurgery**. This involves a very focused radiation treatment right to the area of the pituitary tumor.



CyberKnife®

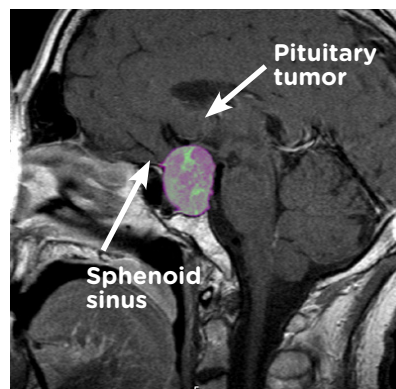
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Large Prolactinoma. MRI revealed a large mass (5.6 cm by 6.9 cm) invading the skull base (Panels A and B, arrows). After treatment with cabergoline, the prolactin level declined to 10,823 μg per liter. By the time of the 3-week follow-up visit, the prolactin level had further declined, to 772 μg per liter, and the patient's neurologic symptoms had resolved. After 40 months, the prolactin level was maintained at 25 μg per liter and the tumor had regressed substantially (Panels C and D, arrows).

Mohammed Ahmed, M.D., and Omar Al-Nozha, M.D.,
N Engl J Med 2010; 363:177 July 8, 2010 DOI: 10.1056/
NEJMicm0906033.

I will usually perform this treatment in one session with the **Gamma Knife®**, or in five sessions with the **CyberKnife®** or **Novalis TX™** linear accelerator devices, depending on the size of the tumor, and the proximity to the optic nerves. Higher doses are used for secretory tumors (Acromegaly or Cushing's). In treating pituitary tumors, I will only rarely use standard, wide field, external beam radiation therapy – radiation that is performed over several weeks in numerous small fractions -- for example, when the tumor that needs to be treated is very large. After radiation treatment, patients should be followed for possible subsequent hypopituitarism (low hormone levels), particularly thyroid hormone and cortisol levels, that might require hormone supplementation.



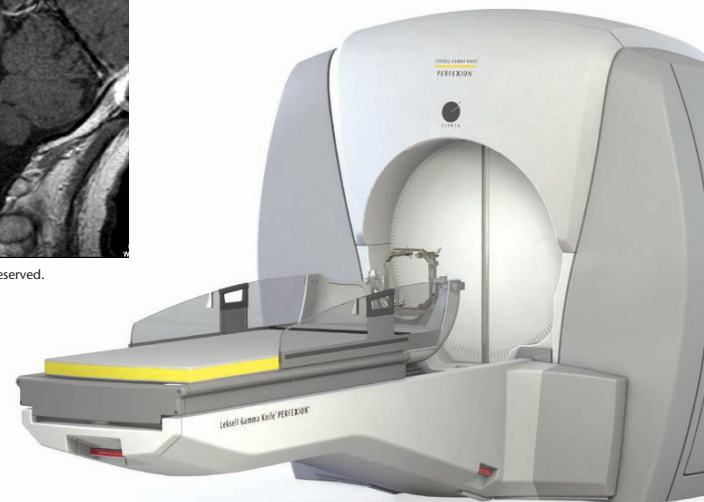
MRI Image: ©2013 Cedars-Sinai. All Rights Reserved.

Medicines for Pituitary Tumors

There are two categories of medicines commonly used for patients with pituitary tumors – (1) hormonal replacement medicines to supplement patients with insufficient hormone production and (2) hormonal suppression medicines for patients with overproduction of certain hormones.

Patients with pituitary tumors will sometimes have hormonal deficiency, particularly if they have had surgery, radiation, or pituitary apoplexy. Hormones that a person must have replaced if they are deficient are cortisol, thyroid hormones, and antidiuretic hormone. These three hormones can all be replaced with the oral, synthetic substitutes **hydrocortisone (Cortef)**, **levothyroxine (Synthroid®)**, and **desmopressin (DDAVP)**. Other hormones can also be replaced as needed.

Patients with secretory pituitary tumors may have higher than normal hormone levels, and patients with any pituitary macroadenoma may have modestly high elevations of prolactin (due to the **stalk effect**). Prolactinomas, and prolactin elevations can be effectively treated with the dopamine agonists **bromocriptine (Parlodel®)** or **cabergoline (Dostinex®)**. Prolactinomas, even very large tumors, will usually shrink dramatically and normalize prolactin levels in response to bromocriptine or cabergoline. For Prolactinomas, medical management is usually the treatment of choice, except in some rare cases of pituitary apoplexy or intolerance to medication, or lack of response to medication.



Gamma Knife® Perfexion™

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Acromegalics, whose growth hormone levels cannot be normalized with transsphenoidal surgery or stereotactic radiosurgery, are treated with **octreotide (Sandostatin®)**, a somatostatin analogue (the natural inhibitor of growth hormone) or **pegvisomant (Somavert®)** a growth hormone receptor antagonist. Octreotide and pegvisomant are both administered by subcutaneous injection. Cabergoline may also normalize growth hormone levels in a minority of cases, possibly because some of these tumors co-secrete prolactin.

Cushing's Disease patients whose cortisol levels cannot be normalized with transsphenoidal surgery or stereotactic radiosurgery, can be treated with **ketoconazole**, an imizodale derivative usually used as an antifungal medicine, that also inhibits cortisol synthesis. **Paseriotide (Signifor®)** a **somatostatin** analogue given by subcutaneous injection, has also recently been approved for refractory cases of Cushing's Disease.

Mifepristone (Korlym®), is an oral progesterone blocker, that can also be used. It blocks the effects of cortisol and can help control diabetes associated with Cushing's Disease. **Cabergoline** may also normalize cortisol levels in a minority of cases possibly because some of these tumors co-secrete prolactin.



Observation for Pituitary Tumors

Many pituitary tumors can be managed with “observation” only. These include non-secretory microadenomas and asymptomatic microprolactinomas. In these cases, management involves clinical follow up and serial MRI imaging.

GENERAL MANAGEMENT ALGORITHM FOR PITUITARY TUMORS

	1st Line	2nd Line	3rd Line
Non-Secretory			
Microadenoma	Observe		
Macroadenoma	Transsphenoidal Surgery	SRS	
Secretory			
Prolactinoma (asymptomatic)	Observe		
Prolactinoma (symptomatic)	Medicines (Bromocriptine or Cabergoline)		
Acromegaly	Transsphenoidal Surgery	SRS	Medicines (Sandostatin®, Pegvisamont or Cabergoline)
Cushing's Disease	Transsphenoidal Surgery	SRS	Medicines (Ketoconazole, Paseriotide, Mifepristone or Cabergoline)

SRS – Stereotactic Radiosurgery



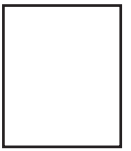
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MICHAEL H. BRISMAN, M.D., F.A.C.S.

Neurosurgeon

After receiving his undergraduate degree with high honors in Biology from Harvard University, Dr. Brisman obtained his medical degree from Columbia College of Physicians and Surgeons. He then completed a General Surgery internship and Neurological Surgery Residency at The Mount Sinai Medical Center in New York City where he was appointed

Board certified by the American Board of Neurological Surgeons and a Fellow of the American College of Surgeons, Dr. Brisman specializes in the treatment of Trigeminal Neuralgia and Brain Tumors. He serves as the Co-Medical Director of the Long Island Gamma Knife® Center at South Nassau Communities Hospital and he has served as the Chief of Neurosurgery and Co-Director of the Neuroscience Institute at NYU-Winthrop Hospital. In addition, Dr. Brisman has formerly served as President of both the Nassau County Medical Society and the New York State Neurosurgical Society.

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Dr. Brisman Treats:

- Trigeminal Neuralgia
- Gliomas
- Brain Tumors
- Brain AVMS
- Pituitary Tumors
- Hemifacial Spasm
- Meningiomas
- Glossopharyngeal Neuralgia
- Acoustic Neuromas
- Skull Tumors
- Brain Metastases

Dr. Brisman is proficient in the use of minimally invasive neurosurgical procedures including:

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- Gamma Knife®
- CyberKnife®
- Novalis Tx®
- Microvascular Decompression
- Neuroendoscopy
- Transsphenoidal Surgery
- Stereotactic-guided Craniotomy
- Percutaneous Trigeminal Rhizotomy