Cancer Association of South Africa (CANSA)

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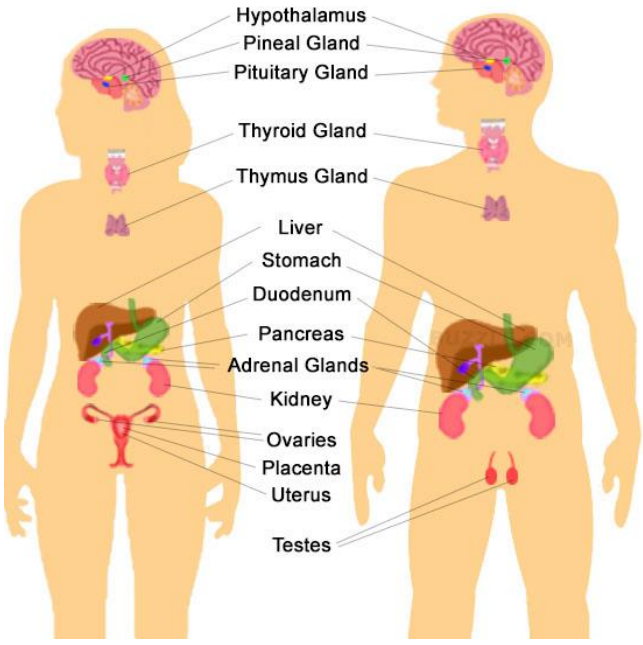
Fact Sheet
on
Pituitary Gland Cancer

Introduction

The endocrine system is a network of endocrine glands and nerves throughout the body. Endocrine glands produce and release hormones, which circulate around the body in the blood. Hormones keep an even balance of chemicals and fluid within the body and help the body respond to changes in the environment. Normally, the hormones released by endocrine glands are carefully balanced to meet the body's needs. There are many more organs in the body capable of secreting hormones than is popularly believed.

Endocrine organs (those capable of secreting hormones) include:

- Hypothalamus
- Pineal body
- Pituitary gland (anterior lobe)
- Pituitary gland (posterior lobe)
- Thyroid
- Alimentary system
  - Stomach
  - Duodenum
  - Liver
  - Pancreas
- Kidney
- Adrenal cortex
- Adrenal medulla
- Reproductive system
  - Testes
  - Ovaries
  - Placenta (during pregnancy)
  - Uterus (during pregnancy)
- Parathyroid
- Skin



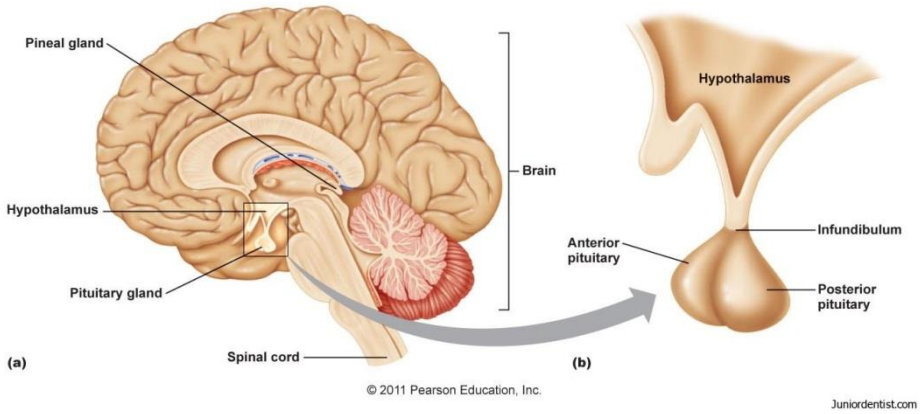
[Picture Credit: Major Endocrine Organs]

Pituitary Gland Cancer

When normal cells change and grow uncontrollably, they can form a mass called a tumour. A pituitary gland tumour can be benign (noncancerous and located only in the pituitary gland) or

malignant (cancerous, meaning it can spread to other parts of the body). Most often, pituitary gland tumours are noncancerous growths and are called pituitary adenomas. However, a pituitary gland tumour can occasionally act like a cancerous tumour by growing into nearby tissue and structures, or rarely, spreading to other parts of the body.

[Picture Credit: Pituitary Gland]



Pituitary gland tumours are NOT brain tumours, as the pituitary gland is located under the brain and is separate from the brain. However, a tumour in this gland can be very serious because a pituitary gland that does not work can cause problems with other organs. The tumour can also press on nearby structures, such as the optic nerves, limiting a person's sight.

Mete, O. & Lopes, M.B. 2017.
"This review focuses on discussing the main changes on the upcoming fourth edition of the WHO Classification of Tumors of the PituitaryGland emphasizing histopathological and molecular genetics aspects of pituitary neuroendocrine (i.e., pituitary adenomas) and some of the non-neuroendocrine tumors involving the pituitary gland. Instead of a formal review, we introduced the highlights of the new WHO classification by answering select questions relevant to practising pathologists. The revised classification of pituitary adenomas, in addition to hormone immunohistochemistry, recognizes the role of other immunohistochemical markers including but not limited to pituitary transcription factors. Recognizing this novel approach, the fourth edition of the WHO classification has abandoned the concept of "a hormone-producing pituitary adenoma" and adopted a pituitary adenohypophyseal cell lineage designation of the adenomas with subsequent categorization of histological variants according to hormone content and specific histological and immunohistochemical features. This new classification does not require a routine ultrastructural examination of these tumors. The new definition of the Null cell adenoma requires the demonstration of immunonegativity for pituitary transcription factors and adenohypophyseal hormones Moreover, the term of atypical pituitary adenoma is no longer recommended. In addition to the accurate tumor subtyping, assessment of the tumor proliferative potential by mitotic count and Ki-67 index, and other clinical parameters such as tumor invasion, is strongly recommended in individual cases for consideration of clinically aggressive adenomas. This classification also recognizes some subtypes of pituitary neuroendocrine tumors as "high-risk pituitaryadenomas" due to the clinical aggressive behavior; these include the sparsely granulated somatotroph adenoma, the lactotroph adenoma in men, the Crooke's cell adenoma, the silent corticotroph adenoma, and the newly introduced plurihormonal Pit-1-positive adenoma (previously known as silent subtype III pituitary adenoma). An additional novel aspect of the new WHO classification was also the definition of the spectrum of thyroid transcription factor-1 expressing pituitary tumors of the posterior lobe as representing a morphological spectrum of a single nosological entity. These tumors

include the pituicytoma, the spindle cell oncocytoma, the granular cell tumor of the neurohypophysis, and the sellar ependymoma."

De Sousa, S.M.C. & McCormack, A.I. 2018.
"Aggressive pituitary tumors (APT) refer to pituitary adenomas exhibiting rapid growth, resistance to conventional treatments and/or early/multiple recurrences, with abandonment of the previous term 'atypical pituitary adenoma'. Pituitary carcinomas (PC) are defined by non-contiguous craniospinal or distant metastasis. Whilst PC is exceedingly rare, comprising only 0.1-0.2% of all pituitary neoplasms, APT may account for up to 15% of all pituitary neoplasms, depending on the definition used. Typically evolving from known pituitary macroadenomas, APT/PC is most commonly diagnosed in the fifth decade of life with corticotroph and lactotroph neoplasms predominating. Diagnosis relies on MRI, hormonal studies and histological assessment including proliferative markers and immunohistochemistry for pituitary hormones and, most recently, transcription factors. Structural and molecular mechanisms have been proposed in the pathogenesis of APT/PC, although there appears to be no contribution from known familial pituitary tumor syndrome genes such as *MEN1*. Treatment is multimodal, ideally delivered by an expert team with a high-volume caseload. Surgical resection may be performed with the aim of either gross total resection or tumor debulking. Radiotherapy may be administered either as fractionated external beam radiation or stereotactic radiosurgery. Standard pituitary medical therapies such as somatostatin analogues have limited efficacy in APT/PC, whereas temozolomide yields a clear survival benefit. Evidence is emerging for the use of peptide receptor radionuclide therapy, tyrosine kinase inhibitors, VEGF inhibitors, and immunotherapy. Avenues for further research in APT/PC include molecular biomarkers, nuclear imaging, establishment of an international register, and routine pituitary tumor biobanking."

Incidence of Pituitary Gland Cancer in South Africa
The outdated National Cancer Registry (2014), known for its under reporting, does not provide any information on the incidence of pituitary gland cancer. It combines all the endocrine cancers together.

According to the National Cancer Registry (2014) the following number of endocrine cancer cases was histologically diagnosed in South Africa during 2014. The term 'histologically diagnosed' means that a biopsy specimen was forwarded to an approved laboratory where a specially qualified pathologist confirmed the diagnosis of cancer:

Group - Males 2014	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	24	1:12 300	0,07%
Asian males	0	-	-
Black males	14	1:15 371	0,13%
Coloured males	4	1:13 558	0,10%
White males	6	1:4 96	0,03%

Group - Females 2014	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	21	1:14 555	0,06%
Asian females	1	1:11 478	0,08%
Black females	13	1:22 930	0,08%
Coloured females	2	1:16 352	0,05%
White females	5	1:5 450	0,003%

The frequency of histologically diagnosed cases of endocrine cancer in South Africa for 2014 was as follows (National Cancer Registry, 2014):

Group - Males 2014	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	9	1	1	5	2	4	2	0
Asian males	0	0	0	0	0	0	0	0
Black males	6	0	0	4	0	3	1	0
Coloured males	1	1	1	0	0	0	1	0
White males	2	0	0	1	2	1	0	0

Group - Females 2014	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	8	2	2	3	3	2	1	0
Asian females	0	0	1	0	0	0	0	0
Black females	7	1	1	2	1	1	0	0
Coloured females	0	1	0	0	1	0	1	0
White females	1	0	0	1	1	1	1	0

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females' , however, always reflect the correct totals.

Signs and Symptoms of Pituitary Gland Cancer

A Pituitary Gland tumour can cause the pituitary gland to produce too much or too few hormones, which can cause problems in one's body. Large pituitary tumours - those measuring about 1cm - are known as macroadenomas. Smaller tumours are called microadenomas. Macroadenomas can put pressure on the rest of the pituitary gland and nearby structures.

Signs and symptoms of pressure from a pituitary tumour may include:

- Headache
- Vision loss, particularly loss of peripheral vision
- Nausea and vomiting
- Symptoms of pituitary hormone deficiency
- Weakness
- Less frequent or no menstrual periods
- Body hair loss
- Sexual dysfunction
- Increased frequency and amount of urination
- Unintended weight loss or gain

<u>Symptoms related to hormone level changes</u>

Some Pituitary Gland tumours, called functioning tumours, also produce hormones, generally causing an overproduction of hormones. Different types of functioning tumours can develop in the pituitary gland, each causing specific signs and symptoms and sometimes a combination of them.

Adrenocorticotropic hormone-secreting (ACTH) tumours

ACTH tumours produce the hormone adrenocorticotropin, which stimulates the adrenal glands to make the hormone cortisol. Cushing's syndrome results from the adrenal glands producing too much cortisol.

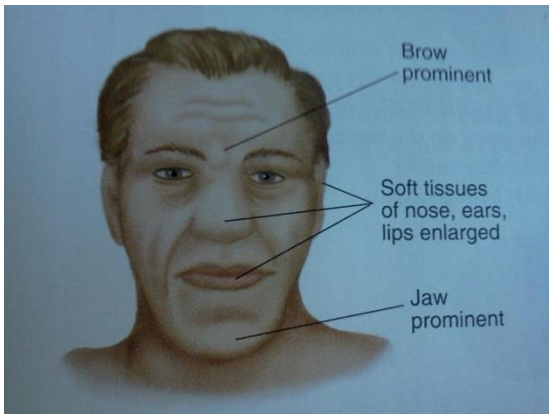
Signs and symptoms of Cushing's syndrome may include:

[Picture Credit: Cushing's]

- Fat accumulation around the midsection and upper back
- Exaggerated roundness of face
- A characteristic hump on the upper part of the back
- High blood pressure
- High blood sugar
- Muscle weakness
- Bruising
- Stretch marks
- Thinning of your skin
- Anxiety, irritability or depression

Growth hormone-secreting tumours

These tumours produce excess growth hormone. The effects from excess growth hormone (acromegaly) may include:



- Coarsened facial features
- Enlarged hands and feet
- Excess sweating
- High blood sugar
- Heart problems
- Joint pain
- Misaligned teeth
- Increased growth of body hair

[Picture Credit: Acromegaly]

Accelerated and excessive linear growth may occur in children and adolescents.

Prolactin-secreting tumours

Overproduction of prolactin from a pituitary tumour (prolactinoma) can cause a decrease in normal levels of sex hormones — oestrogen in women and testosterone in men. Excessive prolactin in the blood can affect men and women differently.

In women, prolactinoma may cause:

- Irregular menstrual periods

- Lack of menstrual periods
- Milky discharge from the breasts

In men, a prolactin-producing tumour may cause male hypogonadism. Signs and symptoms may include:

- Erectile dysfunction (ED)
- Infertility
- Loss of sex drive

Thyroid-stimulating hormone-secreting tumours

When a pituitary tumour overproduces thyroid-stimulating hormone, your thyroid gland makes too much of the hormone thyroxine. This is a rare cause of hyperthyroidism or overactive thyroid disease. Hyperthyroidism can accelerate your body's metabolism, causing:

- Sudden weight loss
- Rapid or irregular heartbeat
- Nervousness or irritability
- Frequent bowel movements
- Feeling warm or hot

Honegger, J., Nasi-Kordhishti, I. & Giese, S. 2019.

"Despite characteristic symptoms the diagnosis of clinically relevant pituitary adenomas is often delayed until an advanced stage due to the rarity of the disease. The typical clinical manifestations are presented in this review article. The recent discovery of the USP8 mutation in Cushing's disease and of X-linked acrogigantism (X-LAG) syndrome in early onset gigantism were milestones in the search for the molecular etiology of pituitary adenomas. The triad of endocrinological, radiological and ophthalmological diagnostics are the main pillars for the diagnostic work-up of pituitary adenomas. The standard treatment modalities, which include surgery, medical treatment and irradiation, have been further developed and refined. For transsphenoidal excision of pituitary adenomas, microsurgery and endoscopy are two equivalent surgical techniques with relatively few complications. Surgery represents the first-line treatment of pituitary adenomas. Prolactinomas are an exception as the medical treatment with dopamine agonists is highly efficient. Nowadays, new medical treatment options are available for acromegaly and Cushing's disease and are used for second-line treatment. The alkylating chemotherapeutic agent temozolomide is used for the first-line chemotherapy of rare aggressively growing pituitary adenomas. Irradiation is indicated if surgical and medical treatment options are insufficiently successful. Stereotactic one-stage irradiation (radiosurgery) is especially suitable for well-demarcated invasive residual or recurrent adenomas in the cavernous sinus. A new development is hypofractionated radiosurgery for protection of structures at risk. Fractionated irradiation is necessary with large radiation volumes and for pituitary adenomas with a close proximity to the optic tract."

Staging of Pituitary Gland Cancer

Staging is a way of describing where a tumour is located, if or where it has spread, as well as whether it is affecting the functions of other organs in the body. Doctors use diagnostic tests to determine the tumour's stage, so staging may not be complete until all of the tests are finished. Knowing the stage helps the doctor to decide what kind of treatment is best and can help predict a

patient's prognosis (chance of recovery). There are different stage descriptions for different types of tumours.

Diagnosis of Pituitary Gland Cancer

Pituitary tumours are usually found when a person goes to the doctor because of symptoms they are having. If there is a reason to suspect that a person might have a pituitary tumour, the doctor will use one or more tests to find out. Signs and symptoms might suggest that the person could have a pituitary tumour, but tests are needed to confirm the diagnosis.

The symptoms and physical examination results may lead the doctor to believe that a patient might have a pituitary tumour. If the doctor suspects a hormone-producing tumour, hormone levels in the blood and/or urine will be measured.

Imaging tests

Imaging tests use x-rays, magnetic fields, or other means to create pictures of the inside of your body. They may be done to look for pituitary tumours or to see if they have grown into nearby structures. In some cases, an imaging test of the head done for another reason may detect a pituitary tumour.

Magnetic Resonance Imaging (MRI) scan - MRI scans use radio waves and strong magnets to create detailed pictures of the inside of the body. The energy from the radio waves is absorbed and then released in a pattern formed by the type of tissue and by certain diseases. A computer translates the pattern into a very detailed image of parts of the body. A contrast material called *gadolinium* is sometimes injected into a vein to improve the quality of the image.

MRI scans are very helpful in looking at the brain and spinal cord and are considered to be the best way to identify pituitary tumours of all types. The images they provide are usually more detailed than those from CT scans (see below). MRI can show macroadenomas of the pituitary gland, as well as most microadenomas. But MRI may not be able to detect microadenomas that are smaller than 3 mm (about 1/8 inch) across. Sometimes the MRI scan will show a small abnormality in the pituitary that has nothing to do with the patient's symptoms. Between 5% and 25% of healthy people have some minor abnormality of the pituitary gland that shows up on an MRI scan.

Computed tomography (CT) scan - the CT scan is an x-ray test that creates detailed cross-sectional images of part of the body. Instead of taking one picture, like a standard x-ray, a CT scanner takes many pictures as the camera rotates around the patient while he/she lies on a table. A computer then combines these pictures into an image of a slice of the body. Unlike a regular x-ray, a CT scan creates detailed images of the soft tissues in the body.

CT scans can find a pituitary adenoma if it is large enough, but MRI scans are used much more often to look at the brain and pituitary gland.

Karimian-Jazi, K. 2019.
Background: In this article, the most common pituitary gland tumors and the various differential diagnoses with focus on (neuro-)radiological diagnostic criteria are presented.
Materials and methods: An intensive, selective search of the literature in PubMed was carried out.
Results: Pituitary adenomas account for approximately 10-15% of all intracranial brain tumors and are the most common tumors of the sellar region. Beyond a size of 10 mm they are called macroadenomas, under 10 mm microadenomas. They can be distinguished into hormone-active and non-active adenomas. Most of the hormone-active adenomas secrete prolactin (50%), more rarely somatotropin (10%) or corticotropin (5%). Tumors in the sellar region can arise from various tissues. Due to the anatomically complex location, local adjacent structures can be affected or compressed by the tumors. Particularly in case of suprasellar extension, visual impairment due to pressure on the optic chiasm is common. Important differential diagnoses for sellar tumors include craniopharyngiomas, meningiomas, metastases, aneurysms and Rathke cleft cysts. The task of image diagnostics is the early detection of the lesions as well as the proliferation pattern into perifocal structures. Gold standard is the thin-section, contrast-enhanced MRI examination. Dynamic contrast administration is crucial for the diagnosis of the microadenoma and the specific enhancement characteristic of some other tumors.
Conclusion: A highly focused imaging protocol is important for the diagnosis of sellar lesions such as pituitary tumors. The current favored modality is contrast-enhanced MRI, preferably with dynamic contrast-enhanced T1-weighted sequences. Early detection of the lesions and identification of the precise anatomical location are of great importance for diagnosis and therapy.

Tests of pituitary tissue samples - in diagnosing tumours of most parts of the body, imaging tests and blood tests may strongly suggest a particular type of tumour, but a *biopsy* (taking a sample of the tumour to examine under the microscope) is usually the only way to be certain of that diagnosis. In many situations, doctors will not treat the tumour until a biopsy has been done.

A pituitary tumour is an exception to this general rule in that a biopsy is not usually needed before treatment. One reason is that the hormone tests for some types of adenomas are very accurate, so a biopsy is not likely to provide much more information. Biopsies in this part of the body can also pose a very small risk of serious side effects. On top of this, some types of adenomas can be treated without surgery, using medicines or radiation therapy.

Treatment of Pituitary Gland Cancer
The prognosis (chance of recovery) depends on the type of tumour and whether the tumour has spread into other areas of the central nervous system (brain and spinal cord) or outside of the central nervous system to other parts of the body.

Treatment options depend on the following:
- The type and size of the tumour
- Whether the tumour is making hormones
- Whether the tumour is causing problems with vision or other symptoms
- Whether the tumour has spread into the brain around the pituitary gland or to other parts of the body
- Whether the tumour has just been diagnosed or has recurred (come back)

Treatment options and recommendations depend on several factors, including the type and stage of the tumour, possible side effects, and the patient's preferences and overall health. Learn more about making treatment decisions.

Active surveillance - active surveillance is an option for some people with a pituitary gland tumour who have no symptoms from the tumour and have hormones that work normally. During active surveillance, the tumour is monitored closely with periodic examinations and tests. Treatment would begin only if the tumour started causing symptoms.

Surgery - surgery is the removal of the tumour and surrounding tissue during an operation. It is the most common treatment for a pituitary gland tumour. Surgery for a pituitary gland tumour is often successful in removing the entire tumour. About 95% of surgeries to remove pituitary gland tumours are done by the transsphenoidal route (through the nasal passage, going along the septum that separates the two nostrils, then through the sphenoid sinus cavity located deep above the back of the throat to the pituitary gland immediately behind it). The rest are done through a craniotomy (an opening in the skull). This can be done using a microscope or an endoscope (a long flexible tube), or both, so the surgeon can see the tumour. Both of these methods are equally safe and effective when done by a skilled surgeon. Talk with your surgeon beforehand to learn about possible side effects based on the type of surgery you will have. Learn more about surgery for a tumour.

Marino, A.C., Taylor, D.G., Desai, E. & Jane Jnr, J.A. 2019.
Pituitary adenomas are a rare but important central nervous system tumor in children. Because of differences in growth and development, the manifestations of pituitary adenomas in children may differ from those seen in adults. Unlike adult patients, the pediatric population more often presents with clinically secretory adenomas. Although medical management is first-line treatment of prolactinomas, transsphenoidal surgery is appropriate for most children with Cushing disease and gigantism. Although some pediatric patients present surgical challenges because of small anatomic dimensions or an incompletely developed sphenoid sinus, transsphenoidal surgery can be safely and effectively undertaken in most children, with low complication rates.

Radiation therapy - radiation therapy is the use of high-energy x-rays or other particles to kill tumour cells. A doctor who specializes in giving radiation therapy to treat a tumour is called a radiation oncologist. The most common type of radiation treatment is called external-beam radiation therapy, which is radiation given from a machine outside the body. A radiation therapy regimen (schedule) usually consists of a specific number of treatments given over a set period of time.

For some patients, stereotactic radiation therapy (delivering a high dose of radiation directly to the tumour) is used when any part of the tumour is left after surgery. Not all patients with part of a tumour remaining after surgery need radiation therapy because some noncancerous pituitary gland tumours do not grow back even when some tumour is left behind after surgery. If the entire tumour is removed, then radiation therapy is not needed.

Lovo, E.E., Campos, F. J., Caceros, V.E., Minervini, M., Cruz, C.B., Ariast, J.C. & \Reyes, W.A. 2019. We report our initial series of terminally ill cancer patients treated with radiosurgery to the pituitary gland to alleviate pain. Methods A fully automated rotating gamma ray unit was used to deliver a high dose of radiation (150Gy) using an 8 mm collimator to the neurohypophysis in 11 patients suffering from opioid-refractory pain deriving from cancer. Results From November 2016 to November 2018, 11 patients were treated, and 10 were eligible for follow-up evaluation. Pain from bone metastases was present in 70%; others suffered from neuropathic and visceral pain. The median survival was 119.7 days (range: 32 to 370). The visual analogue scale (VAS) was nine (7-10) and standardized to 10; eight patients (80%) responded. The average VAS at the time of response was three (range: 1-6), and the average time to response was 2.8 days (range: 2-5). In the first week, 40% of the patients categorized the result as 'excellent', 30% deemed the result 'good', and 20% reported the result as 'poor'. One patient (10%) referred to the result as 'regular'. Those who responded were able to reduce their medications by at least 25%. The one-month average VAS score was five (range: 1-6), 60% reported a 'good' effect, 20% reported 'excellent' results, and 20% had no response. Of the study participants, 60% maintained their level of medicine consumption at lower than baseline. At the end of life, five patients (50%) presented substantial pain, two (20%) never had a therapeutic effect, and three (30%) died without substantial pain. There were no clinical complications that could be attributed directly to the treatment. Conclusion Radiosurgery to the pituitary gland is effective and safe and warrants further investigation to understand its potential role in palliative care in cancer patients.

Hormone replacement therapy (HRT) - HRT is often necessary for patients with a pituitary tumour, and this may include replacement of thyroid and adrenal hormones, growth hormone, and/or testosterone in men or estrogen in women.

Drug therapy – certain drugs may be used to treat the problem.

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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Pituitary Gland
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