**"Radiation Therapy in Pituitary Adenoma: Current Approaches and Emerging Trends"**

**Introduction**

The pituitary gland is given the term “master gland" of the endocrine system, which regulates various hormonal processes throughout the body. Pituitary tumors are abnormal growths that develop in this small, pea-sized gland located at the base of the brain. They can be benign or malignant. A pituitary adenoma is a benign tumor that arises from the pituitary gland. It can cause hormonal imbalances and various clinical manifestations, leading to significant morbidity if left untreated.

**Pituitary anatomy and physiology**

The pituitary gland is a small, endocrine gland whose location is at the base of the brain within a bony depression called the sella turcica, situated in the sphenoid bone. The pituitary stalk connects the pituitary gland and the hypothalamus forming the hypothalamic-pituitary axis. It is in close vicinity to optic chiasma, optic nerve, cranial nerve III, IV, V, and VI axis Despite its small size, the pituitary gland plays a crucial role in regulating various hormonal processes throughout the body.[1]

The anatomy of the pituitary gland is divided into two main parts: the anterior pituitary and the posterior pituitary. These two portions have distinct embryological origins and functions:

1. Anterior Pituitary- it makes up about 75% of the entire gland and is composed of glandular tissue. Growth Hormone (GH), Prolactin (PRL), Adrenocorticotropic Hormone (ACTH), thyroid-Stimulating Hormone (TSH), Follicle-Stimulating Hormone (FSH), and Luteinizing Hormone (LH).
2. Posterior Pituitary: The posterior pituitary makes up about 25% of the gland and is an extension of the neural tissue of the hypothalamus. Nerve cell bodies in the hypothalamus produce hormones, which are transported down nerve fibers (axons) to the posterior pituitary. The posterior pituitary does not synthesize hormones but stores and releases two hormones produced by the hypothalamus Oxytocin and Antidiuretic Hormone (ADH), also known as vasopressin.

WHO 2017 CLASSIFICATION OF PITUITARY TUMOURS

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| --- | --- | --- |
| 1 | Pituitary adenoma | Somatotroph adenomaLactotroph adenomaThyrotroph adenomaCorticotroph adenomaGonadotroph adenomaNull cell adenomaPlurihormonal and double adenoma |
| 2 | Tumours of the posterior pituitary | PituicytomaGranular cell tumor of neurohypophysisSpindle cell oncocytomaSellar ependymoma |
| 3 | Neuronal and para-neuronal tumors | Gangliocytoma and mixed typesNeurocytomaNeuroblastomaparaganglioma |
| 4 | Craniopharyngioma | Adamantinomatous typePapillary craniopharyngioma |
| 5 | Mesenchymal tumors | Meningioma SchwannomaChordomaSolitary fibrous tumor/hemangiopericytoma |
| 6 | Others | Pituitary carcinomaPituitary blastomaGerm cell tumorsHaematological tumorsSecondary tumors |

The new classification is based on IHC for pituitary hormones, transcription factors, and other markers used in routine pathology practice, like low molecular weight cytokeratin (LMWCK) and estrogen-receptor alpha (ERα).Top of Form

**WHO 2022 CLASSIFICATION OF PITUITARY TUMOURS(UPDATED)**

The new classification differentiates the anterior lobe (adenohypophysis) from the posterior lobe (neurohypophyseal) and hypothalamic tumors.

Other tumors arise in the sellar region.

Anterior lobe tumors are (i) well-differentiated adenohypophysis tumors that are now classified as pituitary neuroendocrine tumors (PitNETs)

(ii) Pituitary blastoma,

(iii) Two types of craniopharyngioma.

The new WHO classification provides detailed histological subtyping of a PitNET based on the tumor cell lineage, cell type, and related characteristics. The routine use of immunohistochemistry for pituitary transcription factors (PIT1, TPIT, SF1, GATA3, and ERα) is included in this classification.



**Classification of Pituitary Adenoma**

Pituitary adenomas are classified based on their size, hormonal activity, and histopathological features. The classification of pituitary adenomas includes the following categories:

1. Microadenoma:
	* Tumor size less than 1 centimeter in diameter.
	* Microadenomas are usually considered small and may not cause mass effects on surrounding structures.
2. Macroadenoma:
	* Tumor size 1 centimeter or larger in diameter.
	* Macroadenomas can cause mass effects on nearby structures, leading to visual disturbances, headaches, and hormonal imbalances.
3. Non Functioning adenoma(NFPA) -Prolactinoma: A pituitary adenoma that primarily secretes prolactin (PRL).
4. Functioning Pituitary adenoma(FPA)
5. Tumors that secrete excessive growth hormone(GH), adrenocorticotropic Hormone (ACTH),thyroid-stimulating hormone (TSH),follicle-stimulating hormone (FSH), and/or luteinizing hormone(LH).

**Etiology and pathogenesis**

The etiology and pathogenesis of pituitary adenomas, which are benign tumors originating from the pituitary gland, are complex and multifactorial. Although the exact cause of most pituitary adenomas remains unclear, several factors are involved in their development[2].

 1. Genetic Predisposition: Some people may have an inherited genetic predisposition. Mutations in certain genes such as MEN1, AIP, and PRKAR1A have been associated with an increased risk of pituitary adenoma.

2. Random mutations: In many cases, pituitary adenomas occur randomly without a clear genetic predisposition.

3. Hormonal disorders: disturbances in the regulation of production and secretion of pituitary hormones can influence the development of pituitary adenomas. For example, overproduction of growth hormone (GH) can lead to growth hormone-secreting adenomas, which cause acromegaly.

4. Hormonal stimulation.

5. Pituitary hyperplasia: In some cases, the initial overgrowth of pituitary cells, known as pituitary hyperplasia, can develop into a pituitary adenoma. The factors that contribute to pituitary hyperplasia are not fully understood but may include hormonal imbalances, genetic factors, and other yet unidentified mechanisms.

6. Exposure to radiation: Previous exposure to head and neck radiation is associated with an increased risk of developing pituitary adenomas later in life.

7. Other factors: Some rare hereditary syndromes, such as Carney complex and McCune-Albright syndrome, are associated with an increased risk of developing pituitary adenomas.

 It is more common in people who received radiation in childhood or adolescence for conditions such as brain tumors or cranial radiation for radiation is important to note that the development of pituitary adenomas is likely a result of a combination of genetic, hormonal, and environmental factors. Further research is needed to fully elucidate the underlying mechanisms involved in the etiology and pathogenesis of pituitary adenomas.

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**Clinical presentation**

The clinical picture of pituitary adenomas can vary greatly depending on the size, location, and hormonal activity of the tumor. Some adenomas may be inactive and not secrete hormones, while others may produce too much of certain hormones, causing different symptoms. Here are the common clinical manifestations of pituitary adenomas:

1. Symptoms of mass effect: When pituitary adenomas grow, they can compress surrounding structures such as the optic nerve and optic nerve, causing visual disturbances. These can include blurred vision, visual field defects (such as loss of peripheral vision or bilateral hemianopsia), and double vision (diplopia).

2. Hormonal disorders: galactorrhea in non-pregnant women. In men, it can cause decreased libido, erectile dysfunction, and infertility. Excess growth hormone (GH) can cause acromegaly, dysplasia, enlargement of the nose and lips), Cushing's disease is characterized by weight gain, central obesity, moon face, muscle weakness, easy bruising, hyperthyroidism, and hormonal disorders related to the reproductive system. system and can cause irregular menstrual cycles, infertility, and symptoms associated with low sex hormone levels.

3. Non-functioning pituitary adenoma: Adenomas that do not secrete significant amounts of hormones can still cause symptoms due to the mass effect. These tumors can cause headaches, visual problems, and other symptoms related to pressure on surrounding structures.

4. Headache is a common symptom in people with pituitary adenomas, especially macroadenomas, which cause compression of nearby structures.

5. Hypopituitarism.

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**Diagnosis and evaluation**

The process aims to confirm the presence of the tumor, determine its size and location, assess hormonal activity (if applicable), and evaluate any potential mass effect on surrounding structures.

1. Clinical assessment. A thorough medical history and physical examination are essential to detect all signs and symptoms.

 2. Hormonal evaluation: Depending on the supposed hormone-secreting properties of the adenoma, different hormonal analyzes are performed. Standard hormone tests may include measurements of prolactin, PRL, growth hormone, IGF-1, ACTH, cortisol, TSH, free thyroxine (T4), FSH, luteinizing hormone, LH, and sex hormones.

3. Magnetic resonance imaging (MRI): Dynamic contrast-enhanced T1-weighted MRI of the brain and imaging modality of choice. It is hypointense on T1W MRI and hyperintense on T2W MRI.[3]

4. Computed tomography (CT): CT scans can be used to look at bone destruction.

5. Visual field testing, such as circumference, is done to assess possible visual impairment due to optic chiasm or nerve compression.

6. Pituitary function testing. Evaluation of pituitary function is critical to identify possible hypophysitis (pituitary deficiency) due to a mass effect of a tumor on normal pituitary tissue.

 7. Biopsy (rarely performed): Pituitary adenomas are usually diagnosed based on clinical and imaging findings and a biopsy is not necessary. In unusual situations where the diagnosis is uncertain or when pituitary cancer is suspected, a biopsy may still be performed.

 8. Genetic testing (if necessary): Genetic testing may be recommended in some cases, especially if there is a family history of pituitary tumors or features suggestive of a genetic syndrome (eg, multiple endocrine neoplasia type 1, McCune-Albright).



Fig 1- T1 contrast sagittal section of MRI brain showing pituitary macroadenoma

**Treatment**

Treatment of a pituitary adenoma depends on several factors, such as the size and location of the tumor, hormonal activity (if necessary), the presence of symptoms, and the general health of the patient. The main treatments for pituitary adenoma are:

1. Observation - For small, asymptomatic pituitary adenomas that do not cause significant hormonal imbalance or mass effects on surrounding structures, an observation strategy can be used. Regular follow-up with imaging and hormone tests is important to monitor tumor growth and hormone levels.

2. Medical treatment - Hormone-secreting pituitary adenomas: Medications are usually used to control hormone overproduction. For example, dopamine agonists (eg, cabergoline, bromocriptine) are used to treat prolactinomas, while somatostatin analogs (eg, octreotide, lanreotide) are used to control growth hormone-secreting adenomas and some ACTH-secreting tumors.

 3. Surgery is the primary form of treatment for large adenomas causing mass effects, inoperable symptomatic adenomas, and some hormone-secreting tumors unresponsive to drug therapy. Transsphenoidal surgery: This is the most common approach to surgically removing pituitary adenomas. This is a minimally invasive procedure that is performed through the nasal cavity and sinuses to access the pituitary gland. The surgeon removes the tumor while preserving as much of the normal pituitary gland as possible. Endoscopic transsphenoidal surgery: a newer technique that uses an endoscope to visualize and remove the tumor. This allows for better imaging and access to hard-to-reach tumors[4].

**4. Radiation Therapy**

**INDICATIONS**

Sinus invasion, incomplete resection of large NFPA, recurrent or progressive tumors, inoperable symptomatic tumors, and refractory secretory tumors [5].

Conventional external beam radiation therapy: In cases where surgery is not possible or the tumor is not completely removed, radiation therapy can be used to control tumor growth and hormone secretion.

Stereotactic radiosurgery (Gamma Knife or CyberKnife): A precise form of radiation therapy that delivers a high dose of radiation to the tumor while minimizing exposure to surrounding tissue. It is often used for smaller tumors or residual tumor remnants after surgery. Radiotherapy is often used for pituitary adenomas that recur after surgery or do not respond to therapy [6].

Combination therapy: In some cases, combination therapy may be used to treat pituitary adenomas. For example, surgery may be followed by radiation therapy or drug therapy to achieve better tumor control and hormonal normalization.

Two main types of radiation therapy are used for pituitary adenomas:

Conventional external radiotherapy: In this external radiotherapy, high-energy X-rays are delivered from outside the body to the tumor site[7]. Treatment is usually given in small daily doses over several weeks to minimize damage to surrounding healthy tissue. This form of radiation therapy is suitable for larger or aggressively growing adenomas. It is often used as an adjuvant treatment after surgical removal to reduce the risk of tumor recurrence.

Stereotactic radiosurgery (SRS): is a very precise and targeted form of radiation therapy that delivers a high dose of radiation to the tumor with extreme precision. It uses multiple converging beams of radiation to focus on the tumor while sparing nearby healthy tissue. Gamma Knife [8][9] and CyberKnife are common systems used to deliver SRS. It is often used for small pituitary adenomas or after surgery to target residual tumor tissue. It is a one-time treatment that is usually done in one or a few sessions.

Benefits of Radiation Therapy in Pituitary Adenoma:

* It is an alternative treatment option for patients who are non-surgical or do not prefer surgery.
* It can effectively control tumor growth and stabilize hormone levels in hormone-secreting adenomas.
* Minimizes the risk of damage to surrounding normal brain tissue.
* Can be used with other treatments to improve tumor control and hormone normalization.

Treatment techniques SRS for pituitary adenomas are usually delivered as single-fraction SRS or less commonly as multi-fraction SRS (2-5 fractions). The gamma knife uses 192 radioactive cobalt-60 sources arranged spherically in a uniform internal collimating system throughout the head cast to focus the beams to a central point. With optimal combinations of collimator number, aperture, and location, a highly accurate but inhomogeneous dose distribution and a high central tumor dose can be achieved. Traditionally, patients are placed in a rigid stereotactic frame and the dose is usually set as a 50% isodose to achieve a maximum dose in the center of each selected target and a prescribed dose at the edge of the target.

The LINAC is the most widely used for treatment with SRS in the world and uses multiple fixed fields or arcs formed by a multi-leaf collimator. Dose uniformity can be improved using radiation intensity modulation (IMRS) or volumetric-modulated arc therapy (VMAT).

Patients are typically attached to a highly accurate frameless stereotaxic mask attachment system with a reported accuracy of 1-2 mm. However, the most technologically advanced LINACs offer greater accuracy in repositioning patients using cone beam CT (CBCT) imaging.

fig2-SRS thermoplastic cast

 Adverse Events

Radiotherapy can cause short-term side effects such as fatigue, headache, and mild nausea. These side effects are usually temporary and disappear after treatment.

Long-term side effects may include damage to the pituitary gland, causing hypopituitarism. However, modern techniques aim to minimize the risk of this complication. In general, radiation therapy is a valuable and effective treatment option in selected cases of pituitary adenoma. The decision to use radiation therapy is made based on the characteristics of the tumor, the health of the patient, and the recommendations of the multidisciplinary team. Regular follow-up is essential to assess response and manage potential side effects.

**Follow up**

The follow-up protocol includes hormone evaluation every 3 months after treatment and once every 6 months thereafter. Eye examination every 6 months to assess visual acuity, fundus, and ocular motility every 6 months in patients with baseline abnormalities and annually in patients with normal vision. Follow-up MRI is recommended 3-6 months after therapy and then annually for 5 years and then every 2-3 years until progression [10][11].

**Conclusion-**

Pituitary tumors often require multidisciplinary treatment. Possible treatments include observation, surgery, medication, and radiation therapy. Currently, radiation techniques are very advanced and have better tumor control and good quality of life after SRS without serious side effects compared to surgery. Long-term follow-up is needed to look for long-term effects.

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