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

Introduction

The pituitary gland gets the term master from 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 are classified as benign or malignant. A pituitary adenoma is a benign tumour that arises from the pituitary gland. This can lead to hormonal imbalances and various clinical manifestations that can lead to serious illness if left untreated.

Pituitary anatomy and physiology

The pituitary gland is a very small in size endocrine gland located at the base of the brain in a bony depression called the sella, which is located in the sphenoid bone. The pituitary stalk connects the pituitary gland and the hypothalamus, forming the hypothalamic-pituitary axis. It is located on the axis near the optic nerve, optic nerve, and cranial nerves III, IV, V, and VI Despite its small size, the pituitary gland plays an essential 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 gland and the posterior pituitary gland. These two parts have a different embryological origin and function:

1. Anterior pituitary gland - It makes up about 75% of the entire gland and includes 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 gland: The posterior pituitary gland makes up about 25% of the gland and is a continuation of the hypothalamic nervous tissue. Neurons in the hypothalamus produce hormones that are transported along nerve fibers (axons) to the back of the pituitary gland. The posterior pituitary does not synthesize hormones, but instead stores and releases two hormones produced by the hypothalamus, oxytocin and antidiuretic hormone (ADH), also known as vasopressin.

WHO 2017 CLASSIFICATION OF PITUITARY TUMOURS

1	Pituitary adenoma	Somatotroph adenoma Lactotroph adenoma Thyrotroph adenoma Corticotroph adenoma Gonadotroph adenoma Null cell adenoma Plurihormonal and double adenoma

2	Tumors of the posterior pituitary	Pituicytoma Granular cell tumor of neurohypophysis Spindle cell oncocytoma Sellar ependymoma
3	Neuronal and para-neuronal tumors	Gangliocytoma and mixed types Neurocytoma Neuroblastoma paraganglioma
4	Craniopharyngioma	Adamantinomatous type Papillary craniopharyngioma
5	Mesenchymal tumors	Meningioma Schwannoma Chordoma Solitary fibrous tumor/hemangiopericytoma
6	Others	Pituitary carcinoma Pituitary blastoma Germ cell tumors Hematological tumors Secondary 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).

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 have a classification which is 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. Certain tumors that secrete growth hormone(GH) in excess and few others like adrenocorticotropic Hormone (ACTH),thyroid-stimulating hormone (TSH),follicle-stimulating hormone (FSH), and/or luteinizing hormone(LH).

Etiology and pathogenesis

The etiopathogenesis of pituitary adenomas is very 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 are more at risk of developing pituitary adenoma.

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

3. Hormonal disorders: Disorders in the regulation of pituitary hormone production and secretion can affect the development of pituitary adenomas. For example, overproduction of growth hormone (GH) can lead to growth hormone-secreting adenomas that 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 introduction to radiation to the head and neck is related to an expanded chance of creating pituitary adenomas afterward in life.

7. Other components: A few uncommon innate disorders, such as the Carney complex and McCune-Albright disorder, are related to an expanded hazard of creating pituitary adenomas.

It is more common in individuals who have gotten radiation in childhood or youth for conditions such as brain tumors or cranial radiation for radiation is critical to note that the improvement of pituitary adenomas is likely a result of a combination of hereditary, hormonal, and natural components. Advanced investigation is required to completely illustrate the fundamental components included within the etiology and pathogenesis of pituitary adenomas.

Clinical presentation

The clinical picture of pituitary adenomas can change significantly depending on the measure, area, and hormonal movement of the tumor. A few adenomas may be dormant and not discharge hormones, whereas others may create as well much of certain hormones, causing distinctive side effects. Here are the common clinical appearances of pituitary adenomas:

1. Symptomatology of mass impact: When pituitary adenomas develop, they can compress encompassing structures such as the optic nerve and optic nerve, causing visually unsettling influences. These can incorporate obscured vision, visual field absconds (such as misfortune of fringe vision or reciprocal hemianopsia), and twofold 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: Even adenomas that do not secrete significant amounts of hormones can cause symptoms due to the mass effect. These tumors can cause headaches, blurred vision, 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.

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 T1 weighted MRI and hyperintense on T2 weighted MRI.[3]

4. Computed tomography (CT): bone destruction is more evident on CT.

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: Assessment of pituitary function is important to detect the possibility of hypophysitis (pituitary deficiency) due to the mass impact of the 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): In some cases, genetic testing may be recommended, especially if you have a family history of pituitary tumors or traits that suggest an inherited syndrome (such as multiple endocrine neoplasia type 1 or McCune-Albright).

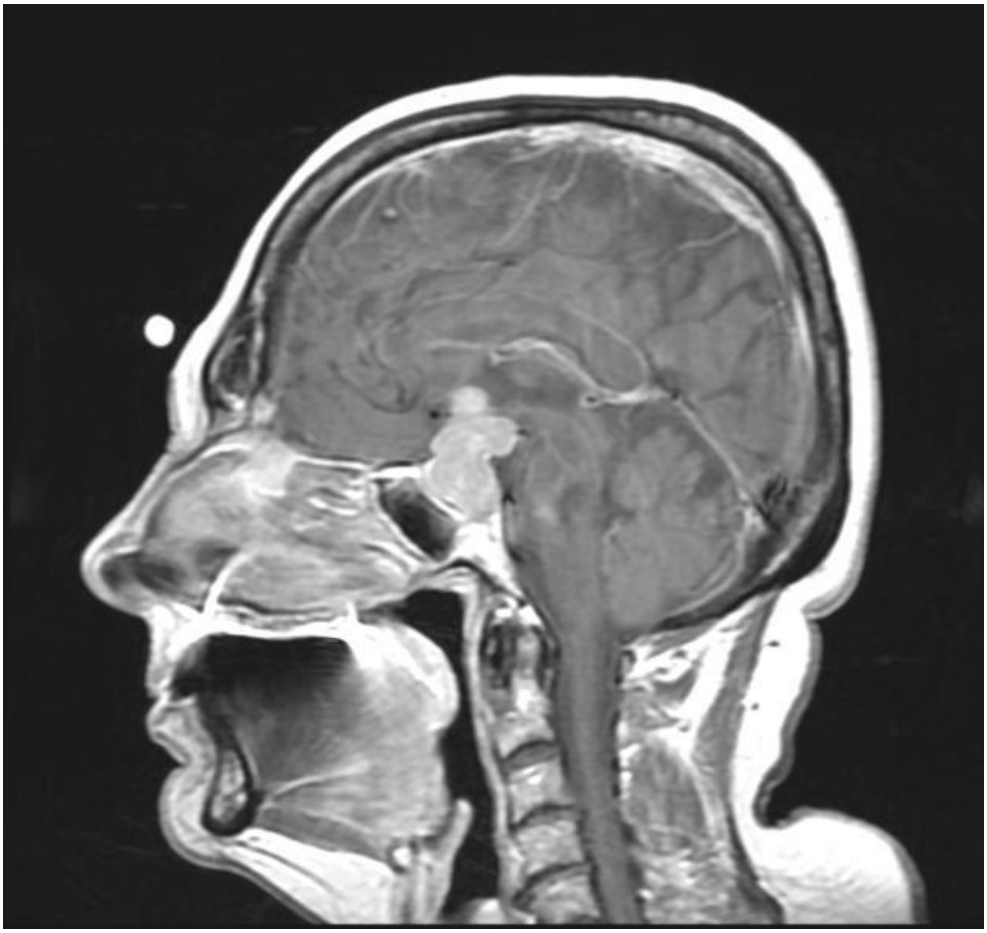

Fig 1- T1 contrast sagittal section of MRI brain showing pituitary macroadenoma

Treatment

Treatment of a pituitary adenoma depends on a few variables, such as the size and site of the tumor, hormonal status (in case vital), the nearness of side effects, and the common well-being of the persistent. Most medications 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 main treatment for large adenomas that cause mass impact, inoperable symptomatic adenomas, and some hormone-secreting tumors that do not respond to drug therapy.

Transsphenoidal surgery: This is the most common approach to surgical removal of pituitary adenomas. This is a minimally invasive procedure performed to access the pituitary gland through the nasal and sinus cavities. The surgeon removes the tumor while sparing as much of the normal pituitary gland as possible. Endoscopic transsphenoidal surgery: A new technique that uses an endoscope to visualize and remove tumors. This improves imaging and improves access to difficult-to-access tumors [4].

4. Radiation Therapy

INDICATIONS

Sinus invasion, residual lesion after surgery 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 very high dose of radiation to the tumor simultaneously minimizing exposure to normal 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 can be used to treat pituitary adenoma. For example, after surgery, radiation therapy and drug therapy may be continued to achieve better tumor control and normalization of hormones.

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

Conventional external radiotherapy: In this external radiation therapy, high-energy X-rays are directed at the tumor site from outside the body [7]. Treatment is given in small doses daily for several weeks to minimize damage to surrounding healthy tissue. This form of radiation therapy is suitable for larger or actively growing adenomas. It can be used as adjuvant therapy after surgery to reduce the risk of local tumor recurrence.

Stereotactic radiosurgery (SRS): it is a form of radiation therapy that delivers a high dose to the tumor with extreme precision. It uses multiple converging beams of radiation to focus on the tumor while saving the normal surrounding 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 methods SRS for pituitary adenomas are as a rule conveyed as single-fraction SRS or less commonly as multi-fraction SRS (2-5 divisions). The gamma knife employments 192 radioactive cobalt-60 sources organized circularly in a uniform inner collimating framework all through the head cast in order to center the beam to a central point. With ideal combinations of collimator number, opening, and area, a profoundly precise but inhomogeneous dosage conveyance and a very high central tumor dose can be accomplished. Customarily, patients are set in an inflexible stereotactic outline and the measurements are as a rule set as a 50% isodose to realize the greatest dosage within the center of each chosen target and an endorsed dosage 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 mask attachment system having an accuracy of 1-2 mm. However, the most technologically advanced LINACs offer better precision in repositioning patients using cone beam CT (CBCT) imaging.

fig2-SRS thermoplastic cast

Adverse Events

Radiotherapy can cause side effects like tiredness, headache, and mild nausea. These side effects last for a few days 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 an effective treatment option in selected cases of pituitary adenoma. The decision for treatment with radiation is made based on the characteristics of the tumor, the performance status of the patient, and the opinions

of the disease management group. 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 before starting treatment and annually in patients with normal vision. Follow-up MRI is recommended 3-6 months after therapy and then yearly for 5 years and then every 2-3 years till the disease progress. [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 well-being of life after SRS without serious side effects compared to surgery. We need Long-term follow-up is needed to look for late side effects.

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