GAMMA KNIFE RADIOSURGERY FOR FUNCTIONING PITUITARY ADENOMAS

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By

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ABBERVIATIONS

Abbreviation	**Full Meaning**
3D	Three Dimensional
ACTH	Adrenocorticotropin Hormone
ACTH-oma	Adrenocorticotropin Hormone Secreting Adenoma
CRH	Corticotropin Releasing Hormone
CS	Cavernous Sinus
CSF	Cerebro Spinal Fluid
CT	Computerized Tomography
D2	Dopamine 2
DA	Dopamine Agonist
ENT	Ear Nose And Throat
FSH	Follicle Stimulating Hormone
FPA	Functioning Pituitary Adenoma
GH-oma	Groth Hormone Secreting Adenoma
GH	Growth Hormone
GnRH	Gonadotropin Releasing Hormone
GHRH	Growth Hormone Releasing Hormone
HE	Hematoxylin–Eosin
ICA	Internal Carotid Artery
IGF-1	Insulin Growth Factor 1
IPSS	Inferior Petrosal Sinus Sampling
IRMA	Immunoradiometric Assay
LH	Luteinizing Hormone
MEN	Multiple Endocrine Neoplasia
MRI	Magnetic Resonance Imaging
NFA	Clinically Nonfunctioning Adenoma
OGTT	Oral Glucose Tolerance Test
PRL	Prolactin
PRL-oma	Prolactin Secreting Adenoma
T4	Free Thyroxin
TRH	Thyrotropin Releasing Hormone
TSH	Thyroid Stimulating Hormone
UFC	Urine Free Cortisol
VEP	Visual Evoked Potentials
WHO	World Health Organization

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1. INTRODUCTION

RATIONALE AND JUSTIFICATION OF STUDY

Pituitary adenomas are amongst the most common intracranial lesions, constituting 10-20% of primary brain tumors. They have a reported annual incidence in the general population close to 20%[1]. Pituitary adenomas are generally classified as either "functioning" or "non-functioning," with the former (secreting adenomas) representing about 70% of all pituitary tumors[2, 3]. Classically, pituitary adenomas present with a **clinical** triad related to hypersecretion/hypopituitarism, mass effect or as incidentalomas; occasionally as pituitary apoplexy, or rarely as cerebrospinal fluid rhinorrhoea[4].

A suspected case of pituitary adenoma will require a coordinated two step **diagnostic approach** to establish the endocrine and the anatomical diagnosis via an initial clinical assessment, complemented by a spectrum of endocrinologic and neuroimaging tests. Additionally a neuroophthalmologic assessment is routinely required[4].

The management of pituitary adenomas requires a multidisciplinary approach. The current therapeutic armamentarium includes medical, surgical and radiotherapeutic methods with the latter being rapidly replaced by radiosurgery. Pituitary tumors are well-suited for radiosurgery, since radiation can be focused on a well circumscribed region, while adjacent neural structures in the suprasellar and parasellar regions are spared [2, 3, 5-9].

Stereotactic radiosurgery uses sophisticated 3-D computerized imaging to precisely target an ionizing ray and deliver a high concentrated dose of radiation to the lesion. Stereotactic radiosurgery differs and is advantageous over conventional surgery because there is no incision involved and general anesthesia is not required for adults, and short treatment duration amongst others[5, 6].

The expected dominance of the time-honored microscopic pituitary surgery technique as the “gold standard” for pituitary surgery seems to be fading out while the endoscopic techniques are on a rise. Microsurgical resection alone provides a long-term tumor control rate of only 50% to 80% and a long-term remission rate of endocrinologic normalization after surgical resection that often falls short of expectations. Reoperation for residual or recurrent tumors is associated with the more difficult complete resection and the endoscopic method alone is insufficient to solve all problems associated with these cases[7]. There is thusneed for a complementary technique.

Most studies involving SRS for nonfunctioning pituitary adenomas (NFAs) have shown excellent tumor volume control, with a mean tumor control rate of 93% (range: 68%-100%). However in FPAs, this type of treatment remains challenging. Literature onSRS for FPAs is variable with reported rates of 35-83% for Cushing’s disease, 42-60% for acromegaly, and 26-43% for prolactinomas[5].

The main goals of SRS for FPAs are to normalize excessive hormonal production and control tumor growth [7]. The rationale of our study is to define accurately the effectiveness, safety, complications, and role of theGamma Knife Radiosurgery for the treatment of secretory pituitary adenomas in our population.

2. OBJECTIVES

GENERAL OBJECTIVE

To assess the effectiveness, safety, complications, and role of the gamma knife for the treatment of functioning pituitary adenomas (FPAs).

SPECIFIC OBJECTIVES

- To evaluate the effectiveness of Gamma Knife Radiosurgery in terms of biochemical remission and tumor control and explore factors affecting them.
- To assess the morbidity association with Gamma Knife Radiosurgery for functioning pituitary adenomas

3. REVIEW OF LITERATURE

3.1 HISTORICAL PERSPECTIVE

The anatomy of the pituitary gland has been known since the Greek and Roman antiquity through the works of Hippocrates and Galen. The latter propagated that the pituitary was the route for the « disposal of waste products of the brain », a concept taught to medical students for millennia. The work of Vespasian during the Renaissance raised questions about the concepts introduced by Galen but the relationship between « disease » and « pituitary tumors » only actually began with the introduction of anatomical and clinical methods in the 17th century[10].

Andreas Vesalius (1543) believed the pituitary produced mucus, secreted by the brain into the nasal cavity hence the name “glandula pituitaria” (pituita=mucus).
Jean Louis Petit (1674-1750) showed that the development of a pituitary tumor can cause blindness.
Pierre Marie (1853-1940), in 1886, demonstrated the relationship between symptoms of acromegaly and pituitary tumor.
The link between Hypopituitarism and malfunction of the pituitary gland was established in 1901 by A Froelich (1871-1953) and H Cushing in his book "The Pituitary Body and Its Disorders" describing the different clinical pictures of hypo or hyper secretion[10].
The pituitary gland (master gland) controls the activities of the other endocrine glands. Knowledge of its anatomy and physiology is important for proper management of pituitary tumors.

3.2 EMBRYOLOGY OF THE PITUITARY

The sella develops as a depression in the body of the sphenoid, is lined with dura and houses the pituitary gland**.** The pituitary gland develops from two different structures[11]:

An Upward Ectodermal Growth [Oral ectoderm of the primitive buccal cavity (stomatodeum)] from the roof of the pharynx that passes cranially as the Rathke's pouch forming the anterior portion of the pituitary (adenohypophysis).

A Downward Neural Growth (projection of the hypothalamus) from the floor of the third ventricle (base of the diencephalon) forming the posterior lobe (neurohypophysis) and pituitary stalk.

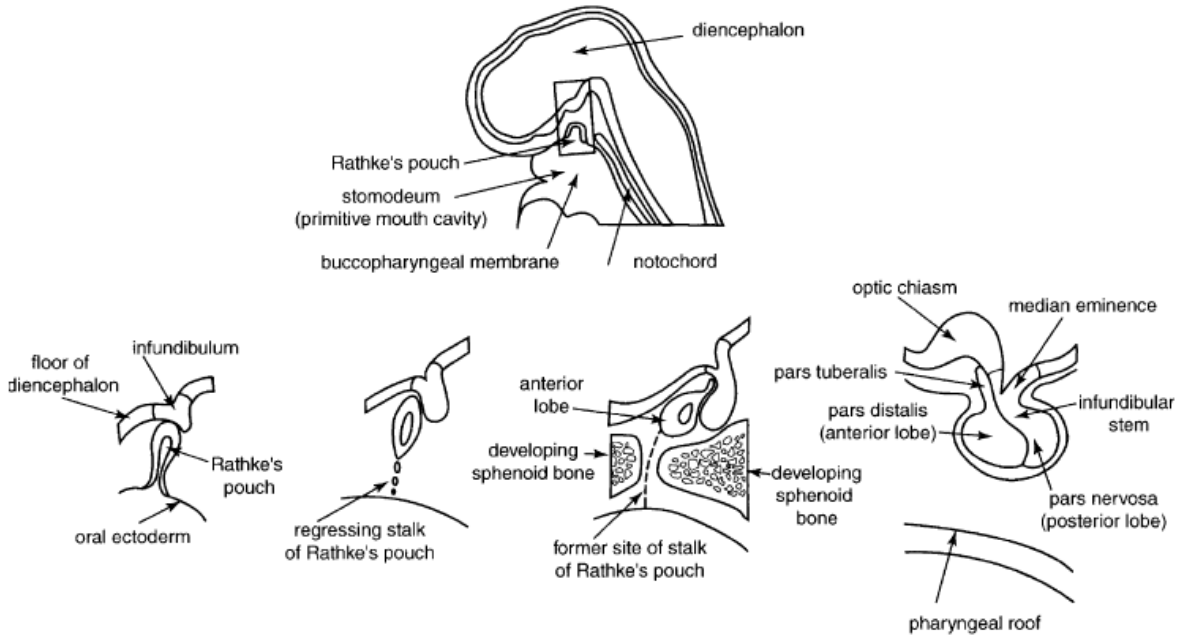

Figure 1: Embryogenesis of the pituitary gland

These two meet in the sella turcica and the stalk of the Rathke's pouch degenerates (loses connection with the pharynx) while the stalk of the neural growth persists and forms the pituitary stalk (infundibulum).

The Rathke's pouchdevelops into three parts : Pars Distalis (pars glandularis), Pars Tuberalis and Pars Intermdia .

*The downward neural growth*develops into the pars nervosa forming the posterior lobe to which the intermediate lobe becomes closely adherent and is separated from the anterior lobe by a remnant of *Rathke's pouch* called the *Rathke's Cleft.*

This composite gland is distinct and separate from the primitive stomatodeum by the seventh week of gestation and further develops under the influence of the hypothalamus through a series of permissive and specific trans-acting proteins[11]**.**

3.3 ANATOMY OF THE PITUITARY GLAND AND SELLA

The pituitary gland is a small reddish grey gland **0.5-1 g** in weight.It is situated in*the sella turcica (hypophysial fossa)*and is attached to the floor of the third ventricle of the brain by a stalk *(infundibulum)*[12]. On a coronal section through the brain the pituitary gland reference structure (Figure 2).

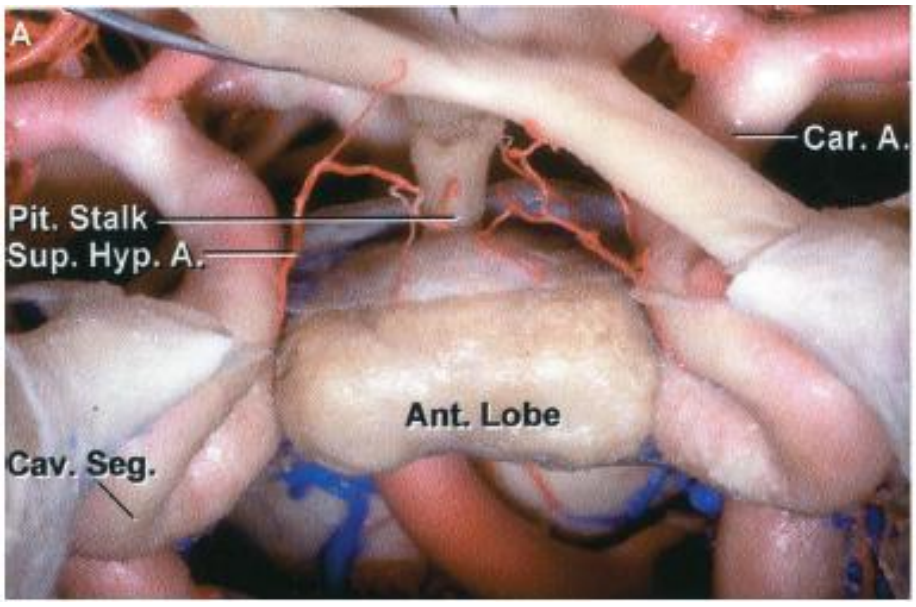

Figure 2: The pituitary gland and its relationships

(Courtesy of Roton [12])

The pituitary measures **7 mm x 9mm x 11mm** in the height, antero-posterior and transverse diameter respectively.

It has three lobes: A large glandular anterior lobe (the adenohypophysis or anterior pituitary gland), a small intermediate lobe (rudimentary in humans) and a large neuronal posterior lobe (the neurohypophysis or posterior pituitary gland)[12].

The **Adenohypophysis** has three regions[12]:

The *pars tuberalis* which is applied to the median eminence and upper infundibular stem (rostral region of the neurohypophysis) and is an extension of the glandular hypophysis that lies above the sella turcica.

The *pars intermedia* is applied to the lower portion of the lower infundibular stem and the infundibular process (caudal regions of the neurohypophysis)

The *pars distalis*, the main bulk of the adenohypophysis is composed of epithelial cells arranged in a glandular pattern, folliculostellate cells arranged in a syncytium and fenestrated capillaries and has no axonal terminals.

The **Neurohypohysis** based on regional morphologic specialization is subdivided into three regions[12]:

The *Median Eminence* which together with the two lateral eminences make up the *tuber cinereum* visible on the inferior surface of the brain,caudal to the *optic chiasm* and rostral to the paired *mammilary bodies*

The *Infundibular Stem* is the neural portion of the pituitary stalk.

The *Neural Lobe* is the pars nervosa.

Dural, Neural & Vascular Relations Of The Pituitary[12, 13]

The pituitary by virtue of its position is related to many vital structures.

Inferiorly: It sits in the sella turcica separated from the bone by dura.

Superiorly: Optic chiasm and nerves

Laterally: The cavernous sinus with its content.

Posteriorly: basilar artery and brain stem