

MICROSCOPIC PITUITARY SURGERY

A SYSTEMATIC REVIEW AND META-ANALYSIS

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award of a Master Degree in Neurosurgery*

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DEDICATION

This piece of work is dedicated to all the patients with pituitary problems in the hope that a better understanding of the material contained herein will result in a more rational approach in the management of these patients!

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LIST OF ABBREVIATIONS

Abbreviation	Full Meaning
3D	Three Dimensional
ACTH	Adrenocorticotropin Hormone
CCD	Charge Coupled Devices
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
ES	Effect Size
FEPS	Functional Endoscopic Pituitary Surgery
FSH	Follicle Stimulating Hormone
GH	Growth Hormone
GnRH	Gonadotropin Releasing Hormone
GHRH	Growth Hormone Releasing Hormone
HD	High Definition
HE	Hematoxylin–Eosin
ICA	Internal Carotid Artery
IGF-1	Insulin Growth Factor 1
IPSS	Inferior Petrosal Sinus Sampling
IRMA	Immunoradiometric Assay
LCD	Light Coupling Diode
LH	Luteinizing Hormone
MEN	Multiple Endocrine Neoplasia
MIB-1	Mindbomb Homolog 1
MRI	Magnetic Resonance Imaging
NFA	Clinically Nonfunctioning Adenoma
OGTT	Oral Glucose Tolerance Test
PAS	Periodic Acid–Schiff
PRL	Prolactin
RER	Rough Endoplasmic Reticulum
T4	Free Thyroxin
TFT	Thin Film Transistor
TRH	Thyrotropin Releasing Hormone
TSH	Thyroid Stimulating Hormone
UFC	Urinary Free Cortisol
VEP	Visual Evoked Potentials
WHO	World Health Organization

1. INTRODUCTION

I. RATIONALE AND JUSTIFICATION OF STUDY

Close to half a century after the introduction of the microscope for pituitary surgery, the expected dominance of this time-honoured technique as the “gold standard” for pituitary surgery seems to be fading out. While the microscopic transphenoidal approaches still retain their merited indications and remains the dominant and preferred surgical approaches for the surgical management of a vast majority (>95%) of pituitary adenomas, the traditional transcranial microscopic approaches though are on a continuous decline remain a vital part of the neurosurgical armamentarium for 1 to 4% of these tumors with specific indications(1;2). The reasons for this dwindling being partly attributable to the advent of novel minimally invasive microsurgical techniques to the pituitary, the reported low morbi-mortality and tumor recurrence with the transphenoidal surgery(2-5). Nonetheless the microscopic transcranial approaches still uphold a number of distinctive indications the most common practical indication being failure of the transphenoidal approach to achieve the desired result at the first operation(1). Other indications include: Dumbbell-shaped with severe constriction at the diaphragma sellae, parasellar extension, inaccessible suprasellar extension, fibrous pituitary adenoma with large suprasellar extension, non-pneumatized, active sphenoid sinus infection, coexistence of pituitary adenoma and adjacent aneurysm and ectatic intrasellar “kissing” carotid arteries(1). Clinically, pituitary adenomas present with classic semiologic triad related to hypersecretion, hypopituitarism, mass effect or as incidentalomas discovered during neuroimaging for management of other disorders, occasionally pituitary apoplexy, or rarely as cerebrospinal fluid rhinorrhoea(2).

The management of pituitary adenomas is multidisciplinary involving the neurosurgeon/neurologist, endocrinologist, neuroradiologist, neuroophthalmologist and at times rhinologist(6). A suspected case of pituitary adenoma will require a coordinated two step diagnostic approach, firstly, establishing the endocrine diagnosis: to confirm, define and establish the aetiology as well as for the assessment of treatment and secondly, to secure an anatomical diagnosis. This is achievable via a

spectrum of endocrinologic and neuroimaging tests in addition to the initial thorough clinical assessment. Additionally neuroophthalmologic assessment is routinely required and occasionally for the transphenoidal approach, nasal functionality test and rhinomanometry(2;6).

Current therapeutic options for pituitary tumors include medical, surgical and radiotherapeutic methods. The principles of surgical treatment differ between secretory and nonsecretory pituitary adenomas. Therapeutic goals of pituitary surgery for secretory adenomas are: improved quality of life and survival; relieve/elimination of mass effect and reversal of related signs and symptoms; normalization of hormonal hypersecretion; preservation or recovery of normal pituitary function; prevention of recurrence of the pituitary tumor and to provide tissue for pathological and scientific study(7). The primary goal of surgery for nonsecretory adenomas is decompression of neural structures, especially the optic chiasm and subfrontal brain. Surgical cure is attempted only when the opportunity presents with minimal risk, because residual tumor is well controlled by radiation(1). This can be achieved via a manifold of routes and techniques each with its indications, pros and cons and complications.

Through a wide systematic review and meta-analysis we intend to evaluate the results of about 50 years experience of microscopic pituitary surgical approaches, assessing short term results viz: operative time, extent of tumor resection, clinical resolution, hormonal control, peri-operative complications rate and length of hospital stay as well as long term tumor control and complications of the different surgical routes to the pituitary. In our review we will be using pituitary adenomas as a reference, because they are the most representative and homogeneous group in sellar pathology, and the presence of remission criteria makes a comparative study between microscopic surgery approaches easier.

Amidst this wide multiplicity of routes and techniques for same pathology (pituitary adenoma) we think an up-to-date **reviewing** and **pooling** of available data will summarize the current state of knowledge on the surgical management of pituitary adenomas so as to provide strong evidence that will help redefine the role of microscopic pituitary surgery amongst other microsurgical approaches.

II. GOAL

To review and summarize available knowledge on microscopic pituitary surgery techniques.

III. OBJECTIVES

i. GENERAL OBJECTIVE

To review, revise and redefine the current role of microscopic pituitary surgery with the advent of novel minimally invasive endoscopic approaches for pituitary surgery.

ii. SPECIFIC OBJECTIVES

- + To assess the **safety** and the **complications** of microsurgical pituitary approaches
- + To evaluate the **efficacy** and **effectiveness** of microscopic pituitary surgery
- + To compare the safety and complications, efficacy and effectiveness of **transcranial** with respect to **transphenoidal** microscopic approaches
- + To compare the results of our review (safety and complications ,efficacy and outcome) to those of endoscopic pituitary surgery

2. LITERATURE REVIEW

HISTORY OF (MICROSCOPIC) PITUITARY SURGERY(8)

Ancient Egyptians: The history of pituitary surgery dates as far back five thousand years in the Ancient Egyptians Era where the transnasal route was used to reach and remove the brain through a spheno-ethmoidal breach during the process of mummification so as to avoid disfigurement of the face of the deceased(9;10). Recently studied mummies provide clear evidence of their method(Figure 1)(11).

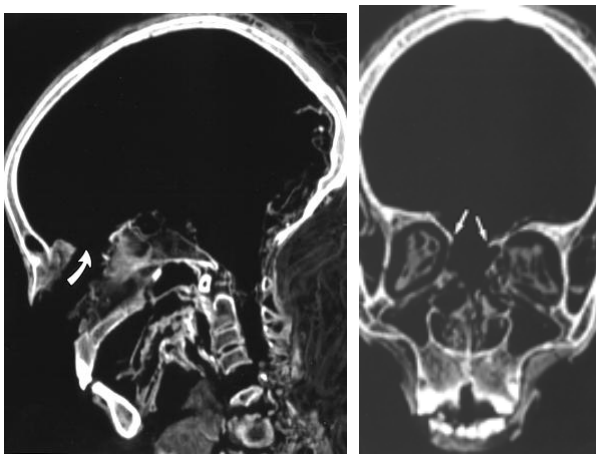


Figure 1:Sagittal & Coronal CT of Mummy.

Sagittal & Coronal CT scan of a mummy showing the transnasal passageway for brain removal (arrow).

Early Neurosurgery:

Initially: Pituitary tumors approached transcranially, using either the subfrontal or the subtemporal route.

1889: Sir *Victor Horsley* attempted the first craniotomy for a pituitary lesion, although it was unsuccessful, in 1906, he reported on ten patients treated with craniotomy, using a subfrontal approach and a lateral middle fossa approach with a mortality rate of 20%.

1905: *Fedor Krause*, a surgeon in Berlin, performed the first recorded successful resection of a pituitary tumor utilizing an extradural transfrontal approach avoiding extensive retraction of the frontal lobe.

Subsequent modifications and improvements were made by neurosurgeons such as *Walter Dandy*, *George Frazier*, *George Heuer*, and *Harvey Cushing*. These

approaches, however, had significant morbidity and mortality, due to retraction of the frontal lobes and lack of good antiseptics.

Development of Transphenoidal Route:

Late 1800s: *Davide Giordano* of Venice (Italy) performed an anatomical study which provided an approach to the sella turcica through an extracranial transfacial transphenoidal exposure.

1907: Based in part on Giordano's observations, the first successful transphenoidal resection of a pituitary tumor was done by *Hermann Schloffer* of Vienna, in, as a three stage operation. (Stage 1: Nasal incision extended to glabellar, nose laterally reflected and nasal turbinates and septum removed; stage 2: Removal of vomer and sphenoid rostrum; stage 3: Opening of sellar floor with a chisel.)

Theodor Kocher modified Schloffer's approach by sub mucosal removal of the septum, allowing better visualization.

1910: *Oskar Hirsch*, a rhinologist developed a completely endonasal transseptal transphenoidal operation.

1910 in Chicago (United States), *Albert Halstead* modified the curvilinear incision through the nasolabial junction - suggested by *Allen Kanavel* - allowing more retraction of the cartilaginous septum compared to the endonasal approach, improving exposure and providing better cosmetic results. Other attempts at the development of sellar approaches include *Ottokar Chiari's* transthemoidal approach and *Preysing's* transpalatal approach(12).

1912: Driven by the discouraging results of his transcranial approaches, *Harvey Cushing* adopted the transphenoidal approach, initially using Schloffer's procedure. He performed his first transphenoidal operation in 1909 for a patient with acromegaly. By 1912, he had modified the procedure by combining Halstead's sublabial incision and Kocher's sub mucosal septal dissection with the use of a nasal speculum (a modified pediatric vaginal speculum), resulting in the operation still performed by most neurosurgeons today.

From **1910 to 1925**, Cushing operated on 231 pituitary tumors using the sublabial transphenoidal approach with a mortality rate of only 5.6%.

Abandonment of the Transphenoidal Approach: Cushing continued at his time to have intense interest in intracranial surgery urging him to pursue and develop transcranial approaches to the pituitary gland. As he developed expertise and confidence in these approaches and reduced his mortality rate with the transcranial approach to 4.6%, essentially eliminating any significant difference in surgical mortality when compared to the transphenoidal approach. By **1929**, Cushing had virtually abandoned the transphenoidal operation, performing pituitary surgery exclusively via the transfrontal route. His rationale was that reoperation in cases initially done transphenoidally was more difficult than in cases done transcranially, visual restoration was better in transcranial surgery and that many pituitary lesions were not adenomas or adenomas with suprasellar extension which were easier to be treated transcranially under direct vision. As might be expected, the majority of the neurosurgical community followed Cushing's lead abandoning the transphenoidal approach for the next 25 years except for *Norman Dott*.

Norman Dott (1879-1973), who learned the transphenoidal approach in 1923 from Cushing during a traveling in Boston, returned to the Edinburgh where he continued to advocate this procedure. He designed a speculum with a lighted tip which allowed superior visualization during the operation. This interim stage preserved the transphenoidal approach from extinction. Another key factor in the preservation of the transphenoidal approach was the contribution of Hirsch and Hamlin. *Oskar Hirsch* immigrated to the United States, collaborated with *Hannibal Hamlin*, a neurosurgeon in the Boston community and extolled the virtues of the transphenoidal approach and reported excellent long term results. Despite their enthusiasm, transfrontal approaches remained the most popular methods throughout the 1950's and 60's.

Revival of the Transphenoidal approach

Numerous innovations introduced in the 1950s played an important role in the resurgence of interest in transphenoidal surgery. With the introduction of cortisone and antibiotic therapy, total hypophysectomy could be performed with significantly reduced mortality and better long-term success.

The two persons credited for the revival of the transphenoidal approach are ***Gerard Guiot*** and ***Jules Hardy***. In **1956**, Gerard Guiot visited Dott, observed his meticulous technique and outstanding surgical outcomes, and returned to Paris where he reintroduced the transphenoidal approach. He further enhanced surgical accuracy by

introducing intraoperative radiofluoroscopy to define the anatomy of the anterior skull base while maneuvering surgical instruments. This allowed him to apply the transphenoidal approach to suprasellar and parasellar lesions, and thus he played a pivotal role in the resurrection of the transphenoidal approach during the following two decades.

The spread of the transphenoidal approach across North America was initiated by *Jules Hardy* upon his return to Canada. As a trainee under Guiot in Paris, Hardy of Montreal continued the use of televised radiofluoroscopic control, and adopted routine use of preoperative angiography, polytomography of the sella and intraoperative air encephalography. Later in **1967**, Hardy introduced the use of the operating microscope during this procedure, and designed his own microsurgical instruments. The microscope and microtechnique permitted safer and more effective resections of pituitary tumors and other sellar and parasellar lesions, with no serious morbidity or mortality in the first 50 patients. His landmark paper in **1971** described the use of the operating microscope for improved illumination and intraoperative fluoroscopy for improved localization of tumors and guidance of instruments.

The operation as described by Hardy has undergone further refinements by other neurosurgery pioneers (Figure 2), to enumerate some, not referring to all: *Laws*, in the States, with a personal series of more than 4000 procedures, and *Fahlbusch*, in Europe, with more than 3200 operations, and has become the primary surgical procedure used by most neurosurgeons for the excision of pituitary tumors and other sellar lesions for the last 30 years. Mortality rates dropped below 1% in expert hands, rendering the procedure reasonably safe and highly effective.

However, transcranial surgery for pituitary tumors maintained its importance in approaching lesions in the suprasellar area. It was *Gazi Yasargil*, who demonstrated advantages of transcranial surgery for large eccentric suprasellar pituitary tumors utilizing the pterional approach by minimizing brain retraction after splitting the Sylvian fissure and opening of the basal arachnoid. *John Jane Sr. et al.* were the first to describe the “*Supraorbital approach*” in 1982, as a modification of the old frontal craniotomy allowing excellent access to the floor of the frontal fossa with less brain retraction.

In the late 1990s, *Axcel Perneczky* reintroduced and practically applied the “*keyhole*” concept which was first described by *Donald Wilson* in 1971. Through a limited subfrontal approach with a Supraorbital craniotomy via an eyebrow skin incision, a