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Research Paper

Late Effects of Transsphenoidal/ Trans-Nasal Endoscopic Resection of Pituitary Macro-Adenoma and Gamma Knife Radiosurgery on Tumour Outcome

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ABSTRACT:

BACKGROUND:

Studying pituitary tumours outcome.

OBJECTIVE:

To evaluate the late outcomes after transsphenoidal endoscopic resection and post stereotactic gamma knife radiosurgery on pituitary macroadenomas in terms of clinical features and radiological response.

PATIENTS AND METHODS:

This prospective and retrospective study was conducted at two training centers, Ghazi Al-Hariri hospital for surgical specialties and Saad Al-Witry neuroscience teaching hospital, in the period extended from January 2020 to January 2023. It included a total number of 113 cases gathered from two neurosurgical teams specialized in pituitary cases handling, skull base team, with experience in transsphenoidal pituitary resection and functional and oncologic for cases treated by radiosurgery.

The selectionfor either intervention was based on clinical picture and according to scientific guidelines.

The patients were observed during their initial visit on the day of the procedure then 1 year following intervention to check response.

The parameters involved includes: the clinical presentation, vision status, hormonal abnormality and imaging findings.

RESULTS:

A total of 113 cases of pituitary macroadenomas were treated and followed up over a period of 2 years. 57 cases were treated by transsphenoidal resection while 56 cases were treated by stereotactic radiation. 40 cases of the total number presented with prolactinoma (35%). (19 patients in the transsphenoidal group, 21 patients in the gamma-knife group). Of those, 28 had laboratory improvement in serum prolactin (70%) (15 patients in the transsphenoidal group, 13 patients in the gamma-knife group). The remaining 73 cases presented with non-functioning tumours (65%).

Total tumour volume reduction to a normal gland size was achieved in 42 cases of the total patient number (37%) (All of which were of the transsphenoidal group), small tumour residual (residual mass less than 50% its original size) was found in 37 cases (33%) (11 patients in the transsphenoidal group, 26 patients in the gamma-knife group), large tumour residual (residual mass more than 50% its original size) was found in 34 cases (30%) (4 patients in the transsphenoidal group, 30 patients in the gamma-knife group).

CONCLUSION:

Transsphenoidal resection is ideal for young fit patients with large tumours manifesting with visual compromise, non-response to medical therapy or as an emergency case with intra-tumoural haemorrhage (apoplexy).

Stereotactic radiosurgery, is best suitable for residual or recurrent disease or in patients whom surgery is deemed extremely hazardous such as elderly patients or patients with comorbidities.

KEYWORD: Pituitary adenoma,transsphenoidal resection, gamma knife radiosurgery

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Iraqi Postgraduate Medical Journal, 2026; Vol. 25(1): 78-86
DOI: 10.52573/ipmj.2025.156161 Received: January 14, 2025 Accepted: April 13, 2025

INTRODUCTION:

Pituitary adenomas are traditionally defined as benign tumours of the pituitary gland. [(1)]

Pituitary adenoma is formed via a process that is thought to be derived from the clonal expansion of

single abnormal cells owing to somatic genetic mutations or chromosomal abnormalities. [2]

Pituitary adenomas account for 10% to 15% of all intracranial masses. [3]

microadenoma is defined as intra-sellar tumour with size less than 10 mm in maximum diameter, and macroadenoma with size greater than 10 mm in diameter. Giant pituitary tumours as defined by Symon et al., are tumours having an extension of more than 40 mm from the midline of the jugum sphenoidale. [4].

Pituitary adenomas are categorized based on primary cell origin and type of hormone secreted. If the adenoma does not secrete a sufficient level of hormones to be detectable in the blood or to result in clinical manifestations, it is considered nonfunctioning. [3]

Pituitary adenomas present clinically in three ways:

- Syndromes of hormone hypersecretion or deficiency.
- Neurologic manifestations from mass effect of an expanding gland.
- An incidental finding on imaging done for an unrelated issue.

Treatment goals

- reducing hormone hypersecretion and its clinical manifestations
- decreasing tumor size to improve symptoms of mass effect
- correcting hormone deficiencies. [3]

treatment modalities

Medical management:

The majority of prolactinomas can be managed medically with dopamine agonists by inhibiting the release of prolactin from the anterior pituitary.

Medical management of growth hormone– and ACTH-secreting tumors is less effective than for prolactinomas, and surgery via transsphenoidal resection is the preferred treatment.

Nonfunctioning microadenomas and micro prolactinomas in asymptomatic patients do not require immediate treatment.

Surgical Resection

Surgery is indicated for pituitary tumors in the following settings: mass effect, especially in the presence of impending or actual visual loss; excess hormone secretion not controlled by medical management, and pituitary apoplexy. [11]

Successful surgical resection of hormone-secreting pituitary adenomas in carefully selected patients via microsurgical, endoscopic, or combined (microscopic and endoscopic) approaches can result in immediate tumor eradication and biochemical remission while preserving normal pituitary endocrine function.

Surgery can provide direct relief of mass effect and improvement in vision in cases with significant compression of the optic chiasm or nerve. Risks associated with resection of pituitary adenomas include postoperative cerebrospinal fluid leak, injury to the normal pituitary gland causing hypopituitarism, transient/permanent diabetes insipidus, and transient isolated hyponatremia. Less frequent potential risks include neurovascular injury and epistaxis. [12]

Radiosurgery

Indications for radiation included unresectable residual disease following subtotal resection, growing recurrence postoperatively, and definitive management for poor surgical candidates. [16]

Stereotactic techniques have been developed with the aim to deliver more localized irradiation and minimize the long-term consequences of treatment. The techniques used for treatment of pituitary adenomas involve either photon energy with cobalt-60 radiation-emitting sources (Gamma Knife, GK) or a modified linear accelerator (LINAC), and are given as a single-fraction stereotactic radiosurgery (SRS) or as fractionated stereotactic radiotherapy (FSRT). [15]

The Gamma Knife (Elekta AB, Stockholm, Sweden) operates by precisely aligning the gamma-ray emissions from an array of cobalt 60 sources so they intersect at a point called the *focus point*. Each beam has a fairly low dose rate. However, the summation of the beams at the focus point creates a very concentrated dose.

The recommended dose of SRS given in a single fraction is 12–14Gy for nonfunctioning adenomas and 16–20Gy for secretory tumors, given in single session, multi-session or as a fractionated dose. [13]

Late toxicity of pituitary RT includes hypopituitarism, neurocognitive impairment, neuropsychological dysfunction, optic neuropathy, cerebrovascular accidents, and second malignant neoplasms. Clinically apparent acute toxicity is extremely uncommon during RT for pituitary adenomas due to lesser overall dose delivered in conventional fractionation (45Gy–50.4Gy in 25–28 fractions) and very small volume being irradiated in SRS. [13]

Progressive development and improvement in SRS during the last decade, have made it one of the ideal choices for managing patients medically unfit for surgery, for tumours left behind after incomplete resection, and to restrict the growth of residual

tumours showing disease progression. SRS works by disintegrating DNA strands directly as a result of radiation, as well as by causing the release of free radicals, and by progressively obliterating vascular supply to the tumour. [14]

AIM OF THE STUDY:

To evaluate the late outcomes after transsphenoidal endoscopic resection and post stereotactic gamma knife radiosurgery on pituitary macroadenomas in terms of clinical features and radiological response. To address the benefits of advanced interventional modalities in treating pituitary adenomas with minimal tumour residual and with the least side effects.

PATIENTS AND METHODS:

This study, a combination of retro and prospective, was conducted at two training centers, Ghazi Al-Hariri hospital for surgical specialties and Saad Al-Witry neuroscience teaching hospital in the period extended from January 2020 to January 2023. The study included a total number of 113 cases gathered from two neurosurgical teams specialized in pituitary cases handling. The first team is a skull base one, with experience in transsphenoidal pituitary resection. The second team is specialized in functional and oncologic neurosurgery for the cases treated by stereotactic radiosurgery.

The selection of cases for either intervention was based on clinical picture and was according to scientific standardized guidelines.

Only cases with macro or giant adenomas were included, in whom medical therapy has either failed to control the symptoms or was not suitable as a sole therapeutic option.

Cases with microadenomas were excluded.

The patients were observed during their initial visit to the clinic, the day of the procedure then 1 year following intervention to check the response.

The parameters involved in this study includes: the patients' demographic data, clinical presentation, vision status, hormonal abnormality and imaging findings at time of intervention then after 1 year of procedure, all parameters were recorded using excel sheet. Patients' consents were taken for both interventions as well as for using the mentioned information for educational and research purposes.

Case selection

Cases treated by transsphenoidal approach were 57 cases, 29 females and 28 males, ages range from 14 to 70 years, were selected randomly while attending the neurosurgical outpatient clinic of Ghazi Al-Hariri hospital for surgical specialties or the private clinic and were referred for surgical intervention. They presented with pressure symptoms or with failed medical therapy and were suitable candidates for surgical decompression with acceptable anaesthetic risks.

Cases treated by gamma knife were 56 cases, 30 females and 26 males, ages ranged from 18 to 70 years, they were selected from the outpatient clinic in Saad Al-Witry neuroscience teaching hospital and private clinic. They were either intolerant for surgical decompression or were with stable disease and not indicated for decompression.

Patient preparation

For both modalities of intervention, general assessment was the same. All patients presented detailed history and were subjective to meticulous general and neurological examination focusing on hormonal manifestations and vision status. All patients were sent for formal ophthalmological testing which included visual acuity, visual field and fundoscopic examination. Lab work included basic lab values (CBC, RBS, RFT, LFT, S. electrolytes) and hormonal panel (PRL, T3, T4, TSH, ACTH, CORTISOL, LH, FSH, GH, ILGF-1). Imaging included brain MRI (1.5 T) with gadolinium enhancement in dynamic pituitary view and brain CT scanning, bone window with thin slices and PNS view (for transsphenoidal cases).

Anaesthesia evaluation performed on all patients, and preoperative nasal endoscopy performed for patients who were opted for resection to check the nasal cavity anatomy.

Procedure

Transsphenoidal

Patients were admitted to the hospital the day before the operation. Preoperative evaluation undertaken and consent to surgery is taken. Patients should have stopped all anticoagulant medications at the appropriate time frame but kept on drugs for chronic illnesses. Patients are instructed to use a nasal decongestive spray the day before intervention to prepare the nasal passages and are advised to be fasting at least 8 hours before operation.

At morning of surgery, prophylactic antibiotics are given to the patient one hour before commencing the surgery (usually a third-generation cephalosporin if no drug allergy). A stress dose of steroid is given to patients with adrenal insufficiency (100 mg of hydrocortisone).

Patients are wheeled to the operating theatre and anaesthetized. Positioning the patient in supine position with head slightly extended and tilted towards the surgeon. The right thigh of the patient is positioned in internal rotation and is prepped

together with the patient's lower face and chin to facilitate harvesting fascia lata flaps or fat pads in cases with dural breach.

After prepping and draping the surgical field the nasal cavity is packed with a mixture of decongestant and vasoconstrictor to control bleeding intraoperatively. The ENT team now steps into action during the nasal stage of the procedure. First a 0-angle endoscope is introduced through one nares, identification of inferior turbinate is done which is then reflected laterally, then the middle turbinate then the superior one, following is localization of the sphenoid ostium which is found at the postero-inferior edge of the superior turbinate or medial to the superior turbinate which is enlarged to enter the sphenoid phase. A bi-nostril approach is performed by excision of the posterior part of the nasal septum.

The sphenoid phase is reached upon entering the sphenoid sinus in which the surgeon excises the lining mucosa and enlarging the operative pathway. The anterior wall of the sella should be visible at this time with the characteristic landmarks including the carotid prominence bilaterally, the clivus inferiorly and optic canal superiorly, here the neurosurgical team takes charge of the upcoming stage.

The sellar phase is then reached by drilling open the posterior sphenoid wall, this step could also be done by chiseling the thinned bone. Dura is then incised using a sickle shaped knife in a cruciate fashion. Aspiration is done if there is a cystic portion. A number of different shaped ring curettes with multiple sizes are used to safely separate the tumour from adjacent structures and tumour pieces picked up with tumour forceps and collected for histopathological examination.

After completion of resection, care should be taken to inspect the operative site for missed pieces of tumour. The use of angled endoscopes could aid in this step.

Haemostasis could be achieved by packing with gel foam or Surgicel.

If satisfactory resection is performed and secure haemostasis is achieved the procedure had come to an end. The endoscope is withdrawn slowly to check the surgical corridor, controlling any mucosal bleeding encountered during the way out. The gel foam packing is secured in place by replacing the turbinates to their original position and packing Merocel lateral to it. Nasal packing is done.

The patient is awakened from anaesthesia and followed up in the ICU for the first 24 hours after the procedure for development of immediate complications (DI, hypotension from adrenal insufficiency) with frequent monitoring of conscious level, vital signs, serum electrolytes.

Post operatively, the nasal packing is removed after 24 hours by the ENT team. A blood sample is withdrawn and sent for basic lab investigations and serum cortisol.

The patient is discharged on D0-1 postoperatively if no complications arose.

Gamma knife

The patients are instructed to be admitted at the day of the procedure. The patients' data are transferred to the main computer system. Leksell frame was used for all the cases, frame cap fits. The MRI and CT imaging are co-registered together and used as pre-plan reference. The tumour margin is delineated as well as risk areas (the optic apparatus). The tumour is either approached in single session or staged in multiple sessions according to tumour size and function. Radiation doses ranged from 12-20 for non-functioning to 20-40 for functioning tumours.

The patient is then seated in the preparation room. Subcutaneous local anaesthetic is injected into pins' site. The frame is positioned so that the tumour lies central to the frame's indicators and fixed in place with 3 or 4 screws after prepping the area. The patient is then mounted on the treatment table and the frame secured to the table.

Either CT with frame on or CBCT is requested and defined as stereotactic reference after co-registering with the pre-plan imaging. Ensuring that the patient is lying comfortable for the beginning of the treatment plan.

After completion of treatment, the frame is removed, the site of pins sterilized and the patient's head bandaged. If patient is stable, no need for admission, he be discharged on oral antibiotic, simple analgesic and steroid injection for few days in anticipation of early post-radiation oedema. Medications to decrease gland size are continued until satisfactory radiological regression occurs.

Follow-up

All patients included in the study were followed up 1 week, 1 month, 6 months and then 1 year after either procedure.

At the 1 year follow up visit, new hormonal essay and complete visual assessment are obtained as well as new brain MRI is requested to asses tumour size.

RESULTS:

A total of 113 cases of pituitary macroadenoma were treated and followed up over a period of 2 years. 57 cases were treated by transsphenoidal resection of the adenoma while 56 cases were

treated by stereotactic gamma radiation. Of the total number of cases 59 (52%) were females and 54 were males (48%) (table 1). Ages of the patients range from 14 to 70 years (mean 41.1).

Table 1: Sex distribution of the study subjects.

Sex/ Approach	Transsphenoidal	Gamma knife	Total
Female	29 (49%)	30 (51%)	59 (52%)
Male	28 (52%)	26 (48%)	54 (48%)
Total	57 (50.4%)	56 (49.6%)	113 (100%)

Presenting symptoms

Headache was the presenting symptom in 99 patients (87%) (50 patients in the transsphenoidal group and 49 in the gamma knife group).

Visual compromise was the lead symptom in 88 cases (77%) (46 patients in the transsphenoidal group, 42 patients in the gamma knife group)

Endocrine abnormalities constituted the main presenting symptom in 82 cases (72%) (37 patients in the transsphenoidal group, 45 patients in the gamma knife group) (table 2).

Table 2: The main presenting symptoms.

Symptoms/ Approach	Trans-sphenoidal (57)	Post op improved	Gamma knife (56)	Post op improved	Total improved	Total (113)
Headache	50 (50.5%)	49 (98%)	49 (49.5%)	41 (83%)	90 (90%)	99 (87%)
Visual complaint	46 (52%)	32 (69%)	42 (48%)	29 (69%)	61 (69%)	88 (77%)
Endocrine symptoms	37 (45%)	27 (73%)	45 (55%)	25 (55%)	52 (63%)	82 (72%)

Clinical assessment

Visual symptoms

Out of the 88 cases presenting with visual compromise, 60 patients had visual field abnormalities (68%) (29 patients in the transsphenoidal group, 31 patients in the gamma knife group). 41 patients with field abnormalities had improvement in their 1-year follow up perimetry exam (68%) (22 patients in the transsphenoidal group, 19 patients in the gamma knife group).

66 out of 88 patients had papilledema on preoperative fundoscopic exam (75%) (36 patients in the transsphenoidal group, 30 patients in the gamma knife group). Of those, 50 patients had clinical improvement 1 year following intervention (75%) (30 patients in the transsphenoidal group, 20 patients in the gamma knife group).

13 patients out of the 88 presenting with visual symptoms were blind at initial examination (14%) (6 patients in the transsphenoidal group, 7 patients in the gamma knife group). Of those, only one patient had clinical improvement in his vision following transsphenoidal resection (table 3).

Table 3: Visual abnormalities and their outcome.

Visual abnormality/ Approach	Trans-sphenoidal (46)	Post op improved (32)	Gamma knife (42)	Post op improved (20)	Total improved	Total (88)
Field	29 (48%)	22 (75%)	31 (52%)	19 (61%)	41 (68%)	60 (68%)
Fundus	36 (55%)	30 (83%)	30 (45%)	20 (66%)	50 (75%)	66 (75%)
Blindness	6 (46%)	1 (16%)	7 (54%)	0 (0%)	1 (7%)	13 (14%)

Hormonal assessment

40 cases out of the total number presented with prolactinoma (35%). (19 patients in the transsphenoidal group, 21 patients in the gamma knife group). Of those cases 28 had laboratory improvement in serum prolactin (70%) (15 patients in the transsphenoidal group, 13 patients in the gamma knife group).

The remaining 73 cases presented with non-functioning tumours with only mild elevations in prolactin levels (65%) (table 4).

Table 4: Endocrinological profile.

Hormone /approach	Trans-sphenoidal (57)	Post op normal	Gamma knife (56)	Post op normal	Total improved	Total (113)
Prolactinoma	19 (48%)	15 (78%)	21 (52%)	13 (61%)	28 (70%)	40 (35%)
Non functioning	38 (52%)	-	35 (48%)	-	-	73 (65%)

Previous intervention

70 cases out of the total number were approached for the first time (62%) (48 patients in the transsphenoidal group, 22 patients in the gamma knife group), in comparison with 43 cases who had residual or recurrent tumour following previous attempt at resection (38%) (9 patients in the transsphenoidal group, 34 patients in the gamma knife group) (table 5).

Table 5: Primary vs redo intervention.

Previous /approach	Transsphenoidal (57)	Gamma knife (56)	Total (113)
Primary surgery	48 (69%)	22 (31%)	70 (62%)
Residual and or recurrent	9 (21%)	34 (79%)	43 (38%)

Imaging Initial tumour size

Macroadenoma was encountered in 97 cases (86%) (44 patients in the transsphenoidal group, 53 patients in the gamma knife group), while giant adenoma was found in only 16 cases (14%) (13 patients in the transsphenoidal group, 3 patients in the gamma knife group) (table 6).

Table 6: Tumour size.

Size/approach	Transsphenoidal (57)	Gamma knife (56)	Total (113)
Macro > 10 mm	44 (45%)	53 (55%)	97 (86%)
Giant > 40 mm	13 (81%)	3 (19%)	16 (14%)

Extent of resection

Tumour volume was calculated using the orthogonal ellipsoid equation which is: (A.B.C.)/2

Where A, B and C are the maximal orthogonal diameters in each dimension. [17]

The tumour volume ranged from 0.8 cc to 90.7 cc with a mean volume of 34.6 cc

Total tumour volume reduction to a normal gland size was achieved in 42 cases out of the total patient number (37%) (all of which were of the transsphenoidal group), small tumour residual (residual mass less than 50% its original size) was found in 37 cases (33%) (11 patients in the transsphenoidal group, 26 patients in the gamma knife group), large tumour residual (residual mass more than 50% its original size) was found in 34 cases (30%) (4 patients in the transsphenoidal group, 30 patients in the gamma knife group) (table 7).

Table 7: Extent of resection.

Volume /approach	Transsphenoidal (57)	Gamma knife (56)	Total (113)
Large residual	4 (12%)	30 (88%)	34 (30%)
Small residual	11 (30%)	26 (70%)	37 (33%)
Total removal	42 (100%)	0 (0%)	42 (37%)

DISCUSSION:

our study tracks patients' outcome following transsphenoidal resection of pituitary adenoma or gamma knife radiosurgery after 1 year of intervention. It is not a comparative study, as cases indicated for resection cannot be approached by gamma radiation. The choice for either approach was based on established guidelines for pituitary adenoma management.

Clinical features

The most common presenting symptoms in our study were headache (87%) and visual symptoms (77%), this in comparison with the results of the study published by Imithri Bodhinayake [20], in which headache was found in 44% of cases and 40% complained of vision abnormality.

Of patients undergoing transsphenoidal resection, 99% of patients presenting with headache had improvement in their headache after surgery. 70% of patients experienced improvement in visual function. Compared with results from the study published by R G Aiyer [21] in which headache was alleviated in all cases and 83% of patients had improvement in visual function.

Of patients treated by gamma knife, 83% had improvement in headache, 69% had improved visual function. This in comparison with the results published by Shen CC [25] in which 86% of patients experienced improved vision after gamma knife therapy.

Hormonal profile

In this study 35% of cases were functioning adenomas, all of them were prolactinoma, while the remaining 65% were nonfunctioning masses. This is compared with the results published by R G Aiyer [21], in which 57% of patients had functioning pituitary adenomas.

Of all the prolactinomas included in this study, 79% of the transsphenoidal group had normalization of hormonal profile, while 55% of the gamma knife group had normal hormonal essay on follow up. This in comparison with the study by R G Aiyer [21] in which all patients had normalization of hormonal profile following transsphenoidal resection and in results published by I Cohen [24] in which he reported 50% normalization of hormonal level in cases of prolactinomas treated by gamma knife.

Previous intervention

In our series the cases with previous intervention comprised 38%, which included either post transcranial, transsphenoidal, gamma knife or combination. These numbers were comparative with the results published by Kyle Jurascka [22], in which 79.5% were primary cases, 16.4% had redo surgery and 4.1% had previous SRS.

Extent of resection

Extent of transsphenoidal resection was estimated to be total in 74%, in 20% of patients, small tumour residual was encountered and in only 6% large residual was left, due to extensive intracranial extension with cavernous invasion and carotid encasement. This was consistent with the results reported by Almutairi RD [23] in which he reported total tumour removal to be 74% of the cases.

For cases treated by gamma knife, follow up MRI after 1 year showed that small tumour residuals with less than 50% of its original size to be 46% of the cases while large tumour residual of more than 50% of its original size were found in 54% of the cases. This was compared with results published by Sallabanda K [26] in which 63% of his cases showed tumour reduction to less than 50% its original size, and in 30% the tumour volume was more than 50%.

CONCLUSION:

Transsphenoidal resection is ideal for young fit patients with large tumours manifesting with visual compromise, non-responding to medical therapy or as an emergency intra-tumoural haemorrhage (apoplexy).

It is a minimally invasive procedure, relatively safe in the hands of an experienced surgeon, can provide access to the deep-seated area of the sella with minimal tissue sacrifice but excellent panoramic view of the surgical field and easy manipulation of operative angle and depth.

Limitations being difficult access to tumours with lateral extension and invasion of critical adjacent neurovascular structures.

Stereotactic radiosurgery, on the other hand, is best suitable for residual or recurrent disease or in

patients in whom surgery is deemed extremely hazardous such as elderly patients or patients with medical comorbidities. It gives best results for macroadenomas with minimal pressure symptoms and controlled endocrine disease. In experienced hands, it has low risk profile with high efficacy and tolerability.

Recommendation

Proper use of radiotherapeutic option can give excellent results in terms of growth restriction or shrinkage and control of medical symptoms.

Transsphenoidal resection remains the mainstay treatment modality for larger tumours with pressure symptoms and is typically indicated for pituitary apoplexy.

Longer follow up duration is recommended for future studies to document the later improvements after stereotactic radiosurgery, as these changes require longer durations to occur.

Statement of conflict

We have no conflicts of interest to disclose. All authors declare that they have no conflicts of interest.

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