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Reoperation Versus Radiosurgery in Cases of Recurrent Secreting Pituitary Adenoma

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ABSTRACT

Background: Pituitary adenomas accounted for nearly 10% to 15% of all surgically treated primary central nervous system tumours. Prolactinoma is the most common subtype of Pituitary adenomas. The majority of pituitary adenomas are sporadic tumours.

Aim and Objectives: To identify the best option for treatment of recurrent secreting pituitary adenoma and evaluate the risks and advantages of each option.

Patients and Methods: This Cross-sectional analytic study enrolled 52 patients with secreting pituitary adenomas that were previously operated upon by transsphenoidal surgery collected from neurosurgery department in Kasr Alainy Hospitals and the international medical center.

Results: There was a statistically significant difference between Gamma knife and Reoperation regarding need to medical treatment and time to hormonal control. There was no statistically significant difference between Gamma knife and Reoperation regarding age, sex, the type of secreting adenomas, size of the adenoma, the cavernous sinus invasion, mild complications, Growth control and Hormonal control.

Conclusion: Reoperation and Stereotactic irradiation by gamma knife radiosurgery are safe and effective treatment modality for patients with recurrent secreting pituitary adenomas after unsuccessful surgery or after recurrence.

Keywords: *Pituitary adenomas, Stereotactic irradiation, Gamma Knife radiosurgery (GKRS)*

1. INTRODUCTION

Pituitary adenomas accounted for nearly 10% to 15% of all surgically treated primary central nervous system tumours. The majority of these lesions are benign, and affected patients typically present with hormone hypersecretion syndromes and/or signs of mass effect, depending on tumour size. Some small intrasellar tumours are silent and can only be detected as a result of an incidental finding on magnetic resonance imaging (1).

The majority of pituitary adenomas are sporadic tumours, though a small percentage (approximately 5% of all cases) occur in the context of hereditary syndromes like multiple endocrine neoplasia type 1 (MEN1), Carney complex (CNC), and familial isolated pituitary adenomas. All of these are rare autosomal dominant situations with variable penetrance caused by mutations in suppressor genes like MEN1, PKAR1a, and AIP. Pituitary adenomas can also be found in patients with McCune-Albright syndrome (caused by postzygotic mosaic mutations in the GNAS (guanine nucleotide binding protein a stimulating) gene) and in patients with SDH (succinate dehydrogenase) mutations (2).

Imaging and postmortem studies in general populations revealed a 20-25 percent incidence of pituitary adenomas; however, only about one-third of them are clinically evident (3).

Prolactinoma is the most common subtype of Pituitary adenomas, accounting for 40% to 66 percent of all clinically diagnosed cases. Non-functional pituitary adenomas are the second most common subtype (14% to 43%), followed by growth hormone secreting (GH)-PA and adrenocorticotropic hormone secreting (ACTH)-PA (4).

Pituitary adenomas is also more common among females than males, with an incidence rate of 3.11 per 100,000 in females and 2.71 per 100,000 among males in the United States (5).

According to the World Health Organization (WHO) guidelines for pituitary tumour classification in 2017, Pituitary adenomas were previously classified as invasive or non-invasive, typical or atypical, and aggressive or non-aggressive pituitary adenomas based on their radiological characteristics, pathologic features, and clinical behavior (6).

The aim of the study was to identify the best option for treatment of recurrent secreting pituitary adenoma and evaluate the risks and advantages of each option.

2. PATIENTS AND METHODS

This Cross-sectional analytic study enrolled 52 patients with secreting pituitary adenomas that were previously operated upon by transsphenoidal surgery collected from neurosurgery department in Kasr Alainy Hospitals and the international medical center.

The study was approved by the local ethics committee and consents were obtained from involved participants.

Inclusion criteria: Patients who previously operated by transsphenoidal approach for removing secreting pituitary adenoma, all age groups, and both sexes.

Exclusion criteria: Patients who previously operated by transcranial approach, patients who previously operated by trans nasal trans spenoidal more than one time and non-secreting pituitary adenoma.

Methodology

Patients were evaluated before new intervention with: History taking, Full laboratory, including hormonal profile, Visual assessment and Imaging study.

Patients after intervention either by reoperation or radiation was evaluated with: Assessment of early complications, visual field and hormonal profile, MRI Brain soft tissue and follow up for 3 months, then 6 months and then one year from the intervention.

Potential risks: CSF leak (rhinorrhea), Visual affection, Bleeding, Infection, Vascular injury, Hypothalamic injury, Electrolyte imbalance, Diabetes insipidus and Syndrome of inappropriate anti diuretic hormone secretion (SIADH).

Risk of radiation: Hypopituitarism, Visual affection, Hair loss, Fatigue and Malignant transformation.

Sample size

We calculated the sample size using Medcalc software regarding our primary outcome that was the hormonal level after the intervention. We increased the study power to 90% to have precise results. Using alpha error of 0.05 and study power of 90%, a minimum number of 46 patients (23 patients per group) was needed for the study. The number was increased to 52 patients (26 patients per group) to compensate for possible dropouts; 26 patients were treated in second time by reoperation (trans nasal trans sphenoidal resection), and 26 patients were treated by radiosurgery by Gamma knife.

Surgical procedure: All cases were operated upon by endoscopic endonasal trans-sphonidal approach by neurosurgeon and otolaryngologist. Corticosteroids were given to all patients the night before the day of operation and stopped in few days later unless there was any indication to continue.

All cases underwent general anesthesia under normotensive conditions.

Nasal and shenoidal phase: During this step we held the endoscope with the left hand and an instrument with the right hand. The nasal mucosa of the middle turbinate and the septal mucosa were injected with a 1:100,000 epinephrine solution to induce vasoconstriction. The middle turbinate was lateralized and the sphenoid ostium located then the nasal septum was fractured and pushed away from the rostrum of the sphenoid sinus; the contralateral sphenoid ostium was exposed sub-mucosally. A wide sphenoidotomy followed by removal of inter and intra-sensual septa and exposure of, sellar floor, optic prominences, carotid prominences, optic carotid recess were done.

sellar and suprasellar phase: The sellar floor was removed using Kerrison rongeurs or high-speed drill if thinned out or still thick accordingly. The dura mater was opened and sellar content exposed. The endoscope was then introduced inside the sellar in patients with macroadenomas and a careful search for tumor remnants was made. In the case of macroadenomas with supraselar extensions the endoscope was further directed to the suprasellar region and the tumor removed .an angled 30 ° endoscope was then advanced sequentially into the tumor resection cavity to inspect the hidden corners for ay tumor remnant in some. In case of significant intraoperative cerebrospinal fluid (CSF) leak, a multilayer sellar reconstruction was made done fat graft, fascia lata, Gel foam.

Gamma knife procedure and neuroimagining

Application of the steretactic frame was under local anesthesia on the same day of the surgery. MRI was done with frame to

help in identifying and targeting the pathology. Leskell gamma knife model 4c -APS was used in all cases. Mri slices thickness is 1.5 mm without any gap on zero angle. T1 coronal, axial and sagittal before infection of the contrast and after injection were the stereotactic Mri sequences. T2 and fat suppressions are very useful in recurrent cases. T2 sequence is useful in post-surgical cases to help to identify the visual apparatus on the other hand the fat suppression sequence was useful in differentiation of the fat graft used to pack the sellar.

The sequences were transmitted to the Leskell gamma plan after which the plan is transmitted to the leskel gamma knife control unit where the patient received the treatment automatically with APS. Either the 8 mm or the 4 mm colliomatorhelmet was used to avoid injury to neural structures and also to provide comfortability to patients.

Statistical analysis

Statistical package for social science (SPSS) software, version 20 for Microsoft Windows (SPSS inc., Chicago, iL, USA) was used for data analysis.

Categorical data was presented as frequency (%) and analysed by square test.

Continuous data was checked for normality using Shapiro-Wilk test and was presented as mean (standard deviation) or median (interquartile range) as appropriate. Continuous data was analysed using unpaired t test or Mann Whitney as appropriate. Repeated measures were analysed using analysis of variance (ANOVA) for repeated measures with post-hoc pairwise comparisons using the Boneferroni test. A P value less than 0.05 was considered statistically significant. We used Mann-whitney-u and fisher s exact test to analysis the outcome of the two groups.

3. RESULTS

In this section, we present the findings of our comparative study between reoperation and Gamma Knife radiosurgery. Our goal was to assess which approach offered better hormonal control, fewer complications, and faster clinical outcomes. The results are drawn from 52 patients treated at two specialized neurosurgical centers. Key outcome measures include tumor growth control, hormonal remission, and the need for postoperative medical therapy.

Table (1): Demographic characteristics among the studied groups

Variables	Measures	Gamma knife (N=26)	Reoperation (N26)	p-value
Age (years)	**Mean±SD**	38.3±11.8	34.6±9.5	0.216
	Range	12.0–58.0	18.0–53.0	
Sex (n, %)	**Male**	17 (65.4%)	13 (50.0%)	0.262
	Sex	9 (34.6%)	13 (50.0%)	

Independent t-test. #Chi square test.

Age in Gamma knife and Reoperation was 38.3±11.8 and 34.6±9.5 respectively with no significant difference (p=0.216). Regarding sex, males in Gamma knife and Reoperation were17 (65.4%) and 13 (50.0%) respectively with no significant difference (p=0.262) as shown in table (1)

Table (2): Tumor characteristics among the studied groups

Variables	Measures	Gamma knife (N=26)	Reoperation (N26)	p-value
Type	**Acromegaly**	12 (46.2%)	14 (53.8%)	0.827
	Prolactin	10 (38.5%)	8 (30.8%)	
	Mixed	2 (7.7%)	1 (3.8%)	
	Cushing	2 (7.7%)	3 (11.5%)	
Size	**Micro**	11 (42.3%)	13 (50.0%)	0.578
	Macro	15 (57.7%)	13 (50.0%)	

Cavernous sinus invasion	**Positive**	9 (34.6%)	8 (30.8%)	0.768
	Negative	17 (65.4%)	18 (69.2%)	

Chi square test. Fisher's Exact test.

The study demonstrated the tumor characteristics among the studied groups regarding the type of secreting adenomas, size of the adenoma and the cavernous sinus invasion. Concerning types, Acromegaly, Prolactin, Mixed and Cushing in group A were 12 (46.2%), 10 (38.5%), 2 (7.7%) and 2 (7.7%) respectively, while they were in group B 14 (53.8%), 8 (30.8%), 1 (3.8%) and 3 (11.5%) respectively, with no significant difference (p=0. 827). Micro size (less than 1 cm) in diameter in Gamma knife and Reoperation was 11 (42.3%) and 13 (50.0%) respectively, with no significant difference (p=0.578). Cavernous sinus invasion in Gamma knife and Reoperation was 9 (34.6%) and 8 (30.8%) respectively, with no significant difference (p=0. 768) as shown in table (2).

Table (3): Complications among the studied groups

Variables	**Measures**	**Gamma knife (N=26)**	**Reoperation (N26)**	**p-value**
Mild complications	**Positive**	3 (11.5%)	5 (19.2%)	0.703
	Negative	23 (88.5%)	21 (80.8%)	
Severe complications	**Positive**	0 (0.0%)	0 (0.0%)	NA
	Negative	26 (100.0%)	26 (100.0%)	

NA: Not applicable. Fisher's Exact test.

The study showed that: Mild complications in Gamma knife and Reoperation were 3 (11.5%) and 5 (19.2%) respectively, with no significant difference (p=0.703). Severe complications did not occur in either study group. Mild complications included CSF leak (without further intervention) bleeding per nose, electrolyte imbalance, diabetes insipidus, hair loss and fatigue. sever complications included CSF leak with further surgical intervention, visual affection, vascular injury, meningitis, hypopituitarism and malignant transformation as shown in table (3)

Table (4): Presence of medical treatment

Measures	**Gamma knife (N=26)**	**Reoperation (N26)**	**p-value**
Positive	26 (100.0%)	1 (3.8%)	**<0.001***
Negative	0 (0.0%)	25 (96.2%)	

#Chi square test. *Significant

The study revealed that the need to medical treatment among the studied groups and it was a highly statistically significance between the two groups. Group A all of them needed a medical treatment in order to provide the patients with hormonal control till the achievement of the hormonal control by destruction of the abnormal secreting cells. On the other hand, after the redo surgery only one case needed a medical treatment which gave the trans nasal and trans sphenoidal surgery an obvious advantage over the radiosurgery since the radiosurgery was more expensive than the redo surgery not to mention the medical treatment which was costy and essential for almost all the cases of the radiosurgery as demonstrated in table (4).

Table (5): Control among the studied groups

Variables	**Measures**	**Gamma knife (N=26)**	**Reoperation (N26)**	**p-value**
Growth control	**Positive**	26 (100.0%)	26 (100.0%)	NA
	Negative	0 (0.0%)	0 (0.0%)	
Hormonal control	**Positive**	19 (73.1%)	20 (76.9%)	0.749

	Negative	7 (26.9%)	6 (23.1%)	
Time to control (months)	**Mean±SD**	33.3±17.0	1.7±0.8	**<0.001**
	Range	13.0–96.0	1.0–4.0	

NA: Not applicable. ^Independent t-test. *Significant

Growth control was achieved in all cases in both groups. Hormonal control was achieved in gamma knife group in 19 cases (73.1%) and in reoperation group 20cases (76.9%) with no significant difference (p=0.749). Time to hormonal control was longer in gamma knife group 33.3±17.0 than in reoperation group 33.3±17.0, the difference was statistically significant (p<0.001) as shown in table (5).

4. KEY RESULTS

In our study involving 52 patients with recurrent secreting pituitary adenomas, both treatment options—reoperation and Gamma Knife radiosurgery—showed excellent tumor control, with a 100% success rate in halting tumor growth. Hormonal control was also comparable between the two groups (76.9% for reoperation vs. 73.1% for Gamma Knife). However, there were two key differences: first, patients in the reoperation group achieved hormonal normalization much faster (average 1.7 months) compared to those treated with Gamma Knife (average 33.3 months). Second, while nearly all patients treated with Gamma Knife required ongoing medical therapy after the procedure, only one patient in the reoperation group needed additional medication. Mild complications were slightly more frequent in the reoperation group (19.2%) than in the Gamma Knife group (11.5%), but no severe complications were reported in either group.

5. DISCUSSION

In the group treated by reoperation; regarding the characters of participants' lesions we found that main lesions were Acromegaly (53.8%), Prolactin (30.8%), Cushing (11.5%) and Mixed (3.8%) tumors, Micro size was represented (50.0%) of patients in this group, and cavernous sinus invasion was found among (30.8%) patients in this group. Mild complications were reported in 5 patients (19.2%). Moreover, no severe complications were reported. As well as only one case needed further medical treatment.

Regarding postoperative control, Growth control was achieved in all cases and hormonal control was found in 20 patients (76.9%) of reoperation group, Time needed to control was 1.7±0.8 months in reoperation group.

Our results is comparable with Espinosa-de-Los-Monteros et al., who compared the short- and long-term success of various secondary interventions for persistent and recurrent Cushing's disease and reported that early remissions were recognised in 66.6% of the reoperated patients and only 33.3% of patients reached a long-lasting remission. However, as operating times increased, so did the incidence of complications such transitory diabetes insipidus and arachnoid tears necessitating surgical re-intervention (7).

The results of our study were supported by Almeida et al., meta-analysis of endonasal endoscopic series, which found that 63.6% of patients with growth-hormone secreting adenomas experienced biochemical remission following revision surgery (8).

In the current study we used SRS by gamma knife radiosurgery among 26 patients; regarding the characters of participants' lesions we found that main lesions were Acromegaly, Prolactin, Mixed and Cushing as 12 (46.2%), 10 (38.5%), 2 (7.7%) and 2 (7.7%) respectively, Micro size was among (42.3%). Cavernous sinus invasion was among (34.6%) of patients in this group

Mild complications in Gamma knife were reported in 3 patients (11.5%) and severe complications did not occur in any patient. Need to medical treatment was more frequent in Gamma knife group 26 (100.0%). Growth control was achieved in all cases in the group. Hormonal control was in 19 patients (73.1%). Time to control was 33.3±17.0 months.

Regarding our knowledge the data on re-irradiation for recurrent secreting PAs are limited.

Both the extent of the remaining tumour and its proximity to the eye's visual system are major factors in deciding between standard CRT and SRS. Biochemical remission rates did not differ between CRT and SRS in Li et al., recent meta-analysis (9).

Time to normalization by SRS is related to preirradiation hormone levels, not the technique of radiation, as shown by other studies with median timeframes to normalisation between 30 and 66 months, similar to CRT (10).

Kong et al., compared the efficacy and safety of SRS and EBRT for the treatment of 125 patients with PAs. Although no significant difference was found in either biochemical remission or tumor growth control, the time to biochemical remission after SRS was much shorter than that following EBRT (26 vs. 63 months) (11).

According to the Clinical Practice Guidelines initiated by European Society of Endocrinology (12), SRS is not suitable for the tumor < 3 cm) or tumor location near the optic apparatus and brainstem (<5 mm) (13).

In the present study by comparing both groups (Reoperation and Radiosurgery by gamma knife) we found that no statistically significant difference between them regarding gender, age, tumor type, size or cavernous sinus invasion, initial hormonal level, post intervention complications, Growth control and Hormonal control as both groups showed good remission, low mild complication and no sever complications. However, we found statistically significant difference regarding need to medical treatment as it was more frequent in Gamma knife group (100.0%) than in Reoperation (3.8%), also we found higher significant time needed to control in gamma knife group (33.3±17.0) months than reoperation group (1.7±0.8) months.

In accordance with Bodaghabadi et al., who compared repeated Transsphenoidal Surgery and Gamma Knife Radiosurgery in Recurrent Cushing Disease after Transsphenoidal Surgery; Fifty-two patients who had CD recurrence following TSS were included, and the next therapeutic approach for them was either further surgery or GKRS. Magnetic resonance imaging (MRI), physical examinations, and hormone measurements were performed on them over the course of 3.05± 0.8 years. There was no difference between the two groups in terms of gender, average age, adenoma type, follow-up time, or baseline hormone levels. There was no correlation between disease-free months or tumour volume and cortisol levels in urine collected 24 hours before to surgery. According to their data, the GKRS group had a longer time between recurrences than the TSA group did. GKRS may be a viable option to repeat TSA for recurrent CD due to its extended recurrence free time (14).

6. STUDY LIMITATIONS

This study has several limitations. Notably, the two treatment modalities—reoperation and stereotactic radiosurgery (SRS)—were performed at different centers, which may introduce variability in patient selection, treatment protocols, and outcome assessment. This center-specific difference limits the ability to directly compare the two approaches under uniform conditions. Additionally, the relatively small sample size and the limited number of centers involved reduce the generalizability of the findings. We recommend future multicenter studies with larger cohorts and longer follow-up periods to provide more robust comparative data. Continued advancements in imaging technologies, dose planning, and radiobiological understanding—particularly in the context of Gamma Knife radiosurgery—are also expected to improve outcomes in future research.

7. CONCLUSION

Reoperation and Stereotactic irradiation by gamma knife radiosurgery are safe and effective treatment modality for patients with recurrent secreting pituitary adenomas after unsuccessful surgery or after recurrence. Both approaches provide excellent tumor control (100%), with normalization of hormone hypersecretion in (76.9%) and (73.1%) in Reoperation and gamma knife respectively. However, Medical treatment was needed among all gamma knife patients that were statistically significant higher than reoperation group. Moreover, gamma knife group need significantly longer time to control the hormonal level than reoperation group.

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