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REOPERATION VERSUS IRRADIATION IN CASES OF RECURRENT OR PERSISTENT GROWTH HORMONE SECRETING PITUITARY ADENOMA

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Abstract

Background: Acromegaly is an uncommon disorder, with a prevalence of five to six patients for every one hundred thousand populations and an incidence of three to four for every million. The third most common intracranial neoplasm is pituitary adenomas which arise from adeno hypophysial cells of the anterior pituitary gland.

Aims and objectives: To identify the best option for treating recurrent and persistent acromegaly and evaluate the risks and advantages of each option.

Patients and methods: The study was conducted on operated cases with retrospectively collected follow-up data from 11 cases admitted to the Cairo University Hospitals in the period between March 2019 and April 2020 and 13 cases from the International Medical Center Cairo, Egypt, suffering from recurrent pituitary adenomas.

Results: There was a significant variance in age among the two groups (P = 0.015), but there was no significant variance among the two groups concerning type of adenoma (P = 0.123), pre-intervention GH mean levels among the two groups (P = 0.325), cavernous sinus affection between the two groups (P = 1.00), or outcome (P = 0.300).

Conclusion: In a carefully chosen group of acromegalic patients who had undergone prior operations at our center, both gamma knife stereotactic radiotherapy and sphenoidal surgery were effective and safe. While our study outcomes favor more trans-sphenoidal surgery over gamma knife stereotactic radiotherapy due to high rates of reduction of GH, less need for post-intervention treatment, and less time for achieving remission,

Keywords: Irradiation, Recurrent growth hormone, Acromegaly, Pituitary adenoma

BACKGROUND

Overproduction of GH, the hormone responsible for growth, is the primary cause of acromegaly **(1).** For most patients, endonasal transsphenoidal surgery (TSS) is the first treatment they choose. Cytoreduction of GH-secreting cells may quickly fix high serum GH levels. The problem of

recurrence or persistence following surgery persists, despite the fact that several studies have established the safety, repeatability, and durability of TSS in establishing biochemical remission of this illness **(1, 2).**

Acromegaly therapy depends on the utilization of an efficient medication. Following the failure of initial therapy or the return of acromegaly, medical treatments, surgery, and radiation are all viable choices for treatment. The progressive decrease of the recognized growth hormone (GH) level has been the subject of much discussion over the concept of a cure for acromegaly **(3).**
Recurrent pituitary adenoma is defined as a recurrence of a previously removed tumor, while the regrowth of a persistent, incompletely excised tumor is the definition of residual pituitary adenoma. Both are customarily placed under the general category of recurrence **(4)**. Regarding the size of Pituitary adenomas; they can be classified into three categories: micro adenomas which are less than 1 cm that represent 90% of pituitary adenomas **(5);** macro adenomas, which are more than 1 cm; and third-type giant adenomas, whose sizes are more than 40 mm **(6)**. Outside of the sella, microadenomas can spread to the suprasellar, infrasellar, and/or cavernous sinus regions **(7-9)**.
Our study's primary objective was to recognize the best option for treating recurrent and persistent acromegaly and evaluate the risks and advantages of each option.

Patients and methods

The study was conducted on operated cases with retrospectively collected follow-up data of 11 cases in the Cairo University Hospitals admitted in the period between March 2019 and April 2020 and 13 cases from the International Medical Center Cairo, Egypt, suffering from recurrent pituitary adenomas. The study was carried out to identify the best option for treating recurrent and persistent acromegaly and evaluate the risks and advantages of each option.

Inclusion criteria

The study was conducted on 24 cases suffering from recurrent or persistent GH-secreting pituitary adenomas; 11 cases were operated on by endoscopic end-nasal trans-sphenoid excision and 13 cases were managed by radio surgery.

Exclusion criteria

Cases that were previously operated on by transcranial approach or those with other types of pituitary adenomas

Methods

Each individual was given a thorough physical and neurological evaluation. The patient's history, physical examination, blood pressure, glucose level, and Glasgow Coma Scale (GCS) score were recorded. Diabetes mellitus, liver disease, heart disease, and the utilization of any medicines (particularly antihypertensive, anti-platelet, and anticoagulant therapies) were all factored into the analysis. Evaluation by laboratory means: CBC, bleeding profile (PT, PC, INR, PTT), liver and kidney function tests (ALT, AST, serum urea and creatinine, salt, and potassium), and other routine preoperative laboratory studies. The hormonal profile included ACTH, cortisol AM PM, GH, PRL, TSH, T3, T4, LH, FSH, and insulin-like GH. Surgical procedure: All cases were operated upon by an endoscopic endonasal trans-sphonidal approach by a neurosurgeon and otolaryngologist. Corticosteroids were given to all patients the night before the day of operation and stopped a few days later unless there was any indication to continue. All cases underwent general anesthesia under normotensive conditions.

Results

Table 1: Baseline characteristics (age and sex) in both groups

Variable		group A (total = 13)		Group B (total = 11)		P Value
		Mean	(SD)	Mean	(SD)	
Age, M (SD)		43	12	33	5	0.015
Sex*	male	7	53.85%	6	54.55%	
	female	6	46.15%	5	45.45%	1.00

Age data are represented as mean and standard deviation (SD).* Sex data is represented as a number and percent (%).
There was a significant variance in age among the two groups (P = 0.015). 53.85% of group A patients were males and 46.15% were females. On the other hand, 54.55% of group B patients were males and 45.45% were females. There was no significant difference in both groups regarding sex (P = 1.00). (Table 1)

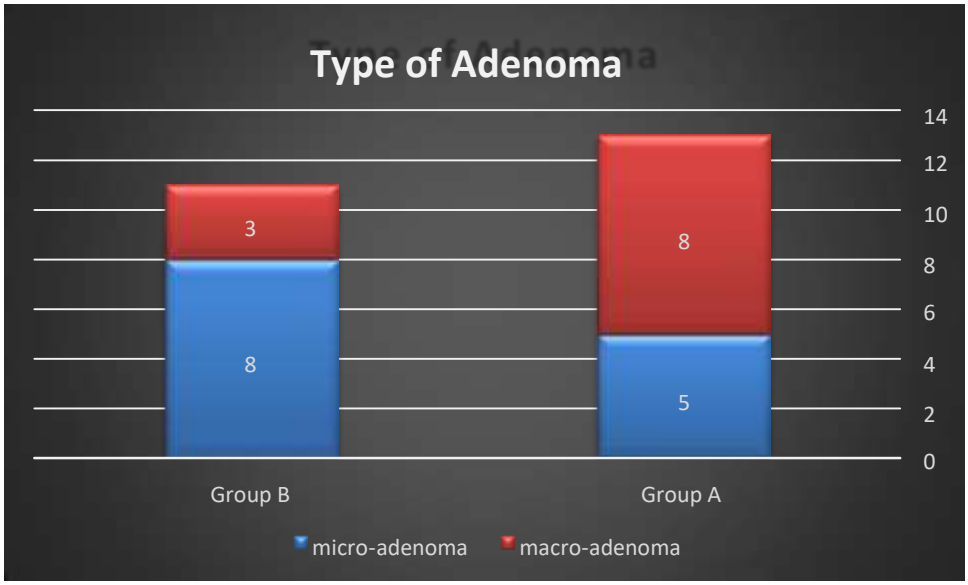

Chart 1: Type of adenoma in each group

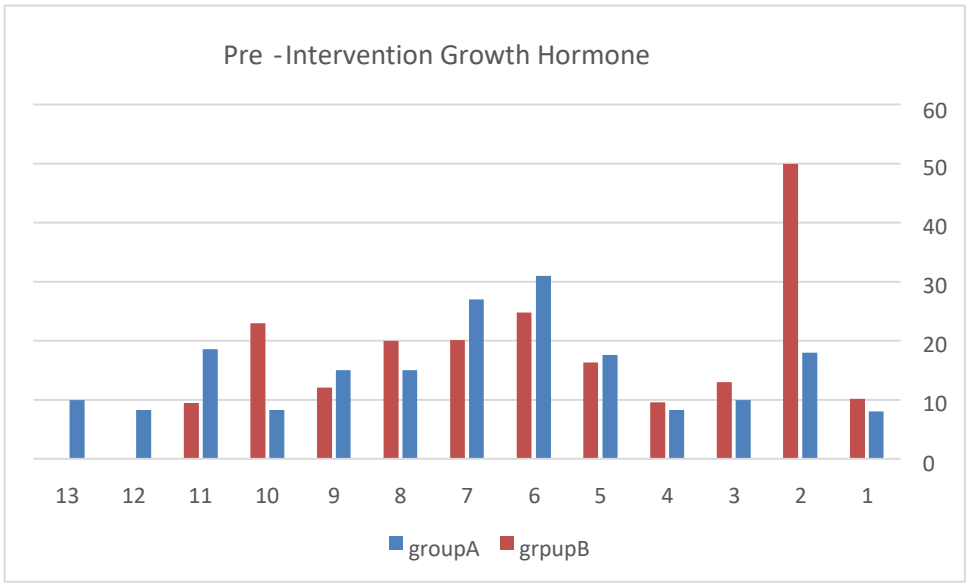

Chart 2: Pre-Intervention Growth Hormone for Each Patient

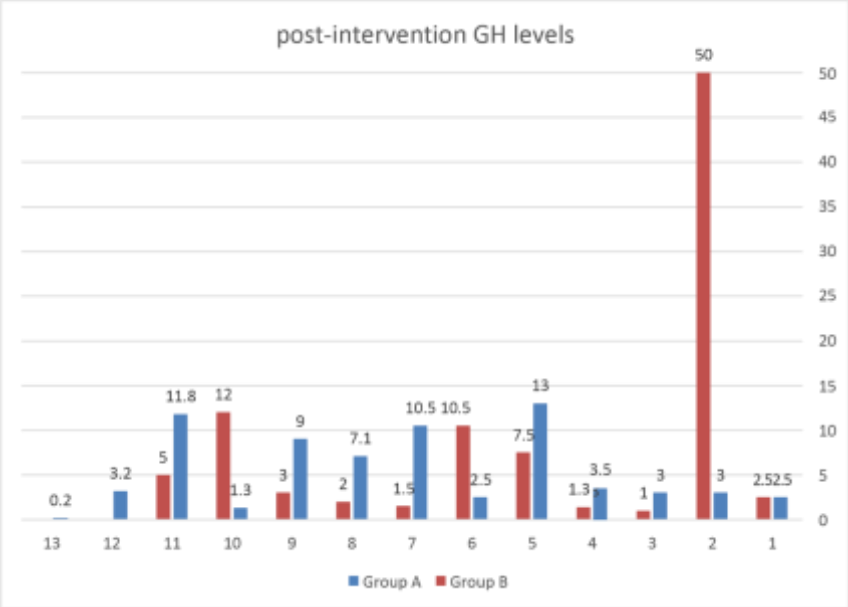

Chart 3: post-intervention GH levels for each patient in both groups

Table 2: number of cases below 2.5 ng/mL

Variable	Group A (total = 13)		Group B (Total = 11)	
	number	percent	number	percent
Success level GH	4	30.77%	5	45.46%

Data are represented as numbers and percents (%).

The success rate of intervention in each group to reduce GH to normal levels (≤ 2.5 ng/ml) In group A, four patients out of 13 reached normal GH levels. Meanwhile, five patients out of 11 reached the normal levels of GH in group B. Figure 5 illustrates the success rate in both groups. (Table 2).

Table 3: 50% reduction rate of GH levels in each group

Variable	Group A (total = 13)		Group B (Total = 11)	
	number	percent	number	percent
50% reduction rate of GH level	10	76.92%	8	72.73%

Data are represented as numbers and percents (%).

Our findings revealed that out of 13 patients in group A, ten (76.92%) have been managed to reduce GH levels up to 50% or less post-intervention compared to pre-intervention, while in group B, eight (72.73%) patients have been managed to reduce GH levels up to 50% or less post-intervention compared to pre-intervention. (Table 3)

Table 4: Time until cure in each group

Variable	Group A (total = 13)		Group B (Total = 11)	
	Mean	SD	Mean	SD
Time to cure	39 (months)	22	2 (weeks)	1

Data are represented as means and standard deviations (SD).

The duration of intervention until cure in each group Group A showed a markedly longer duration (months) than Group B (weeks only). The mean time till cure in group A was 39 (±22 SD) months, while in group B, the time till cure was 2 (±1 SD) weeks. (Table 4)

Table 5: cavernous sinus invasion in each group

Variable	Group A (total = 13)		Group B (Total = 11)		P value
	number	percent	number	percent	
Cavernous sinus invasion	3	23.08%	3	27.27%	1.00

Data are represented as numbers and percents (%).

Three patients in each group had cavernous sinus invasion and in the rest, there was no cavernous sinus affection. There was no significant variance in cavernous sinus affection amongst the two groups (P = 1.00). (Table 5)

Table 6: complications in each group

Variable	Group A (total = 13)		Group B (Total = 11)		P value
	number	percent	number	percent	
Mild complications	1	7.69%	3	27.27%	0.300
Sever complications	0.00		0.00	___	

Data are represented as numbers and percents (%).

There were no severe complications among all patients in group B as well. There was no significant variance in this outcome among the two groups (P = 0.300). (Table 6)

Case presentation

Case No. 1

A 40-year-old, male patient presented with a headache and diminished vision. Hormone profile: showed high GH

MRI: revealed sellar and suprasellar pituitary adenoma.

The patient was managed with an endoscopic trans-nasal trans-sphenoid approach one year ago and remanaged with a trans-nasal trans-sphenoidal approach again.

Figure 1: preoperative MRI showing revealed sellar and suprasellar pituitary adenoma.

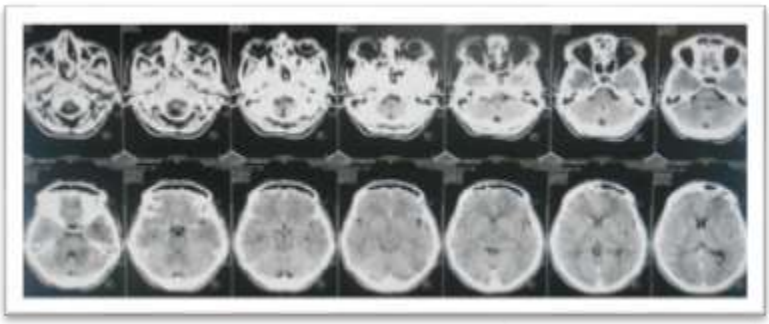

Figure 2: postoperative CT scan.

Discussion

Benign lesions known as pituitary adenomas originate from the proprial cells of the anterior pituitary gland. Surgery or pharmacologic treatment is typically the primary course of action. When these interventions fail to achieve the desired results or when a recurrence occurs, radiation therapy should be contemplated **(10)**.

According to the Serri et al. **(11)** study, the number of included patients for trans-sphenoidal surgery was on average 50±12 SD and nearly half of them were males and the rest were females. According to Bir et al. **(12),** who included 57 consecutive cases for Gamma Knife radiosurgery treatment, the average age of the included patients was 56 years; about 56% of them were males and 34% were females. In the current study, the mean age for the gamma knife stereotactic radiotherapy group was 43 ±12 SD years; 53.85% of this group patients were males and 46.15% were females, while in the trans-sphenoidal surgery group the mean age was 33 ±5 SD years; 54.55% of this group patients were males and 45.45% were females. There was a significant variance in age among the two groups in terms of age and sex (P = 0.015, P = 1.00, respectively).

As stated by the Serri et al. **(11)** study, they incised 25 patients with acromegaly for transsphenoidal selective adenomectomy. Eight patients had microadenomas, and 17 had macroadenomas. According to Nomikos et al. **(1),** they reported on a time-ordered series of 688 individuals with acromegaly who had transsphenoidal adenomectomy over the course of 19 years. According to Bir et al. **(12),** 57 consecutive patients with nonfunctioning pituitary adenomas were done. Fifty-three patients out of 57 had tumors that returned or were not completely removed despite microsurgical excision. Following receiving Gamma Knife radiosurgery, the study population underwent a series of clinical and imaging assessments. The type of pituitary adenoma for patients in each group was five patients in the gamma knife stereotactic radiotherapy group had micro-adenoma compared to eight patients in the trans-sphenoidal surgery group had micro-adenoma. The rest in both groups had macro-adenoma. There was no significant variance in both groups regarding the type of adenoma (P = 0.123).

According to Nomikos et al. **(1),** they reported on a time-series analysis of 688 individuals with acromegalic disease who were treated during a 19-year span. Having a normalized baseline GH level, suppressed GH levels to below 1 ng/ml following an oral glucose load, and normalized IGF-I levels were all considered biochemical cure criteria. After the initial TSS, 57.3 percent of the 506 patients who were treated met the criteria. Biochemical 'cure' was shown to be proportional to pre-treatment GH levels, tumor size, and tumor invasion. The rate of complications was less than 2% overall. One person out of 688 died throughout this study period, or 0.1%. Only two recurrences (0.4%) were found throughout a follow-up duration of 10.7 years. Transcranial surgery and subsequent surgery both had a low success rate in curing patients (5.2% and 21.3%, respectively). They came to the conclusion that surgery is still, almost without exception, the go-to treatment for acromegaly because (i) it has a high cure rate, (ii) it has a low morbidity rate, (iii) it has a low recurrence rate, and (iv)it causes an immediate drop in GH. Current diagnostic and treatment standards mean that relapses are quite rare. Patients with large, invasive tumors that secrete a lot of secretions are unlikely to recover fully from surgery alone and will require additional adjuvant therapy.

Freda et al. **(13)** found a group of people who had surgery and had acromegaly that was in remission. These people had normal IGF-I levels but a small problem with their GH levels going down after taking glucose by mouth. In order to examine the importance of this anomaly, additional comprehensive GH secretion testing and longitudinal follow-up with a subset of these individuals were done. A total of 110 postoperative patients who underwent an oral glucose tolerance test for acromegaly were analyzed. A normal IGF-I level among these cases indicated that 76 were in remission. Among those in remission, 50 had a normal nadir GH (<0.14 microg/ml) (group I), while 26 had an abnormal nadir GH (>0.14 microg/ml) (group II). A total of fourteen subjects who were in remission were subjected to supplementary testing. On a distinct day, arginine stimulation testing was

performed alongside hourly GH sampling for 8 hours for remission group I and 7 hours for remission group II. Group II had a greater mean hourly GH concentration (0.47 +/- 0.04 microg/liter) than group I (0.19 +/- 0.07 microg/liter; P = 0.002). Group II had a greater GH reaction to arginine than Group I (P < 0.01). Out of the initial cohort of cases in remission, 49 (30 subjects from group I and 19 subjects from group II) experienced longitudinal oral glucose tolerance testing on a serial basis every 1-2 years for a duration of 1 to 6.5 years (mean follow-up, 3.2 years). The majority of patients maintained the initial pattern of GH suppression. IGF-I levels remained normal in all cases comprising group II; however, five subjects from the same group developed an increased IGF-I level, which corresponded to a biochemical recurrence. Group II exhibited a higher incidence of disease recurrence in comparison to Group I (P = 0.003). Certain postoperative subjects with remission-stage acromegaly and normal IGF-I levels exhibit persistently aberrant nadir GH levels following oral glucose administration, which may be accompanied by additional indicators of elevated GH secretion compared with postoperative individuals with normal GH suppression. In certain cases, this atypical pattern of GH suppression might be correlated with an elevated susceptibility to relapse of the disorder.

Conversely, a retrospective analysis was done on 57 consecutive cases with nonfunctional pituitary adenomas from 2000 to 2013. Recurrent or residual tumors were observed in 53 out of 57 individuals following microsurgical resection. The research population was clinically and radiographically assessed subsequent to treatment with Gamma Knife radiosurgery. The mean duration of follow-up was 45.57 months. Significant variations in tumor growth control were observed with Gamma Knife radiosurgery for pituitary adenomas, according to the researchers (growth was inhibited in 21 patients [36.1%], reduced in 32 patients [56.1%], and elevated in 4 patients [7%]). At three, seven, and ten years, the progression-free survival rates following Gamma Knife radiosurgery were 90%, 98%, and 100%, respectively. In comparison to pretreatment, the neurologic signs and symptoms increased significantly following Gamma Knife radiosurgery (14% versus 107%; p < 0.0001). Five patients (8.8%) were determined to need further treatment.

Jezková et al. **(14)** said that after 42 months, half of the patients had a mean GH level below 2.5 microg/l, and their I test (oGTT) went back to normal at 1 microg/l, and their IGF-I levels were normal after 66 months. Not the extent of the adenoma, but initial adenoma hormonal activity (GH and IGF-I serum levels) determined the effectiveness of LGK. In comparison to cases that only underwent laser irradiation, those who underwent primary neurosurgery and then Leksell gamma knife irradiation had better results. All adenoma growth was arrested by irradiation, resulting in a tumor reduction in 62.3% of patients. Twenty-six individuals developed hypopituitarism when functional peritumoral pituitary tissue was exposed to 15 Gy or more of radiation. Hypopituitarism was not observed when reduced dosages were administered. In order to manage post-surgical residues, they concluded that this technique is a valuable adjunct to primary neurosurgery because it can shorten the period of medical treatment. As an alternative treatment option when neurosurgery is impossible. These findings were also confirmed by the Iwai et al. **(15)** study. In our study, in terms of post-intervention GH levels, the group receiving gamma knife stereotactic radiotherapy showed a mean post-intervention GH level of 5.4 ±4.3 SD ng/ml, whereas the group receiving trans-sphenoidal surgery's post-intervention GH level was 8.8 ±14.2 SD ng/ml. There was no significant difference in post-intervention GH mean levels between the two groups (P = 0.429).

Conclusion

Both gamma knife stereotactic radiotherapy and sphenoidal surgery were effective and safe. While our study outcomes favor more trans-sphenoidal surgery over gamma knife stereotactic radiotherapy due to high rates of reduction of GH, less need for post-intervention treatment, and less time for achieving remission, These outcomes still outweigh the slightly safer profile of gamma knife stereotactic radiotherapy.

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