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# Gamma knife surgery in management of secretory pituitary adenoma Preliminary evaluation of role, efficacy and safety

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### Abstract

Historically the treatment armamentarium for secretory pituitary adenomas included neurosurgery, medical management, fractionated radiotherapy and recently gamma knife surgery (GKS), the goal of this study is to evaluate the efficacy, safety and role of gamma knife surgery for treatment of secretory pituitary adenomas regarding hormonal and adenoma size control, between mid of 2005 and of 2012, a retrospective analysis of 54 consecutive patients with secretory pituitary adenomas underwent GKS at the International Medical Center (IMC) Cairo-Egypt, 10 patients with adrenocorticotrophic hormone secreting adenoma, 24 prolactin secreting adenoma and 20 with growth hormone secreting adenoma. In 25 patients GKS was the secondary to a prior surgery with failure of hormonal control even in addition of medical treatment, in the other 29 the secretory pituitary adenomas not controlled with medical treatment alone, the median follow up period was 28 months (12-84 months), achieving hormonal control was either normalization or marked decline of abnormal hormone level > 50%, radiological tumor size control was either tumor size stabilization or reduction, among the 54 patients 31 had microadenoma of 1cc volume or less, overall 34 patients (63%) had hormonal control and 51 patients (94%) had tumor size control after GKS, there was direct correlation between tumor size, prescription radiation dose and post-gamma knife hormonal and size control, 29 out of the treated 31 microadenomas cases showed both hormonal and size control, in conclusions gamma knife surgery is safe and effective treatment for secretory pituitary adenomas failed to respond to medical treatment alone or with postsurgical residual or recurrence especially microadenomas.

## 1. Introduction

Pituitary adenomas are common lesions and represent 20% of all primary brain tumors. [1, 2, and 3]. Pituitary adenomas are classified into two groups. The first is the secretory pituitary adenoma that produce excess of normal pituitary hormones usually they are microadenoma. Such functioning adenomas include those with Cushing's disease (high adrenocorticotrophic hormone-ACTH), Acromegaly (high growth hormone-GH), Prolactinomas with high prolactin hormone-PL, and rarely adenoma can overproduce more than one hormone. Occasionally some secretory

microadenoma may produce pressure symptoms relating to compressing the optic pathway or invasion the cavernous sinus. The second are non-secretory pituitary adenomas that represent approximately 30% of pituitary adenomas, they are usually macroadenomas that enlarge and can extend beyond the confines of the sellaturcica into the cavernous sinus, suprasellar region, infrasellar region, and even invade the clivus. [4]

Surgery, fractionated radiotherapy and medication are the three key elements of the treatment strategy for secretory pituitary adenoma. Transsphenoidal microsurgery has remained the primary treatment for most patients with functioning adenomas causing acromegaly or Cushing's disease. Most prolactinomas can be controlled successfully by medical treatment and transsphenoidal microsurgery is the second treatment step [4].

The persistence or recurrence of secretory pituitary diseases due to tumour invasion into surrounding structures or incomplete tumour resection is quite common and long term tumour control rates after transsphenoidal excision alone vary from 50 to 80% [5]. For residual or recurrent tumours fractionated radiation therapy has been the traditional treatment. However, it has a prolonged latency for its effects and is associated with more frequent side effects as hypopituitarism and visual damage. [3, 4, 6].

In 1968, Leksell treated the first pituitary adenoma patient with the Gamma knife, since that time, stereotactic radiosurgery has become an important tool in the neurosurgical treatment for patients with pituitary adenomas. [7]. Recently gamma knife surgery (GKS) has gained acceptance as primary minimally invasive treatment option for secreting pituitary microadenomas or a complementary treatment option in combination with microsurgery for secreting macroadenomas. GKS can provide adenoma growth control and long-term endocrine control that is superior to that of repeat surgery and the long latency of the radiation response .also GKS limits radiation exposure of the surrounding normal brain structures. [4, 8].

## 2. Materials and Methods

### 2.1. Patient Population

54 consecutive patients with secretory pituitary adenoma were treated with leksell GKS at the International Medical Centre Gamma Knife- Centre-Cairo-Egypt between mid of 2005 till mid of 2012, with a minimum 12 months follow up to 7 years. GKS was utilized in our study as an adjuvant treatment in all the studied 54 cases after being resistant to medical therapies or intolerant to its side effects, with or without previous pituitary surgery. In 25 patients some form of prior surgery such as transsphenoidal resection, or craniotomy had been conducted with presence of residual especially that involve the cavernous sinus or recurrence. The others 29 patients have history of medical treatment

failure without any surgical intervention, 21 of them have microadenomas of 10mm maximum diameter or less, that usually referred directly by endocrinologist .

In all the treated cases optic apparatus was at least 2-3mm distance from the treated adenoma. Radiological (MRI and sometimes CT scan); endocrinological, ophthalmological, and neuroradiological exams were conducted. The initial diagnosis was made on the basis of magnetic resonance imaging (MRI) findings, endocrinological exam , pathological findings (available for postoperative cases), and clinical history. In all patients, initial pre-GKS levels of ACTH, cortisol, and urinary free cortisol (UFC), GH and IGF-I, prolactin (PRL), LH, FSH, testosterone or estradiol, TSH, and free T<sub>3</sub> and T<sub>4</sub> were obtained. Stopping of the antisecretory agent's 1 to 2 months before gamma knife surgery is advised in most of the treated patients.

The results were classified to Group I, where clinical improvement, tumor size control and hormonal control (hormonal normalization or marked decline >50% compare to pre-gamma knife surgery) obtained without any post-gamma knife antisecretory medical treatment.

Group II where some hormonal decline <50% with little improvement or stable clinical condition even with antisecretory drugs, Group III where there was a failure to achieve any hormonal control or decline with persistent clinical condition and sometime even worsen.

### 2.2. Gamma Knife Procedure and Neuroimaging

Application of the stereotactic frame was performed under local anesthesia on the morning of the procedure. Stereotactic MRI then done to determine the pathology. The gamma knife procedure was done using, leksell gamma knife model B version from 2005 to mid of 2010 then leksell gamma knife model 4C-APS version till now. The stereotactic MRI sequences were performed on a 1.5 Tesla magnetic resonance machine. The stereotactic MRI sequences included T1 coronal cuts without contrast first then T1 coronal immediately after contrast injection then axial T1 and sagittal T1. MRI slices thickness is 1.5 mm thickness without any gap on zero angle. T2- coronal sequence may obtained especially in post-surgical cases to optimize visualization of optic apparatus, the Fat suppression techniques MRI sequence can prove useful for differentiating tumor from surgical fat grafts. CT is generally reserved for patients who cannot undergo an MRI (e.g. a patient with a pacemaker).

The stereotactic MRI sequences then transmitted to leksell gamma plan, where treatment plan done after which the treatment protocol pass to the leksell gamma knife control unit where treatment applied automatically with APS. Either the 4mm or the 8mm collimator helmet was utilized especially in microadenoma to achieve conformity and avoiding radiation neural injuries .In some cases plugging was applied to avoid optic structure, occasionally

the 72 degree gamma angle of radiation beams was utilized so that the radiation beams were delivered parallel to the optic nerve avoiding intersection and injuries to optic apparatus. Nevertheless in many treated microadenomas 90 degree gamma angle fulfilled the same purpose.

Follow up: Follow up was conducted regularly each 6 months in the first year post GKS and then yearly, the median follow up period was 28 months (12-84 months).. Follow up criteria including MRI with contrast, endocrinological, ophthalmological, assessment.

### 3. Results

This study is conducted on 54 patients with secretory pituitary adenoma treated with gamma knife surgery at the international medical center between the mid of 2005 and mid of 2012 with median follow up period was 28 months (12-84 months). There was 26 females and 28 males, age ranged between 17 years to 63 years (mean=34.2ys). In all the studied 54 there was failure to control high hormonal level, either postsurgical in 25 cases with residual or recurrences, and in 29 cases after failure of medical treatment alone or intolerance to drugs side effects without any previous surgery, 21 of these cases had adenoma of 1cc volume or less

The clinical characteristics of the treated patients are summarized in (Table1); there were 20 patients with acromegaly (high GH), 10 patients with Cushing's disease (high ACTH and UFC) and 24 patients with prolactinoma (high PRL).

**Table 1.** The clinical characteristics of the treated 54 patients with secretory pituitary adenoma.

Parameter	value
Total of patients with secretory pituitary adenoma	54
Female	26
Male	28
Age (range)	17-63ys (mean-34.2ys)
Follow-up (range)	12-84months
Prior surgical intervention prior to GKS	In 25
No Prior surgical intervention prior to GKS	In 29
Adenoma volume >1cc up to 3.7cc/macroadenoma	23
Adenoma volume of 1cc or less/microadenoma	31

The peripheral prescription dose varied according to tumor size, type of hormonal secretion and proximity to optic apparatus, for acromegaly ranged 20-25Gy, in prolactinomas 18-22Gy and in Cushing's disease usually 25-30Gy. The isodose curve ranged between 35 to 60% with adenoma radiation coverage ranged between 93% to 100%.

Optic apparatus in all cases received <8Gy, 3<sup>rd</sup> cranial nerve in those with cavernous sinus invasion received <21Gy and pituitary gland and stalk received <15Gy. The secretory pituitary adenoma volumes treated in this study ranged between 0.036 to 3.7 cubic centimeters (cc), their distribution were as follow: 3 - 3.84cc in 4 patients, 2cc - 2.85cc in 11 patients, 1.2cc- 1.98cc in 8 patients and 1cc volume or less in 31 patients.

The overall results of gamma knife surgery for the treated 54 patients (Table 2) were as follows:

Group I, where 34 patients (63%) had clinical improvement, tumor size control and hormonal control (hormonal normalization in 23 patients or marked decline >50% in 11 patients compare to pre-gamma knife surgery). Group II, where 12 patients (22%) showed some hormonal decline <50% with little improvement or stable clinical condition. Group III, where 8 cases (15%) had failure to achieve any hormonal control with persistent clinical condition or even worsen. Hormonal control in our study did occur within 12 -36 months although clinical improvement sometimes happened before that.

Regarding adenoma sizes determined by MRI follow up post gamma knife surgery, 51 cases (94%) out of the studied 54 cases showed tumor size control, in 41 of them the adenoma being stable size (local control), and in 10 cases the adenoma reduced in size, such reduction started usually after 12-24 months and sometimes continue..

Among the treated 24 prolactinoma patients, 15 patients (62%) had hormonal control after at least two successive serum prolactin (according to age and sex) most of them responded after 12 months and up to 3 years, all treated with peripheral dose 20-22 Gy and 13 of them had adenoma size of 1cc volume or less. Another 6 patients had hormonal decline <50% and the remaining 3 patients showed failure of hormonal control they had adenoma volume of 2.6cc, 3.3 cc and 3.4 cc respectively, all of them treated with peripheral prescription dose limited to 18Gy because of adenomas sizes and proximity to optic apparatus. (Fig1,2).

In the treated 20 acromegaly patients 12 patients (60%) had hormonal control (GH < 2.5 µg/l), that usually happened after 12-24 months post GKS, 11 of them had adenoma volume of 1cc or less and all treated with marginal dose of 22-25Gy, 5 patients had hormonal decline <50% and the remaining 3 patients had failure of hormonal control, their treated adenomas sizes were 2.6, 2.8 and 3.7cc respectively all these cases treated with peripheral dose of 22Gy or less because of tumor size and proximity to optic apparatus. (Fig3,4).

Among the treated 10 cases with Cushing's disease, 7 patients (70%) had hormonal control with with 24-h free urinary cortisol in the normal range, the given peripheral prescription dose was 25 to 30Gy all of them had microadenoma of 1cc volume or less, one patient has hormonal decline <50% with tumor size 2cc and in the remaining 2 cases there were failure of hormonal control their adenoma volume were 2, 88 and 2.82 cc and the prescription dose was < 25 Gy. (Fig 5, 6).

**Table 2.** Hormonal and adenoma size control in the treated 54 patient with secretory pituitary adenoma

Type of secretory pituitary adenoma	No of patients	*Hormonal control	Hormonal decline <50%	*Adenoma growth control	No of *Microadenoms
Prolactinomas	24	15(62%)	6	23(96%)	13
Acromegaly	20	12(60%)	5	18(90%)	11
Cushing's disease	10	7(70%)	1	10(100%)	7

\*Hormonal control=hormonal normalization or marked decline >50%

\*Adenoma growth control=decreased or stable in size

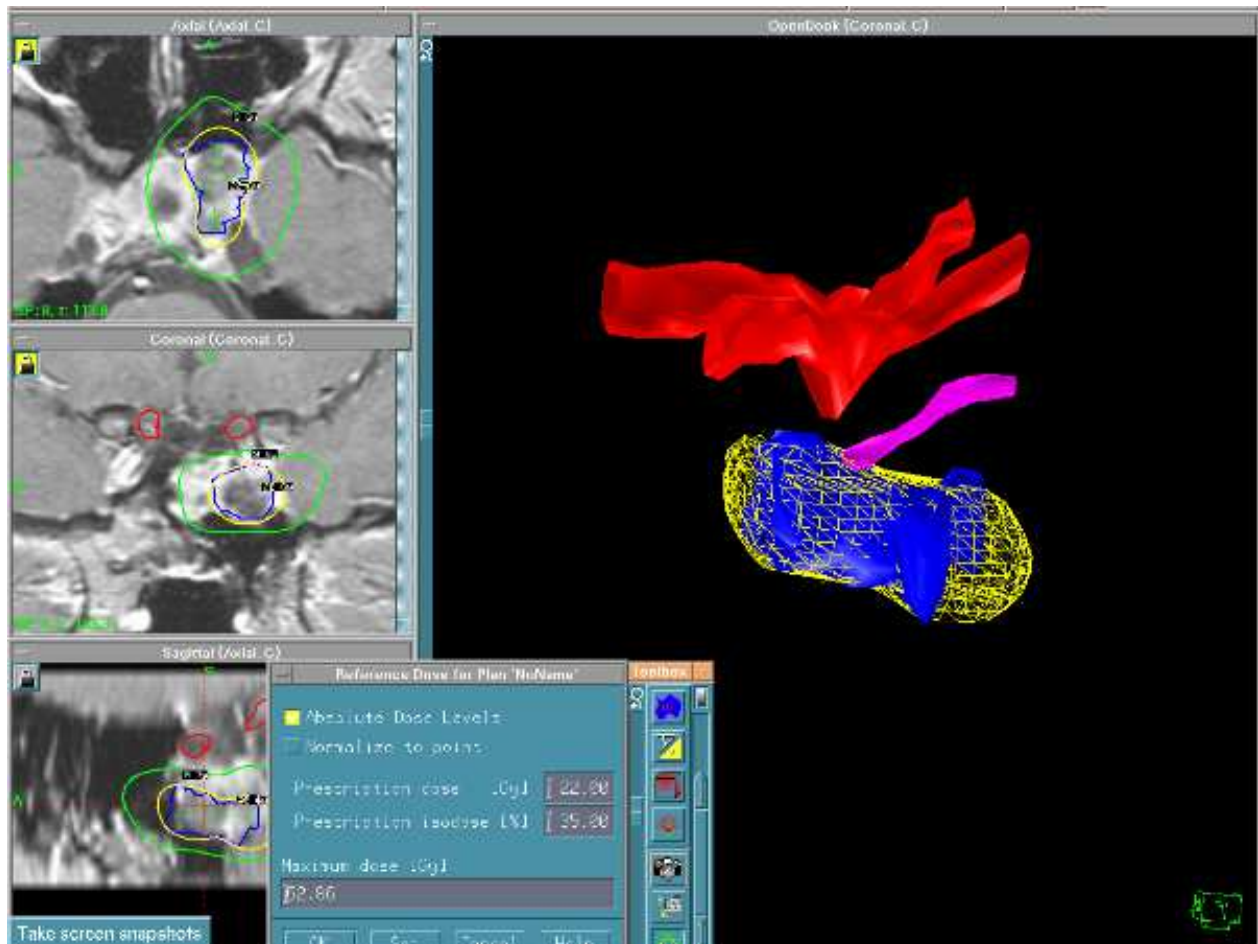
\*Microadenoma=10mm maximum diameter or less

Overall among the 35 patient who showed hormonal control in our study there were 29 with microadenomas? Of 1cc volume or less. Taking into consideration that the whole number of treated micradenomas in our study was 31 cases.

### 4. Complications

One prolactinoma the treated patients developed 3<sup>rd</sup> nerve palsy post-GKS, the patient had large prolactinoma residual with intracavernous sinus extension, he improved gradually with time.

Two patients in this study presented with one anterior pituitary hormone deficiency (gonadotrophic deficiency in one patient with Cushing's disease and thyrotrophic hormone deficiency in one prolactinoma patient), both detected after 36 months of follow up period, hormonal replacement was essential for these patients. None of our studied patients showed pan-hypopituitarism picture through the follow up period. No additional visual complications occurred in all treated cases compare to pre-gamma knife surgery condition.



The Prescription dose was 22Gy to the 35% isodose curve.

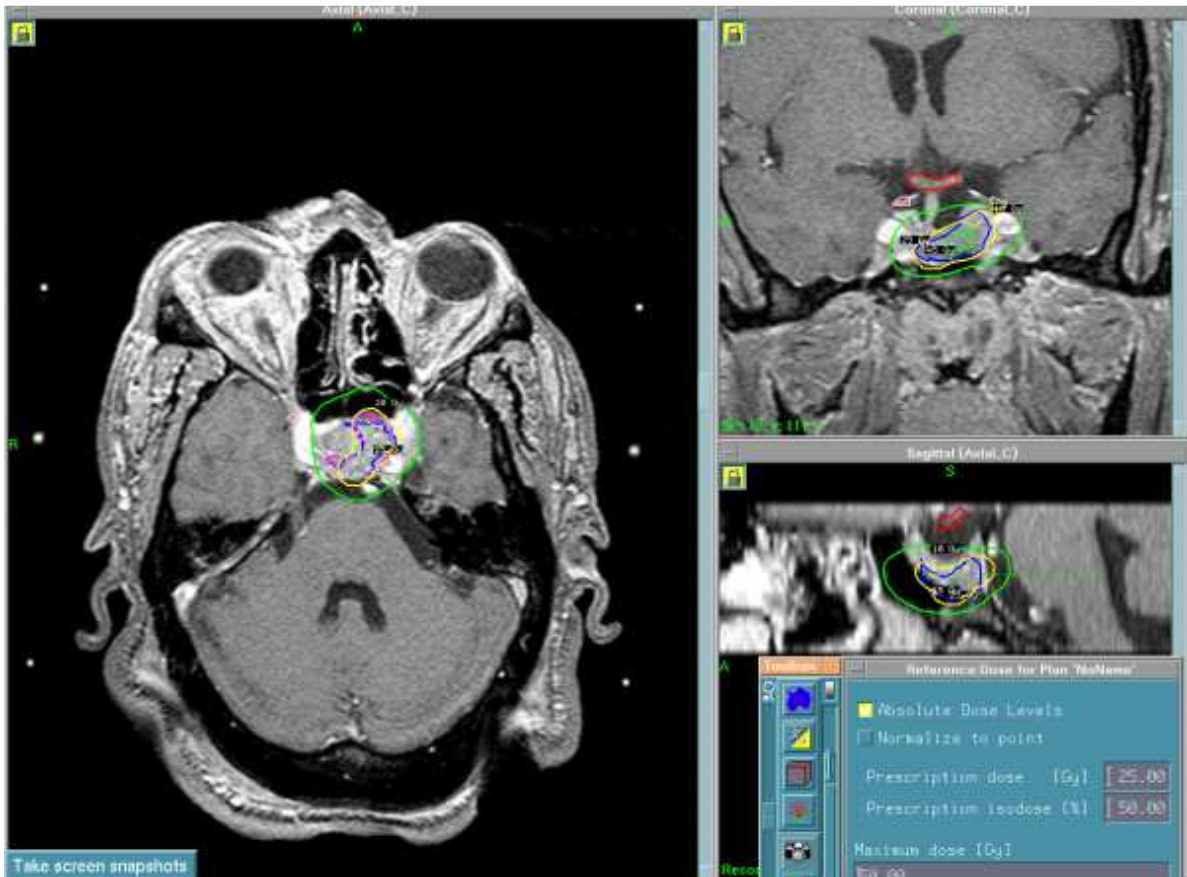
**Fig 1.** Gamma plan for postoperative residual prolactinoma, 1.9cc volume.





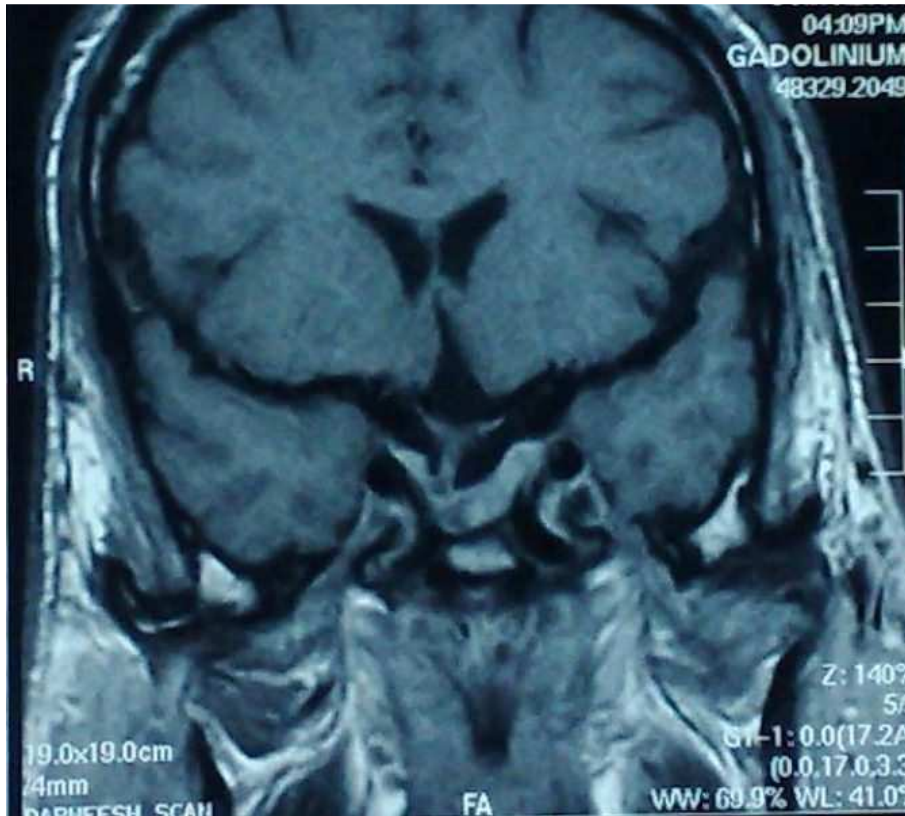
Post- GKS with marked adenoma reduction.

*Fig 2.* Follow up MRI for the same postoperative residual prolactinoma patients 4 years



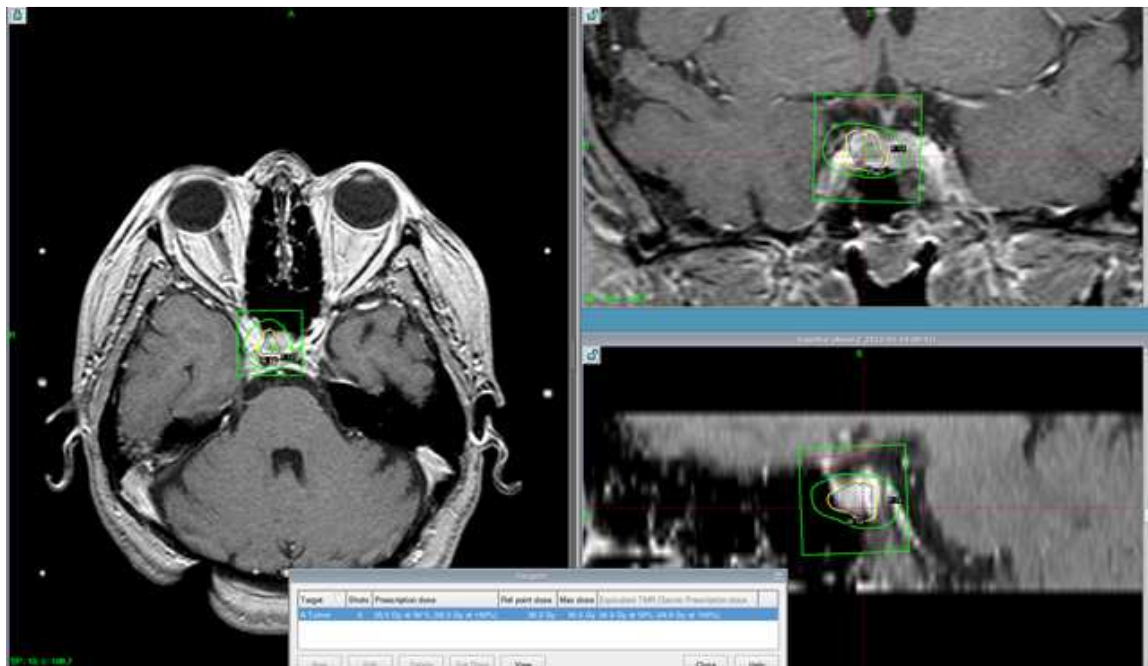
The Prescription dose was 25Gy to 50 % isodose curve.

*Fig 3.* Gamma plan for Acromagelic patient with pituitary adenoma 1.8cc volume.



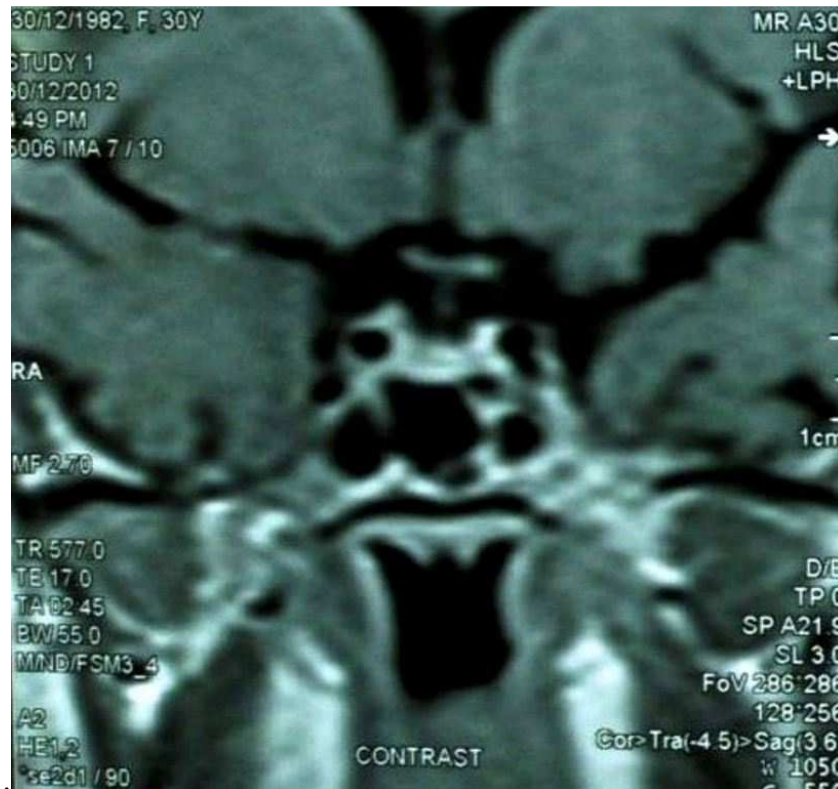
Continue reduction of tumor size.

Fig 4. Follow up MRI for the same acromegalic patient 5 years post - GKS with



The prescription dose was 25Gy to 50% isodose curve.

Fig 5. Gamma plan for Cushing's disease with pituitary microadenoma of 0.249cc volume.



With tumor size reduction, being concave in coronal MRI sequence.

**Fig 6.** Follow up MRI for the same Cushing's disease with pituitary microadenoma 18 months follow up

## 5. Discussion

There are multiple treatment modalities for secretory pituitary adenomas. Radiosurgery is an effective, noninvasive method for treating patients with functioning pituitary adenoma as a complement to the surgery. Pituitary adenoma that compresses the optic pathway should be removed with microsurgery and residual tumor especially in the cavernous sinus, recurrence and or resistant to medical treatment, is a good indication for radiosurgery. [9]. In the treatment of pituitary adenomas, radiotherapy is classically indicated in cases of incomplete resection or recurrent tumors, functioning tumors uncontrolled by medical therapy and patients inoperable or who refuse surgery especially macroadenoma. [10].

In our study, the goal of GKS, in treatment of secretory pituitary adenomas, is to control tumor growth and control high hormonal secretion, GKS was utilized as an adjuvant treatment in all studied 54 cases after being resistant to medical therapies or intolerant to drugs side effects, with or without previous pituitary surgery. In 25 of them a prior pituitary surgery had been conducted with presence of residual or recurrence. The others 29 patients have history of medical treatment failure without pituitary surgery, 21 of these patients have functioning microadenomas of 10mm maximum diameter or less who usually referred from endocrinologist directly.

Secretory adenomas require a higher radiation dose than

nonfunctioning pituitary adenomas. [8]. Laws and Vance estimated that a higher percentage of control of hyperfunctioning syndromes could be accomplished with the higher margin dose. [2]. Ganz suggested that the effective dose for secretory adenomas should be higher than 25 Gy. [11].

The volumes of the secretory adenomas in our 54 studied patients were ranged between 3.7cc to 0.036cc, 31 of them had microadenomas. The peripheral prescription dose varied according to tumor size, type of hormonal secretion and proximity to optic apparatus, for acromegaly adenomas it was ranged 20-25Gy, in prolactinomas 18-22Gy and in Cushing's disease adenomas usually 25- 30Gy. The isodose curve was ranged between 35% to 60% with adenoma coverage ranged between 93% to 100%.

Hayashi et al. 1999, reported that the tumor growth control rate for pituitary adenoma after GKS was between 93% to 94%, and that the tumor shrinkage rate ranged from 46% to 56.7%. [12]. Many studies reported a greater than 95% control of tumor size with follow-up varying from months to years. [2,6]. Izawa et al 2000, after mean follow up of 24 months in 79 secretory pituitary adenoma patients treated with GKS, reported local tumor control in 93.6% of patients, with reduction in 24.1%, they prescribed a mean marginal dose of 22.5 Gy. [13].

Sheehan et al., in his extensive reviewed studies involving 1621 patients of secretory pituitary adenoma treated with radiosurgery showed a mean tumor control rate of 96%. Considering only the series with mean or median



follow-up of 4 years or more, [4, and 10].

Regarding adenoma sizes determined by follow up MRI post-GKS in our study, 51 patients (94%), showed tumor size control, 41 of them the adenomas being stable in size (local tumor control), and in 10 patients the adenoma reduced in size. The reduction in sizes happened usually after 18-24 months of follow up period.

Sheehan's et al 2005, in his extensive reviewed studies reported the hormonal normalization ranged 17-83% in patients with Cushing's disease, 20-96% in patients with acromegaly and 0-84% in patients with prolactinoma. [4].

Castro et al 2010, in their study over 28 cases with functioning pituitary adenomas treated with radiosurgery found hormone control in 67% of patients with Cushing's disease, 40% of acromegalic patients and 44% of patients with prolactinoma. [10].

Petrovich et al 2003, reported a median time to normalization of hormonal after radiosurgery, 22, 18 and 24 months for patients with tumors that produce ACTH, GH and PRL, respectively. [3]. Choi et al. reported a mean time to hormonal normalization of 21 months ranged 1 to 3 years. [14].

Sheehan et al 2011, in his study over 418 pituitary adenoma treated with GKS has found relation between marginal dose and endocrine remission. The tumor margin radiation dose was inversely correlated with time to endocrine remission. Smaller adenoma volume correlated with improved endocrine remission in those with secretory adenomas. Concluded that smaller adenoma volume improves the probability of endocrine remission and lowers the risk of new pituitary hormone deficiency with GKS. A higher margin dose offers a greater chance of endocrine remission and control of tumor growth. [15].

The overall results of gamma knife surgery for the treated 54 cases in this study were as follows: Group I, where 34 patients (63%) had clinical improvement, tumor size control and hormonal control (hormonal normalization in 23 patients and marked decline >50% in 11 patients). Group II, where 12 patients (22%) showed some hormonal decline <50% with little improvement or stable clinical condition. Group III, where 8 patients (15%) had failure to achieve any hormonal control.

Among the treated 24 prolactinoma patients in this work, 15 patients (62%) had hormonal control most of them responded after 12 months and up to 3 years, all treated with peripheral dose 20-22 Gy and 13 of them had microadenomas. In the treated 20 acromegalic patients, 12 (60%) had hormonal control that usually happened after 12-24 months post GKS, in 11 of them the adenoma volume was 1cc or less and they were treated with marginal dose of 22-25 Gy. Among the treated 10 cases with Cushing's disease, 7 patients (70%) had hormonal control with peripheral prescription dose 25 to 30 Gy, all of them had adenoma volume of less than 1cc (microadenomas).

Overall among the 35 patients who achieved hormonal control in our study there were 29 patients with microadenomas of 1cc volume or less, taking into

consideration that the whole number of treated microadenoma was 31 patients, this indicates that secretory pituitary adenoma volume has a great impact on results of gamma knife surgery in controlling the high abnormal hormonal level and controlling adenoma growth, giving chance to apply high prescription marginal and maximum dose and better radiation conformity without injuries of critical neural structures.

The incidence of hypopituitarism after radiosurgery reported in literature is quite variable. Older studies that included patients treated in the pre-computed tomography reported higher incidence. [6].

Most studies suggest a maximum dose to optic apparatus of 8 Gy or less to keep the risk of optic neuropathy close to zero and a minimum 2-5 mm between the tumor and optical apparatus [4, 6]. However, in patients with functioning adenomas where the dose increase may be related to an increase in hormonal control, some authors accept the maximum dose of 10 Gy, since restricted to a small volume of the optical apparatus [15, 16].

In our studied 54 patients optic apparatus received <8 Gy, 3<sup>rd</sup> cranial nerve in those with cavernous sinus invasion received <21 Gy and pituitary gland and stalk received <15 Gy. Two patients in this study developed one anterior pituitary hormone deficiency (gonadotrophic deficiency in one patient with Cushing's disease and thyrotrophic hormone deficiency in one prolactinoma patient), both detected after 36 months of follow up period, hormonal replacement was essential for these patients. One prolactinoma patients developed 3<sup>rd</sup> nerve palsy post-GKS; the patient had large prolactinoma residual with intracavernous sinus extension.

None of our cases showed pan-hypopituitarism picture through the follow up period. No additional visual complications occurred in all treated cases compare to pre-gamma knife surgery visual status.

## 6. Conclusions

Although not usually an initial treatment for patients with secretory pituitary adenomas especially macroadenoma, gamma knife surgery is safe and highly effective treatment for secretory pituitary adenoma patients who showed failure to achieve hormonal control after medical treatment alone, intolerant to its side effects, or postoperative with residual functioning adenoma or recurrence.

GKS is safe and an effective method for controlling secretory pituitary adenoma growth and inducing hormonal control especially in microadenoma with low morbidity and could be a primary minimal invasive option. The hormonal and tumor growth control in treatment secretory pituitary adenoma with GKS are correlated to adenoma size and prescription radiation dose, smaller pituitary permits high marginal dose giving high chance for rapid hormonal and growth control and low risk for pituitary function disturbance or visual apparatus injuries. .



## Authors' Contributions

- Raef Faruok Ahmed Hafez conceived and prepared the manuscript.
- Magad shawky Morgan and Osama Mohamed fahmy participated in the design of the study.
- All authors read and approved the final manuscript.

## Competing Interests

The authors declare that they have no competing interests.

## Abbreviations

Used in this paper: ACTH = adrenocorticotrophic hormone; GH = growth hormone; IGF-I = insulin-like growth factor I; GKS = gamma knife surgery; PRL = prolactin; UFC = urinary free cortisol.

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