

Evaluation of Gamma Knife Effect on Patients with Pituitary Adenoma

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ABSTRACT:

BACKGROUND:

Pituitary adenomas are common benign brain tumors which account for 15% of all primary brain tumors & 25% of benign brain tumors. It's treatment modality includes medical management and surgery either transcranial or trans-sphenoidal. In recent years, gamma knife radiosurgery has emerged as a treatment modality in the management of pituitary adenoma especially for those cases who have residual tumor and/or those who are not candidate for surgery.

PATIENT AND METHODS:

This prospective and retrospective study was conducted on 132 pituitary adenoma patients (54 males and 78 females) with a mean age of 45.6 years. Patients were of four groups, 67 with prolactinoma, 10 with somatotroph adenoma, 22 with Cushing disease (ACTH releasing), and 33 with non-functional adenoma. Before performing the gamma knife treatment, a pre-MRI examination was done to these pituitary adenoma patients, then the post-MRI examination was done after 6 months, 1 year and 1.5 year of gamma knife treatment as well as clinical evaluation by examining the type of secretion and hormonal laboratory investigation with visual field assessment.

RESULTS:

In our study, the most pituitary adenoma group treated with gamma knife was prolactinoma patients (67), with a size of treatment ranging from 2-55 mm, showing 88.05% tumor necrosis; with hormonal level normalization reaching to 82.08%. In the (10) growth hormone releasing adenoma patients, the size of treatment ranged from 5-48 mm, with (90%) tumor necrosis, and (90%) hormonal level normalization. In the (22) ACTH-releasing adenoma patients, the size treated ranged from 3-29 mm, with tumor necrosis of (86.36%), and (81.81%) hormone level normalization, whereas in the (33) non-secretory type of adenoma, the size of treatment ranged from 18-67 mm and the tumor necrosis was 93.93%.

CONCLUSION:

It can be concluded from this study that gamma knife is an effective and safe option to treat pituitary adenomas by it's low incidence of both morbidity and mortality rate; the tumor necrosis is the highest in non-secretory type when the dose was above 18 grey, but the peri-tumoral edema was found in prolactinoma when the dose of irradiation was above 22 grey.

KEY WORDS: Pituitary adenoma, Prolactinoma, Acromegaly, Cushing's disease, Gamma knife

INTRODUCTION:

Pituitary adenomas are usually benign tumors that can be either secreting (growth hormone in acromegaly, adrenocorticotropin hormone in Cushing disease and prolactin in prolactinoma) or non-secreting adenomas^[1,2,3].

Pituitary tumors account for approximately 15% of all primary brain tumors and almost 25% of benign primary brain tumors. According to these measures, pituitary tumors are the third most

common primary intracranial tumor. Autopsy and modern imaging studies suggest that 20% to 25% of the general population harbor pituitary microadenomas. These lesions are usually clinically silent; occur in patients without apparent endocrine symptoms^[4].

Recently, Gamma knife surgery (GKS) has gained acceptance as a primary minimally invasive treatment option for pituitary microadenomas, or as a complementary treatment option in combination with

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microsurgery for both secreting macroadenomas and mass producing non secretory macroadenoma. 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. Moreover, GKS limits radiation exposure to the surrounding normal brain structures^[5]; or to optic nerve and optic chiasm.

THE AIM OF STUDY:

This study aimed to evaluate the effectiveness and safety of gamma knife in the treatment of pituitary adenomas with their associated complications.

PATIENTS AND METHODS:

This clinical study was conducted at the Neuroscience Teaching Hospital during the period from January 2017 to June 2018, Gamma Knife Department on 132 patients who were clinically, radiologically and endocrinologically proven to have pituitary adenoma.

The study population composed of 54 men (40.9%) and 78 women (59.1%) whose age ranged from 13 to 85 years (mean 45.6). The patients had history ranged from 7 months to 14 years (mean 3.4 years) and Gamma knife radio-surgery served as the primary treatment modality.

The diagnosis was made on the basis of magnetic resonance imaging (MRI) findings, endocrinological laboratory findings, the clinical history of patients, ophthalmological examination of the optic field study as well as routine investigations.

All patients were examined (3 weeks, 2 months, and 6 months) post Gamma knife to assess the complications; or to assess improvement in symptoms especially visual field and ophthalmological symptoms. At 6 months visit, they were asked to perform new MRI to observe the changes (some cases had longer follow up which reached to 1 year and others were followed up after 1.5 year). Patients were asked to stay in hospital for few hours and then discharged.

Procedure:

Under local anesthesia with lidocaine 2%, Leksell Frame were applied to patients heads, the frame was calibrated with special helmet, then patients were asked to obtain new MRI (3 tesla MRI) with Leksell frame (or to do CT scan instead of MRI when MRI is contra-indicated). The stereotactic MRI sequences were then transmitted to Leksell gamma plan, and tumor was localized by a software and then tumor was targeted. The doses were applied according to a schedule and at the surgeon's preference. Thereafter, the treatment protocol was passed to the Leksell Gamma knife control unit where treatment was applied automatically, and radiation emission to patients was performed. Either the 4 or the 8 mm collimator helmet was utilized, especially in microadenoma in order to achieve conformity and to avoid radiation neural injuries.

RESULTS:

The number of patients in this study were 132 patient; 78(59.1%) of them were females and 54 (40.9%) were males as shown in "figure 1".

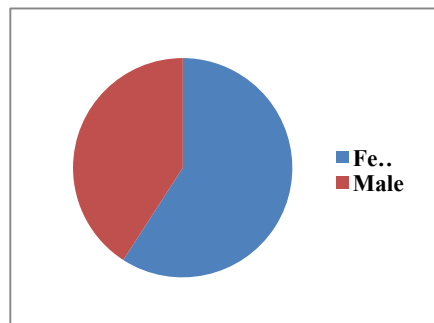


Figure 1: Distribution of pituitary adenoma patients according to gender.

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The ages of patients ranged from 13-85. Our results revealed that 2 of the patients were in the teenage group, 21 in twenties, 27 in thirties, 33 in

forties, 26 in fifties, 9 in sixties, 8 in seventies and 6 in eighties, with a mean age of 45.6 years. As illustrated in "figure 2".

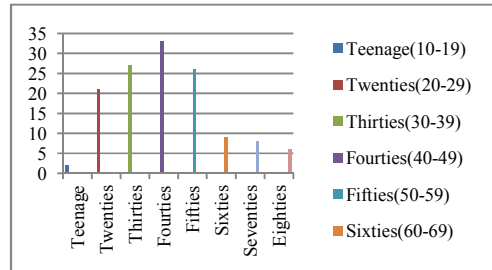


Figure 2: Distribution of pituitary adenoma patients according to age groups.

Types of pituitary adenomas included in this study 67(50.75%) prolactinoma, 10(7.57%) somatotroph adenoma (2 of them were gigantism and 8 were acromegaly), ACTH releasing

adenoma or Cushing disease were 22(16.66%) and non-functioning adenoma were 33(25.02%) patients as shown in "figure 3".

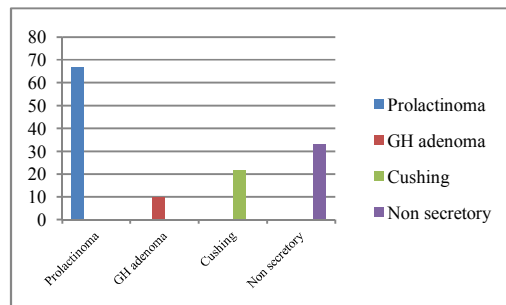


Figure 3: Distribution of pituitary adenoma types included in the study.

Regarding the size of adenoma, 1cm and below were categorized as microadenoma, while those sizes above 1cm were categorized as macroadenoma [4].

Prolactinoma patients consisted of 47 microadenoma (6 males & 41 females) (size 0.2-1cm), while macroadenoma for prolactinoma were 20 patients (15 males & 5 post- menopausal women) (size 1.1-5.5 cm). Cushing disease group consisted of 8 microadenoma patients (3 males and 5 females) (size 0.3-1cm), while

macroadenoma cases in Cushing disease were 14 patients (7 males and 7 females) (tumor size 1.1-2.9cm). GH secreting microadenoma consisted of 3 patients (2 males and 1 female) (size 0.5-1 cm), while GH secreting macroadenoma were 7 patients (2 males and 5 females) (size 1.1-4.8cm). Non-secretory adenomas included only 33 patients with macroadenoma (19 males and 14 females) (tumor size 1.8-6.7 cm) with no microadenoma as shown in "table 1".

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Table 1: Distribution of patients with pituitary adenomas according to the size of tumor.

Type of adenomas		Male	Female
ACTH adenomas	22(16.66%)	10	12
Microadenoma (size, cm3)	8 (0.3-1.0)	3	5
macroadenoma(size, cm3)	14 (1.1-2.9)	7	7
Prolactinomas	67(50.75%)	21	46
Microadenoma (size, cm3)	47(0.2-1.0)	6	41
Macroadenoma (size, cm3)	20(1.1-5.5)	15	5
GH releasing adenomas	10(7.57%)	4	6
Microadenoma (size, cm3)	3(0.5-1.0)	2	1
Macroadenoma (size, cm3)	7(1.1- 4.8)	2	5
Non-functioning adenoma	33(25.02%)	19	14
Microadenoma (size, cm3)	0	0	0
Macroadenoma (size, cm3)	33(1.8-6.7)	19	14

According to patients who do surgical interventions with Gamma knife radiosurgery; 48 patients from 132 case do surgery [36 transnasal, 9 craniotomies & 3 both transnasal then craniotomy] (all 48 patients do surgeries then Gamma knife, except 1 case of these 48 patients (which transformed from non-secretory adenoma to adenocarcinoma) do craniotomy then Gamma knife then 2 craniotomies after Gamma knife). From those 48 patients who do surgeries 34 prolactinoma (32 microadenoma & 2 macroadenoma), 1 acromegally patient (microadenoma, transnasal), 4 Cushing patients (3 microadenoma, 1 macroadenoma) & 9 non secretory macroadenoma patients "table 2".

The total number of cases in this study was 132 who were categorized into 3 groups according to the duration of their follow up period (6 months (50) patients, 1 year (45) patients and 1.5 year (37) patients).

Results of non-specific signs and symptoms in "table 3" showed that:-

All patients with macroadenoma (secretory and non- secretory) presented with headache, while only 3 patients with microadenoma (2 prolactinoma and 1 acromegaly) had headache. After Gamma knife usage, headache was subsided within 6 months except for 1 case with non-secretory macroadenoma who died within 6 months of follow up.

Table 2: Patients having pituitary adenomas doing both Gamma knife and surgery.

Type of surgery	Type of adenoma	Microadenoma	Macroadenoma	Male	Female
Transnasal (39 cases)	Prolactinoma (34 cases)	32	2	2	32
	GH (1 case)	1	0	1	0
	ACTH (4 cases)	3	1	1	3
	No secretory (0 cases)	0	0	0	0
Craniotomy (12 cases)	Prolactinoma (2 cases)	0	2	2	0
	GH (0 case)	0	0	0	0
	ACTH (1 cases)	0	1	0	1
	No secretory (9 cases)	0	9	7	2

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Vomiting occurred only in 5 cases (1 Cushing disease with macroadenoma, 2 prolactinoma macroadenoma and 2 non-secretory macroadenoma patients); vomiting was very mild (occurring once or twice every 3 months). After Gamma knife, all cases with vomiting were relieved within 6 months of follow up.

Vision problems appeared only in cases of macroadenoma, which ranged from unilateral upper quadrantanopia (19), bilateral upper quadrantanopia (15), unilateral temporal hemianopia (17), bitemporal hemianopia (9), blurred vision in one eye (10) and one eye blindness with blurred vision in the other eye (4) cases [depending on the size of macroadenoma]. After Gamma knife, vision problems relieved totally or at least partially (61 cases got better within 6 months and 4 only within 1 year), except 9 cases as there was no relief (5 prolactinoma, 1 Cushing and 3 non-secretory cases).

Abducent nerve palsy with oculomotor nerve palsy occurred only in 3 patient (2 non-secretory and 1 prolactinoma), which didn't get relieved by Gamma knife.

Attacks of fit occurred only in 1 case of non-secreting adenoma with a big size tumor (6.7 cm).

The specific signs and symptoms showed that:-

A- Prolactinoma:-

All female patients (premenopausal 41 microadenoma patients) had lactating breasts before Gamma knife application, and they stopped lactation 6 months after doing Gamma knife, with the use of cabrigoline. Among all the 41 premenopausal female microadenoma patients, 34 were shown to have menstrual abnormality and 7 had no menses at all. However, after Gamma knife use, the menses of 22 patients of the irregular menses group became regular within 6 months, 7 became regular within 1 year and 3 patients became regular within 1.5 year, while 2 patients menses remained irregular. Regarding those 7 women who were having no menses at all, 1 patient showed a regular menses within 1 year, 5 patients had irregular menses (1 within 6 months, 3 within 1 year and 1 within 1.5 year) after doing gamma knife, while only 1 patient of them still remained without menses; as shown in "table 3". All female patients (premenopause 41 microadenoma patients) were infertile (either have no children or they are not married or at

least they become infertile during the start of disease), however, after Gamma knife, 1 patient became pregnant 1.5 year post Gamma knife treatment.

The 5 female postmenopausal patients with macroadenoma who presented with pressure symptoms on optic nerve showed partially better vision after Gamma knife application (2 within 6 months and 1 within 1 year) except for 2 cases which didn't get relieved.

Among the 21 male patients with prolactinoma, 11 were having increase in the size of their breasts (5 microadenoma and 6 macroadenoma). After Gamma knife treatment, 8 of them had the sense of breast size relief (3 within 6 months, 4 within 1 year and 1 within 1.5 year), while the remaining 3 cases (1 microadenoma and 2 macroadenoma) didn't feel better.

All male patients (21 patients) were having loss of libido, no erection and no desire to do sex; after Gamma knife, 12 of them returned their sexual desire (fully or at least partially) (3 within 6 months, 2 within 1 year and 7 within 1.5 years), and the wives of 2 of them became pregnant after 1.5 year. However, the other 9 cases didn't get relieved.

All the 15 male patients with macroadenoma had pressure effect on optic nerve, which after Gamma knife got partially or totally relieved (7 within 6 months and 5 within 1 year) except for 3 patients who didn't get relieved.

B- ACTH secreting adenoma (Cushing disease):

All patients (22 cases) had increase in their body weight, moon face, buffalo hump (found only in 2 cases) and Cushing syndrome. After Gamma knife treatment, these signs were relieved in 19 cases (17 within 6 months and 2 within 1 year), while the rest did not get relieved. Out of the 22 patients, 10 patients had hypertension (3 cases with the start of the disease, while the rest had chronic hypertension); after Gamma knife, the newly onset hypertension (3 cases) got relieved within 6 months.

Out of the 22 patients, 15 patients had Diabetes mellitus (4 cases occurred with the start of the disease and 11 cases had chronic diabetes); after Gamma knife, 3 cases of the newly onset D.M. have relieved within 6 months and only 1 did not get relieved.

C- GH secreting adenoma:

Acromegaly: Coarse head features, increase in head, hands and feet size occurred in 8 patients

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from 10 with increase in GH secretion (all of those 8 patients were above 20 years), their signs & symptoms began to relieve partially (3 within 1 year and the other 5 after 1.5 year).

Gigantism: Very tall patients occurred only in 2 patients (1 was 13 years and the other was 15 years old).

Visual problems: All patients with GH adenoma with macroadenoma (7 cases) had visual problems (1 gigantism and 6 acromegaly cases); after performing Gamma knife, 5 of those patients got better partially or totally within 6 months and 2 of them within 1 year.

D- Non secretory adenoma:

Pressure effect of non-secretory adenoma on normal pituitary causing pressure on normal neurohypophysis and their transport of vasopressin hormone causing Diabetes insipidus, which occurred only in 1 case within 6 months (who then died), and not relieve by Gamma knife.

Pan hypopituitarism: which occurred only in 1 case within 6 months after doing Gamma knife (who then died).

Hydrocephalus: occurred only in 1 case before doing Gamma knife and the patient treated by ventriculoperitoneal (V.P) shunt.

Transformation of non-secretory adenoma to adenocarcinoma: which occurred in 1 case within 1 year of doing Gamma knife (the female patient had both abducent and oculomotor nerve palsies); then she underwent 2 surgical operations (open craniotomy) after Gamma knife treatment.

Pressure symptoms on optic nerve (all the 33 cases) which after Gamma knife got relieved partially or totally (21 within 6 months, 8 within 1 year and 1 within 1.5 year) except for 3 cases which were didn't get relieve.

According to death rate: only 1 case with non-secretory adenoma died within 6 months of doing Gamma knife from all the 132 cases (patient had Diabetes insipidus prior to Gamma knife treatment, but after Gamma knife he developed panhypopituitarism followed by fits, then he died) as shown in "table 3".

Results of normalization of hormonal levels:

According to normalization of hormonal levels of pituitary adenoma in "table 4":- out of 67 prolactinoma patients, 55 patients (82.08%) showed returning of prolactin level to normal after doing Gamma knife (49 returned to normal level within 6 months, 5 within 1 year and 1 within 1.5 year, while the remaining 12 patients didn't return to normal). Those 55 patients were on continuous consumption of cabrigoline (one tab. per week).

Out of the 22 patients with Cushing disease, 18 (81.81%) ACTH and cortisol levels returned to normal after performing the Gamma knife treatment as follows: 17 within 6 months and 1 within 1 year.

Out of the 10 patients with GH secreting adenoma, 9 (90%) patients showed a return of GH hormone levels to normal as follows: 5 within 6 months, 3 within 1 year and 1 within 1.5 years, while all of them were taking sandastatine ampoules (1 amp. Per month).

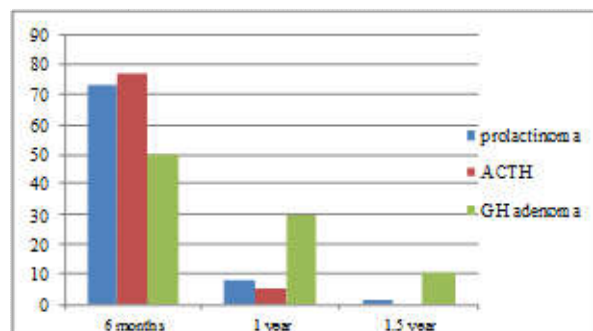


Figure 4: Normalization of hormonal levels of different secretory adenomas in different time intervals (using percentage of patients)

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Table 3: Effect of Gamma knife on signs & symptoms of patients with pituitary adenoma on different time intervals.

Sings & Symptoms	6 months	1 year	1.5 year	No Improvement	P. Value
Headache (77 cases)	76	0	0	1 (die)	<0.001
Vomiting (5 cases)	5	0	0	0	<0.001
Visual problems (74 cases)	61	4	0	9	<0.001
Abducent nerve pulsy (3 cases)	0	0	0	3	1
fits (1case)	1	0	0	0	
Prolactinoma					
Lactation (41 cases)	41	0	0	0	<0.001
Irregular menses (34 cases)	22	7	3	2	<0.001
No menses (7 cases)	1	4	1	1	0.176
Pregnancy (1 case)	0	0	1	0	0.796
Postmenopausal visual problems (5 cases)	2	1	0	2	0.172
Increase breast size in men (11 cases)	3	4	1	3	0.028
Loss of lipido for men (21 cases)	3	2	7	9	<0.001
Visual problem for prolactinoma males (15 cases)	7	5	0	3	<0.001
ACTH adenoma					
Increase body weight (22 cases)	17	2	0	3	<0.001
Hypertension (3cases)	3	0	0	0	0.025
D.M. (4 cases)	3	0	0	1	<0.001
Visual problem (14 cases)	11	2	0	1	<0.001
GH adenoma					
Acromegally (8 cases)	0	3	5	0	<0.001
Visual problem (7 cases)	5	2	0	0	<0.001
Non Secretory					
D.I. (1 case)	1(die)	0	0	0	
Pan hypopituitarism (1 case)	1(die)	0	0	0	
Hydrocephalus (1 case)	0	0	0	0	
Transformation to adenohypophysis (1 case)	0	1	0	0	0.566
Visual problem (33 cases)	21	8	1	3	<0.001
Death (1 case)	1	0	0	0	

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Results of Post gamma knife necrosis:

After follow up MRI done for every patient to detect necrosis in adenoma substance, there were 59 of prolactinomas patients (88.05%) showed necrosis (57 of them within 6 months & 2 within 1 year).

Out of the 22 patients with Cushing disease, 19 (86.36%) new MRI patients showed necrosis (18 of them within 6 months and 1 within 1 year).

Out of the 33 non-secretory adenoma patients, 31 (93.93%) new MRI patients showed necrosis (30 within 6 months and 1 within 1 year).

Out of the 10 patients with GH-secreting adenoma, 9 (90%) new MRI shows necrosis within 6 months post Gamma knife treatment "table 4".

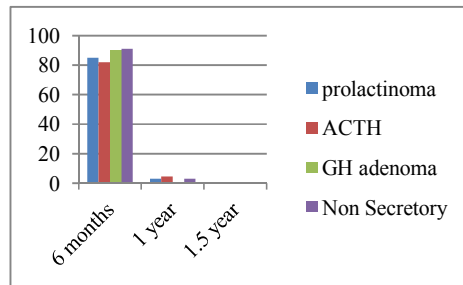


Figure 5: Necrosis occurs in different types of pituitary adenomas in different time intervals (using percentage of patients).

Results of tumor size reduction:

Out of 67 studied prolactinoma patients, only 14 patients (20.89%) showed tumor size reduction (2 of them within 1 year & 12 within 1.5 year).

Out of 22 patients with Cushing disease, 5 (22.72%) showed tumor size reduction (1 of them within 1 year and 4 within 1.5 year).

Out of the 10 patients with GH-secreting adenomas, only 2 (20%) showed tumor size reduction within 1.5 years after Gamma knife treatment.

Out of 33 non-secretory adenoma cases, only 7 (21.21%) patients showed tumor size reduction (1 within 1 year and 6 within 1.5 years) as shown in "table 4".

Note: Tumor size reduction occurs by comparing tumor size in MRI pre-gamma knife with tumor size post gamma knife by 6 months, 1 year, & 1.5 year. (All cases with tumor size reduction had a decrease in tumor size from 3 mm to 7 mm).

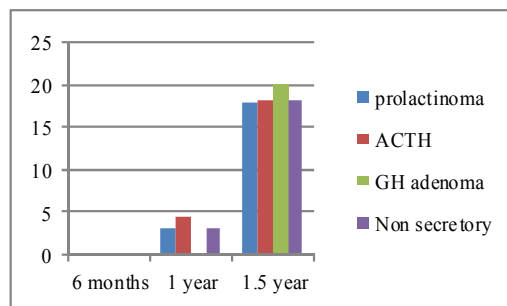


Figure 6: Tumor size reduction of different adenomas in different time intervals (using percentage of patients).

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DISCUSSION:

In the treatment of pituitary adenoma (especially macroadenomas), radiosurgery is classically indicated in cases of incomplete resection or recurrent tumors, in functioning tumors that

cannot be controlled with medical therapy and in patients inoperable or who refuse surgery^[6]. In case of secretory pituitary adenomas, Gamma knife is used for tumor growth control and for endocrinological hypersecretion normalization^[7].

Table 4: Effect of Gamma radiation on pituitary adenomas within different time intervals.

6months	1year	1.5year	Total	P. Value
Normalization of Hormones				
prolactinoma (67 cases)	49 (73.13%)	5 (7.46%)	1 (1.49%)	55 (82.08%) <0.001
ACTH (22 cases)	17 (77.27%)	1 (4.54%)	0 (0%)	18 (81.81%) <0.001
GH adenoma (10 cases)	5 (50%)	3 (30%)	1 (10%)	9 (90%) <0.001
Necrosis				
Prolactinoma (67 cases)	57 (85.07%)	2 (2.98%)	0 (0%)	59 (88.05%) <0.001
ACTH (22 cases)	18 (81.81%)	1 (4.54%)	0 (0%)	19 (86.36%) <0.001
GH adenoma (10 cases)	9 (90%)	0 (0%)	0 (0%)	9 (90%) <0.001
Non secretory (33 cases)	30 (90.9%)	1 (3.03%)	0 (0%)	31 (93.93%) <0.001
Tumor size Reduction				
prolactinoma (67 cases)	0 (0%)	2 (2.98%)	12 (17.91%)	14 (20.89%) <0.001
ACTH (22 cases)	0 (0%)	1 (4.54%)	4 (18.18%)	5 (22.72%) 0.123
GH adenoma (10 cases)	0 (0%)	0 (0%)	2 (20%)	2 (20%) 0.502
Non secretory (33 cases)	0 (0%)	1 (3.03%)	6 (18.18%)	7 (21.21%) 0.048

In this study, Gamma knife was utilized as an adjuvant treatment in all 132 cases after being resistant to medical therapies, or intolerant to drug side effects, with or without a previous pituitary surgical interference.

In accordance with his details, Ganz proposed that the effective dose for secretory adenomas must be greater than 25 Gy^[8].

While Pollock's reported regarding functioning adenomas demonstrated no relationship between the dose of radiation and endocrinological outcome^[9].

In the current study, the lowest effective radiation dose was 16 Gy delivered to the tumor margin with a mean marginal dose of 20 Gy.

The dose of radiation prescribed in this study for pituitary adenoma differs from one type to other,

for prolactinoma, it ranges from 20 Gy to 25 Gy, for GH secreting adenoma it ranges from 20 Gy to 22 Gy, for Cushing disease, it ranges from 18 Gy to 22 Gy, for non-secretory adenoma, the dose ranges from 16 Gy to 20 Gy. While the coverage area for the dose of Gamma rays radiation ranges from 95% to 100% in microadenoma, and from 86% to 95% in macroadenoma.

A correlation between the endocrine remission and marginal dose was found in the study conducted by Sheehan et al. on (418) pituitary adenoma patients who were treated with Gamma knife. There was an inverse relationship between endocrine remission time and dose of tumor margin radiation dose. In patients with secretory adenomas, smaller adenoma volume was found

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to be associated with improved endocrine remission. Thus, they concluded that smaller adenoma volume improves the probability of endocrine remission and lowers the risk of new pituitary hormone deficiency with Gamma knife. The greater opportunity for endocrine remission and tumor growth control can be offered by the higher margin doses^[10].

Stereotactic radiosurgery provided excellent control of tumor growth in almost all published studies. In a study done by Hayashi, it was revealed that tumor control rate for pituitary adenoma following Gamma knife use was between (93% - 94%), and the range of tumor shrinkage rate was between (46%-56.7%)^[11].

However, greater than (95%) of tumor size control was reported by several studies with follow-up varying from months to years^[12]. Local control of tumor in (93.6%) of patients, with reduction in (24.1%) of patients was observed by Izawa et al. after (24) months follow-up among (79) patients with secretory pituitary adenomas who were treated with Gamma knife, with a mean marginal dose prescription of 22.5 Gy^[13].

In this study, the control rate of growth with necrosis for pituitary adenoma ranged from 88.05% in prolactinoma, 86.36% in Cushing's, 90% in GH secreting adenoma and 93.93% in non-secretory adenoma, in a follow up period of 6 months and 1 year; while tumor size reduction ranged from 20.89% in prolactinoma, 22.72% in Cushing disease, 20% in GH adenoma and 21.21% in non-secretory adenoma in a follow up period of 1 year and 1.5 years.

In cases of tumor shrinkage, some studies have even revealed visual function improvement after radiosurgery. There is a tendency of the majority of pituitary adenomas to be slow growing lesions. As such, it may be misleading to assess patients with a relatively short follow-up^[7].

In patients who suffer from dopaminergic drug intolerance or who have tumor extended to cavernous sinuses, the Gamma knife is considered as an appropriate alternative. Pan et al mentioned the largest series of adenomas which can be treated by Gamma knife. Normal levels of serum prolactin for gender was used as a cure criteria by Pan et al, and 15% of endocrinological remission rates were recorded in (128) patients with a (33) months median follow-up. Some studies utilize relatively similar criteria and 'Cure' rates varied from (20-84%)^[14].

In this study, normalization of serum prolactin level occurs in 82.08%.

Cushing disease is a severe catabolic disease requiring a rapid cortisol hypersecretion normalization, making pituitary microsurgery is the primary treatment for Cushing disease. However, Gamma knife surgery can be utilized in case of open surgery contraindication or refusal, or utilized as a secondary treatment in case of open surgery failure or tumor extension into the cavernous sinuses. Several series of studies used the (24) hour urine cortisol collection as part of endocrinological assessment criteria, with an endocrinological 'cure' rate ranging from (17-83%)^[15].

In a recent study, Laws and Vance observed a remission in approximately (60%) of Cushing's disease patients after more than (6) months of follow-up with a mean remission time of approximately one year when gamma knife surgery was used as a complement to open surgery^[16].

In this study, normalization of serum cortisol level occurs in 81.81% of cases in a follow up period of 6 months, 1 year, & 1.5 year.

To control acromegaly, there is still no consistent applied criteria. The most widely accepted guidelines for a remission in acromegaly consist of a GH level less than 1ng/ml in response to a glucose challenge and a normal serum IGF-1 when gender and age are to be matched. Gamma knife results are explained in details for acromegaly patients in some studies with such criteria. In such series, the range of mean radiosurgery margin doses was (15-34) Gy. After radiosurgery, the variation of 'Cure' rates was from (0-100%). The range of endocrinological remission rates was from (20-96%) in these series of at least (16) patients and (2) years median follow-up^[17].

The current study showed that the serum GH level normalization happened in (90%) of cases in a period of (6) months follow up.

Sheehan et al. in their extensively reviewed studies reported that the hormonal normalization ranged between 17 and 83% in patients with Cushing's disease, between 20 and 96% in patients with acromegaly, and between 0-84% in patients with prolactinoma^[5].

Castro et al. in their study on 28 cases with functioning pituitary adenomas treated with radiosurgery reported hormone control in 67% of patients with Cushing's disease, 40% of patients

with acromegaly, and 44% of patients with prolactinoma^[6].

Petrovich et al. reported a median time to normalization of hormonal after radiosurgery of 22, 18, and 24 months for patients with tumors that produce ACTH, GH, and prolactin, respectively^[18].

Stereotactic targeting, allowed by Gamma knife, decrease the incidence of hypopituitarism. Reports in the literature for the incidence of post-radiosurgery hypopituitarism vary widely. Well respected groups have reported a low incidence (0~36%) of pituitary dysfunction following radiosurgery [19].

A long term study from the Karolinska Institute with a mean follow-up of 7 years, however, reported an eventual 42% incidence of hypopituitarism^[20].

In this study only 1 patient [3.03%] (with non-secretory adenoma) develops hypopituitarism. Kokubo reported similar findings^[16].

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 [5]. However, in patients with functioning adenomas when the dose increase may be related to an increase in hormonal control, some authors accept the maximum dose of 10 Gy, as restricted to a small volume of the optical apparatus^[10].

In this study the maximum dose reaches to the optic apparatus is equal to or less than 10 Gy. No additional visual complications occurred in all treated cases compared with pre-Gamma knife visual status.

CONCLUSION:

Gamma knife can be an effective method for controlling tumor growth and inducing hormonal normalization in patients with pituitary adenomas. Complications from the optic apparatus have not been found when the dose to that area is below 10 Gy^[7]. The incidence of post-radiosurgery hypopituitarism is very low and the development of hypopituitarism following radiosurgery can be avoided by observing the maximum mean dose on healthy peritumoral pituitary of 15 Gy^[7]. Brain necrosis, neuropsychological disturbances and secondary brain tumors have not been found with gamma knife radiosurgery^[7].

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