



Original Article

Efficacy of Gamma Knife radiosurgery in the management of pituitary prolactinoma

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ABSTRACT

Background: Gamma Knife radiosurgery (GKR) has been widely used in the management of a variety of intracranial tumors, including pituitary adenomas. Pituitary prolactinoma (Prs) is one of the most common types of these adenomas.

Methods: This prospective study included 50 patients with pituitary Prs over a period from June 2017 to June 2018 at the Neurosciences Hospital, Baghdad/Iraq. The GKR procedure was performed using the Leksell Gamma Knife® Perfexion™, 192 beams of Cobalt 60 radiation were delivered through the intact skull to the pituitary Prs.

Results: There is a significant female predominance 32 (72%). The results after 6 months of GKR showed significant improvement regarding the size of adenoma, prolactin hormone level, contrast enhancement on MRI, and medical treatment.

Conclusion: The study showed that the GKR is a safe and effective modality of treatment in the management of pituitary Prs.

Keywords: Gamma Knife, Pituitary adenoma, Prolactinoma, Stereotactic radiosurgery

INTRODUCTION

The incidence of pituitary adenomas in the autopsy series is almost 25%, but they account for only 15% of intracranial tumors in neurosurgical practice. Pituitary adenomas are classified with the most frequent being prolactinoma (Prs) and null cell adenomas, followed by growth hormone, adrenocorticotrophic hormone, and thyroid-stimulating hormone-producing adenomas. Some adenomas secrete more than 1 hormone.^[1,9]

The main disadvantages of medical therapy are side effects, such as orthostatic hypotension, nausea, and vomiting. The therapeutic effect is only maintained as long as the drug is administered. After withdrawal of the drug, the prolactin hormone (PrH) level is expected to rise again and the tumor frequently reexpands. Surgery is designed for patients with intolerance to medication, those individually not responding to dopamine agonists (which constitute <10% of the cases), and those who for personal reasons reject medical treatment. Remission rates in a large series of surgically treated Prs vary between 54% and 86%.^[2,11]

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Aims of the study

In this study, we assessed the efficacy of Gamma Knife radiosurgery (GKR) in the management of pituitary Prs. The effect is measured by the following parameters:

1. Symptoms of the patients (amenorrhea and loss of libido).
2. The PrH level.
3. Contrast enhancement of the Prs on MRI.
4. Medical treatment.

MATERIALS AND METHODS

This is a clinical prospective study that included 25 patients for the period from June 2017 to June 2018 in the Neurosciences Hospital, Baghdad/Iraq. All patients were referred by the endocrinologist for neurosurgical management. The inclusion criteria of the patients were as follows:

1. Clinical signs and symptoms, native and contrast-enhanced MRI findings, and elevated PrH levels confirming the diagnosis of Prs.
2. All patients were on maximum or tolerable dopamine agonist therapy without a significant reduction in PrH levels or improvement in symptoms.
3. None of the patients had a previous GKR or surgery for the Prs.

Any patient who did not fulfill the above criteria was excluded from the study.

The period of follow was 6 months. By the end of the 6th month post-GKR, clinical, radiological, laboratory, and medical treatment were reevaluated in all the patients.

This is the first trial in Iraq to assess the efficacy of GKR in the management of pituitary Prs.

GKR was performed using the Leksell Gamma Knife® Perfexion™, 192 beams of Cobalt 60 radiation are delivered through the intact skull to the pituitary adenoma. The dose of the radiation was 20–40 Gy (mean = 25)

Statistical analysis

Descriptive analysis in the form of percentage was calculated using Microsoft Office Excel Worksheet and presented in the relevant tables shown below. Chi-square test was used for statistical analysis by utilizing the Statistical Package for the Social Sciences version 17 ($P < 0.05$ was considered statistically significant).

RESULTS

Twenty-five patients were included in this study, 18 (72%) female and 7 (28%) male. The age of the patients ranged between 24 and 45 years (mean = 32.56), amenorrhea was present in 15/18 (83.3%) of the female patients, and loss of

libido in 5/7 (71.4%) of the male patients. There was contrast enhancement of the Prs on MRI in 23/25 patients. All patients were on dopamine agonist medication.

Pre- and post-GKR differences

The PrH levels and the size of the Prs, pre- and post-GKR, are illustrated in [Table 1].

The PrH level pre- and post-GKR mean difference was 128.24 ng/l ($P = 0.001$) [Table 2].

Regarding the size of Prs (in mm), pre- and post-GKR, the mean difference was 5.44 ($P = 0.001$) [Table 2].

There was a statistically significant improvement in amenorrhea, loss of libido, contrast enhancement of the Prs on MRI, and need for medical treatment post-GKR [Table 3].

Complications

Only 3/25 patients (12%) had transient visual deterioration that eventually improved within 2 months post-GKR.

DISCUSSION

PrH level

In our study, the pre-GKR PrH level was 123–456 ng/l (mean = 250.24 ng/l, median = 250 ng/l). The PrH level after 6 months post-GKR was 35–277 ng/l (mean = 122 ng/l). The mean difference was 128.24 ng/l (lower limit = 80.360 ng/l, and upper limit = 176.120 ng/l) which was statistically significant ($P = 0.001$). This improvement in the PrH level ranged from a significant reduction to complete normalization.

Other comparative studies showed variable results. Some studies showed significant improvement of patient's PrH level after GKR. A study by Rahn *et al.* showed normalization of PrH level after GKR in 3/5 cases and a significant decrease in PrH in the other 2/5 cases.^[8] Lim *et al.*, in their series of 18 cases, showed normalization of PrH in 10 cases and a decrease in PrH in the other 6 cases after GKR.^[6] Morange *et al.* showed that all cases expressed lower levels of PrH after GKR but not reached normal levels.^[7] Laws *et al.* and Witt *et al.* in their series found no improvement in PrH level in all their cases except for the one with mild improvement.^[5,10]

Size of adenomas

In our study, the size of pituitary adenomas was measured in the patients. The pre-GKR size of the adenomas was 11–29 mm (mean = 19.08 mm), and the post-GKR size of the adenoma was 4–25 mm (mean = 13.64 mm). The mean difference was 5.44 mm (upper limit = 3.223 mm and

Table 1: Descriptive statistics of PrH levels and size of the Prs, pre- and post-GKR.

Variables	Minimum	Maximum	Mean	Standard deviation	Median
Pre-GKR PrH level (ng/l)	123	456	250.24	81.872	250
Post-GKR PrH level (ng/l)	35	277	122	60.780	123
Pre-GKR PrH size of adenoma (mm)	11	29	19.08	6.344	21
Post-GKR size of adenoma (mm)	4	25	13.64	4.653	13

PrH: Prolactin hormone, Prs: Prolactinoma, GKR: Gamma Knife radiosurgery

Table 2: Differences between pre- and post-GKR of PrH levels, size of adenomas.

Variables	Mean difference	Lower limit	Upper limit	P-value
ProH level (ng/l)	128.24	80.360	176.120	0.001
Size of adenoma (mm)	5.44	3.223	7.657	0.001

GKR: Gamma Knife radiosurgery, PrH: Prolactin hormone

Table 3: Differences between pre- and post-GKR of amenorrhea, loss of libido, contrast enhancement on MRI, and medical treatment.

Variables	Pre-GKR Number (%)	Post-GKR Number (%)	P value
Amenorrhea (female)	15/18 (83.3)	5/18 (27.7)	0.013
Loss of libido (male)	5/7 (71.4)	0/7 (0)	0.042
Contrast enhancement	23/25 (92)	7/25 (28)	0.001
Medical therapy	25/25 (100)	11/25 (44)	0.016

GKR: Gamma Knife radiosurgery

lower limit = 7.657 mm) which was statistically significant ($P = 0.001$). Other studies showed comparative results. Landolt *et al.* reported tumor size control in all of their cases.^[4] Ježková *et al.* reported a tumor size control in 97% of his cases.^[3]

Contrast enhancement of adenoma

In this study, MRI contrast enhancement pre-GKR was present in 23/25 patients (92%), and post-GKR was present in 7/25 patients (28%). This was statistically significant ($P = 0.001$). Unfortunately, no other comparative studies were available in this setting.

Loss of libido and amenorrhea

In this study, amenorrhea was present in 15/18 female patients (83.3%) and loss of libido in 5/7 male patients (71.4%), pre-GKR. Post-GKR amenorrhea recovered in 13/18 female patients (72.3%), and all 7 male patients (100%) recovered from loss of libido. This significant clinical improvement is comparable with other study resulted by Ježková *et al.* and Witt *et al.*^[3,10]

Medical treatment

Our study showed a statistically significant improvement regarding the dose of the dopamine agonist required for patients with prolactinoma post-GKR. In our study, 11/25 patients (44%) continued on medical treatment and no medical treatment was needed in the other 14/25 patients (56%). These results are comparative with other studies.^[3,6]

Complications

In our study, only 3/25 patients (12%) had transient visual deterioration that eventually improved within 2 months post-GKR. This may be explained by the effect of edema and free radicals that resulted from the radiation. This finding is very comparative with the main series in this setting, and furthermore, it is better than the results of other series.^[3,6]

CONCLUSION

The study provided a baseline study in Iraq for pituitary Prs treatment using the GKR. The study showed that the GKR is safe and effective modality in the management of pituitary Prs.

GKR can offer a worthwhile therapeutic option in patients with Prs who cannot achieve normal PrH levels with dopamine agonists and microsurgery. Although medical treatment is the first line in the management of pituitary Prs, and surgery is the next line, the side effects of medical management and the complications associated with surgery make the GKR a good option in the management of pituitary Prs. Future prolonged series may be required for better assessment of the discontinuation of medical treatment in patients with Prs after GKR.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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