ICNSJ Original Article

Pituitary Adenoma: Early Results after Gamma Knife Radiosurgery in Iran

Saeed Oraee Yazdani[1], Alireza Zali[1], Sohrab Shahrzadi[1], Mazdak Alikhani[2], Seyed Morteza Tabatabaei[1]

[1] Functional Neurosurgery Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] Iran Gamma Knife Centre (IGKC), Tehran, Iran

ABSTRACT

Purpose: To study early treatment outcomes and complications of Gamma Knife Radiosurgery (GKRS) in patients with functional and nonfunctional adenomas.
Methods: One hundred patients with a pituitary adenoma who were treated between 2011 and 2014 at Iran Gamma Knife Center were studied. The patients were followed up at least 2 years. Radiosurgery was performed using the Leksell Gamma Unit. The median radiation dose was 18 Gy for non-functional and 24 Gy for functional adenoma. The MRI were compared pre and post operation for any change in tumor size. Endocrine follow up was used to determine the onset of new hormone deficiency when available or decrease in hormonal level.
Results: Our study group comprised 42 men (42%) and 58 women (58%). Ninety-three patients were treated for recurrent or residual disease after Trans-sphenoidal surgery or craniotomy and 7 patients were treated as primary modality because of extensive involvement of cavernous sinus or high risk for surgery. Forty-six patients (46%) had a diagnosis nonfunctional and 54 of patients (54%) had hormone-secreting tumors including growth hormone secreting (23%), prolactinoma (15%) and ACTH-secreting tumor (6%). No mortality was reported. Acute complication was uncommon and of no clinical significance. Late complication was noted in two patients (2%) and consisted of VI cranial nerve palsy with spontaneous resolution. None of the patients developed visual loss. Before GKRS, 8 patients had cranial nerve palsy. After the treatment, the palsy resolved in six (75%) of these patients. Only 9.5% of patients developed hypopituitarism and required replacement therapy. Overall control was 92% (28% decreased in volume and 64% were unchanged), 8% experienced an increase in volume size. Normalization of GH and IGF-1 for GH-secreting hormone was 48% with overall control of 73%. PRL normalization for prolactinoma was 46% with overall control of 67%. ACTH normalization for ACTH-secreting hormone was 35% with overall control of 70%.
Conclusion: It seems that GKRS to be safe and effective method for tumor control and optimal hormonal function.

Keywords: Pituitary Adenoma; Gamma Knife; Radiosurgery; Iran

ICNSJ 2015; 2 (4) :128-132 www.journals.sbmu.ac.ir/neuroscience

Correspondence to: Alireza Zali, MD, Functional Neurosurgery Research Center, Shohada Hospital, Tajrish Avenue, Tehran, Iran; Tel/fax: +98(21)22701022; E-mail: dr_alirezazali@yahool.com
Received: Jan, 2016 **Accepted:** Feb, 2016

INTRODUCTION

Pituitary adenomas account for as many as 20% of all intracranial tumors [1]. Surgery is the "gold standard" in the management of these lesions [1,2], especially in patients with macroadenomas who present with acute symptoms and/or signs of a compromised visual pathway or those with increased intracranial pressure [1-4]. Wide variety of modalities, including surgical excision, hormonal chemotherapy (bromocriptine, somatostatin, cabergoline), fractionated radiotherapy, and stereotactic

radiosurgery are proposed for treatment of these tumors [5]. Patients with microadenomas are treated microsurgically to histologically confirm the diagnosis or to achieve a cure if specific medical therapy does not yield the desired result.

Residual and recurrent tumors may be treated by either conventional radiotherapy (CRT) or radiosurgery. CRT is thought to achieve tumor control rates of 90% to 97% and to significantly reduce the rate of recurrence with a reported progression-free survival of 75% to 90% at 20 years [9,10]. However, there is some concern that CRT carries an increased risk of later complication. This is most commonly seen in the form of hypopituitarism, occurring in 30% to 88% of patients at 10 years. Radiation-induced neoplasia including meningiomas and glial tumors, with a reported incidence of 2% at 20 years is a less common finding [11]. Furthermore, a concern over the long-term neurocognitive impact of radiotherapy has arisen. Taken together, CRT provides adequate tumor control but poses a small risk of serious late-term squeal [12].

To date, gamma knife radiosurgery (GKRS) has most frequently been used as second-line therapy after surgery and/or medical treatment of pituitary adenoma or as a primary treatment modality in select cases [6,7]. GKRS enables the delivery of targeted therapy in a single session, with a steeper dose gradient that minimizes irradiation to surrounding structures. This modality can only be used if the volume of the adenoma is suitable for radiosurgery and if the distance from the adenoma surface to the optic apparatus allows for a safe procedure [8]. In this study, we investigated 100 patients with different types of pituitary adenoma who were treated using GKRS at our institution with at least 2 years of follow-up. We studied changes in tumor volume over time after GKRS treatment and evaluated hormonal changes in functional ones.

MATERIAL AND METHODS

Between 2010 and 2014, a total of 100 patients with pituitary adenomas underwent GKRS procedures at Iran Gamma knife center. Our study population comprised 42 men (42%) and 58 women (58%). Ninety-three patients were treated for recurrent or residual disease after Trans-sphenoidal surgery or craniotomy and 7 patients were treated as primary modality because of extensive involvement of cavernous sinus or high risk for surgery. The patients were followed up at least 2 years.

Radiosurgery was performed using the Leksell Gamma Unit. Dose planning was performed by a neurosurgeon using stereotactic magnetic resonance imaging (MRI) with a goal of achieving optimal tumor irradiation while minimizing exposure to surrounding structures. The Gamma Plan software was used for treatment planning. Pre and post contrast T1-weighted images were obtained. Fat saturation stereotactic imaging was also obtained. The median radiation dose was 18 Gy for non-functional and 24 Gy for functional adenoma defined to the 70% iso-dose line. The mean follow-up periods were 24 months. Special care was done to administer the lowest possible radiation dose to the optic apparatus (<8Gy) and other relevant intracranial structures.

MRI follow-up was obtained at 6, 12, 18 and 24 intervals after GKRS. The Images were compared pre and post operation for any change in tumor size. Tumor volume decrease by more than 25% from baseline was considered as 'shrinkage', <25% tumor size increase or decrease was considered 'static', and more than 25% increase as 'increment' as previously described [13].

Endocrine follow-up information was obtained from clinic visits and written and verbal communication with the patient and referring physician. Laboratory values were used to determine the onset of new hormone deficiency when available or decrease in hormonal level. Hormonal control was introduced as normalization or 50% or more than 50% reduction in hormonal level.

Ophthalmic follow-up was derived, when possible, from formal visual field and acuity testing in clinic notes from ophthalmologists and from referring physicians when these test results were not available.

RESULTS

Forty-six patients (46%) had a diagnosis of hormonally inactive adenoma (nonfunctional) and 54 of patients (54%) had hormone-secreting tumors including growth hormone secreting tumor in 23 patients (23%), prolactinoma (15%) and ACTH-secreting tumor (6%).

Special care was taken to minimize the radiation dose administered to normal pituitary. The other neighboring critical structures such as the chiasm, the optic nerves, the pituitary stalk, the hypothalamus, and the pons were administered radiation doses that we thought were well within the radiation tolerance of these structures. GKRS was tolerated well in the patients. No mortality was reported. Acute complication was uncommon and without clinical significance including transient headache, nausea and vomiting that resolved with some medications.

Late complication was noted in two patients (2%) and consisted of VI cranial nerve palsy, both patients have tumors with cavernous involvement. There was spontaneous resolution of this palsy during follow up. None of the patients developed visual loss. Before GKRS,

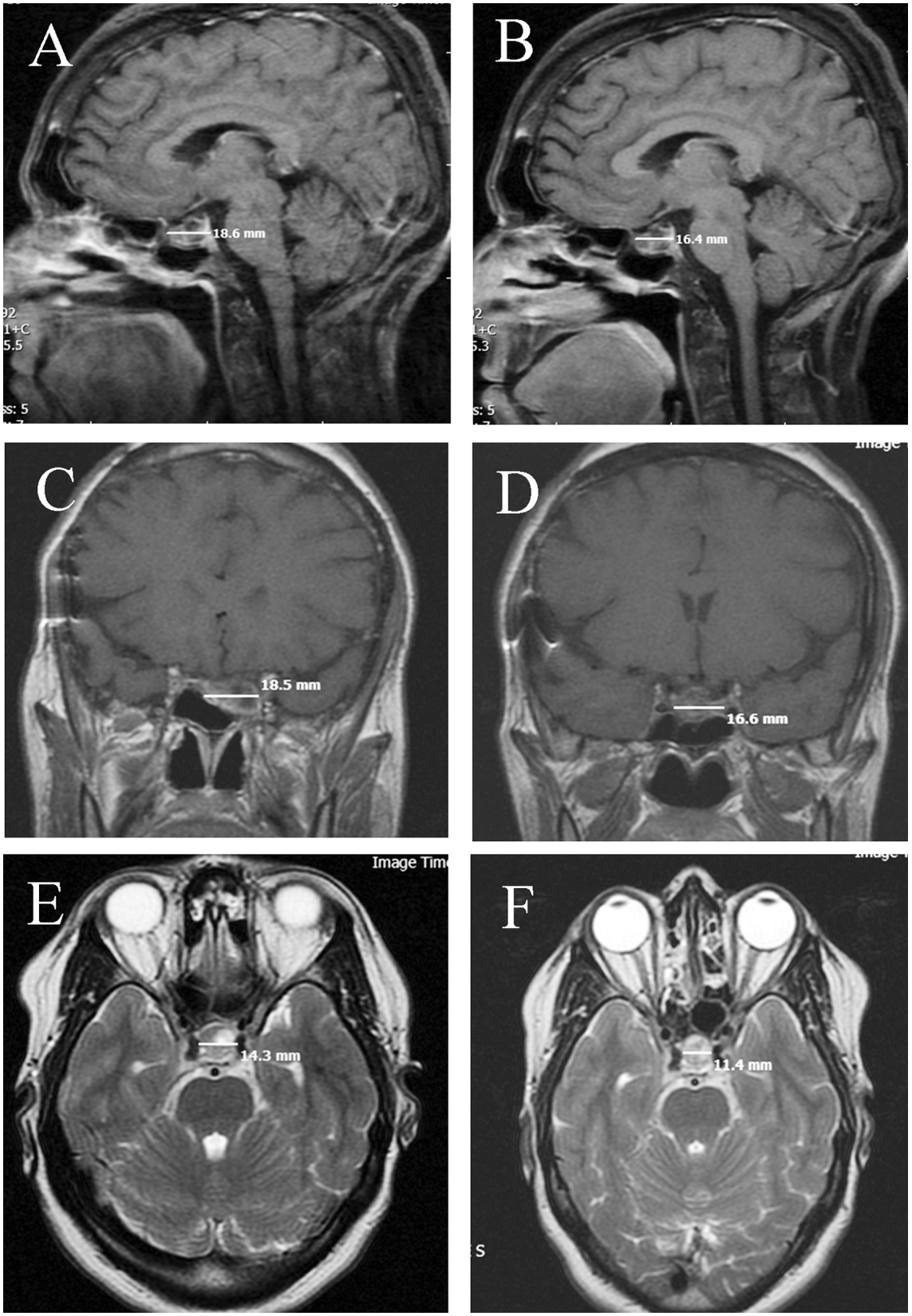

Figure 1. A 54-years old man with GH-secreting pituitary adenoma with history of previous Trans-sphenoidal surgery 1 year ago. Sagittal, coronal and axial MR images before GKRS (A, C, E) and 24 months after GKRS (B, D, F). The images show decrease in tumor size in all dimensions after GKRS.

8 patients had cranial nerve palsy. After the treatment, the palsy resolved in six (75%) of these patients.

Of 63 patients with normal function of hypophysis before GKRS, six patients (9.5%) developed hypopituitarism and required replacement therapy.

Overall control was 92% (28% decreased in volume and 64% were unchanged), 8% experienced an increase in tumor size; three patents from non functional, one patient from GH-secreting, three patients from prolactinoma and one patients form ACTH-secreting group (Figure 1).

The rate of overall control was different between functional and nonfunctional tumors; 93% for functional tumors, 96% for GH-secreting, 84% for ACTH-Secreting and 80% for prolactinoma. Tumor volume reduction was slow, with 28% of patients showing decreased tumor volume (approximately 80% of initial volume average) more than 2 years after undergoing GKRS.

Normalization of GH and IGF-1 for GH-secreting hormone was 48% with overall control of 73%. PRL normalization for prolactinoma was 46% with overall control of 67%. ACTH normalization for ACTH-secreting hormone was 35% with overall control of 70%.

DISCUSSION

Surgical resection is the mainstay for the treatment of patients with a pituitary adenoma. The safety of trans-sphenoidal resection in particular is relatively favorable. Resection also has the advantage of providing tissue for histological analysis. A morality rate of 0.9% has been reported. Anterior pituitary insufficiency (19.4%) and diabetes insipidus (17.8%) were among the most common morbidities of this procedure. Other reported complications included sinusitis (8.5%), cerebrospinal fluid leak (3.9%), hemorrhage (2.9%), and loss of vision (1.8%). These complications were inversely related to the experience of the surgeon [10].

The incidence of pituitary suppression after GKRS is difficult to determine because of the relatively limited follow-up in most of the published studies. It is reported approximately 20% [18]. The Incidence of decreased pituitary function in our study was 9.5%. These low incidence, is probably related to the small volume of normal pituitary that was administered the designated tumor dose. It seems to be reasonable to identify normal pituitary gland, the pituitary stalk, and the hypothalamus as part of treatment planning to minimize radiation dose delivered to these structures.

In the same way, none of the patients were developed visual loss after radiosurgery. These results were in relevance with results of Petrovich et al among the patients who received below 8 Gy to optic apparatus [15]. With consideration of all data, GKRS seems to be well tolerated. In our study, rate of acute and late complication were low. Most of adverse effects were reversible and this procedure revealed no mortality. About overall control that was determined as shrinkage (>25% decreasing in total size) or static state (<25% change in diameters of tumor), the rate was 92% with different rates between functional and nonfunctional tumors. These results are compatible with results of Mack HK et al [13] and Gopalan et al [12].

We know that effects of GKRS have delayed fashion. In our study, 28% of patients showing decreased tumor volume (approximately 80% of initial volume average) more than 2 years after undergoing GKRS. These results show that tumor reduction size is slow that is in compliance with other studies [15].

In addition to tumor control, GKRS offers a high rate of tumor control. Overall control that was mentioned as normalization or 50% or more than 50% reduction in hormonal level, with 73% for ACTH- secreting, 70% for prolactinoma and 67% for ACTH-secreting tumors. These results also were comparable with other studies like in Tinnel et al study that was 60-70% for different functional adenomas [12] and in Kobayashi et al study for GH-producing pituitary adenoma that IGF-1 was significantly decreased in 40.9% of patients and decreased in 39.7% [17].

CONCLUSION

GKRS offers a high rate of tumor control after primary surgical resection for functional and non-functional adenoma. In comparison with surgical procedures, it seems that GKRS to be safe and effective method for tumor control and optimal hormonal function. Although further studies with long-term follow-up are still needed in this field.

DISCLOSURE

The authors have no personal, financial or institutional conflicting interest.

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