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Clinical Article

Stereotactic Radiosurgery with the CyberKnife for Pituitary Adenomas

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Objective : In recent years, CyberKnife has emerged as an important treatment modality in the management of pituitary adenomas. Treatment results after performing CyberKnife and the complications of this procedure are reviewed.
Methods : Twenty-six patients with pituitary adenomas received stereotactic radiosurgery with the CyberKnife (CKRS). The follow-up periods ranged from 7 months to 47 months (mean±SD : 30±12.7 months). The patients consisted of 17 with non-functioning adenomas, 3 with prolactinomas and 6 with acromegaly. The change in the tumor volume, visual acuity, hormonal function, and complications by this therapy were analyzed in each case.
Results : The tumor control rate was 92.3%. Hormonal function was improved in all of the 9 (100%) functioning adenomas. Hormonal normalization was observed in 4 of the 9 (44%) patients with a mean duration of 16 months. In two patients (7.6%), visual acuity worsened due to cystic enlargement of the tumor after CKRS. No other complications were observed.
Conclusion : CyberKnife is considered safe and effective in selected patients with pituitary adenomas. However, longer follow-up is required for a more complete assessment of late toxicity and treatment efficacy.

KEY WORDS : CyberKnife · Pituitary adenoma.

INTRODUCTION

Pituitary adenomas are common benign tumors that are well controlled by various therapeutic interventions[38,40]. About 10% of intracranial tumors are pituitary adenomas. Asymptomatic small pituitary tumors have an estimated prevalence of 16.7% (14.4% in autopsy and 22.5% in radiologic studies)[4,12]. Patients frequently present with visual disturbances and endocrine abnormalities. Surgery may produce excellent immediate symptom relief as well as long-term cure[3,10]. Therefore, surgery is the "gold standard" in the management of these lesions[21,31]. However, many tumors are not completely resectable due to location adjacent to critical neurovascular structures, extension beyond the pituitary fossa, or invasion into the dura[37]. In such circumstances, recurrence after subtotal removal alone is likely.

External beam radiotherapy consisting of 40 to 45 Gy delivered in 1.8 Gy/d fractions administered with the three dimensional conformal approach is a proved, effective therapy in selected patients with pituitary adenomas[5,11,17]. Contemporary radiotherapy is expected to produce a less than 1% incidence of severe toxicity[31]. The disadvantages of external beam radiotherapy include the need for up to 25 daily treatments, a relatively slow tumor regression rate in patients with macroadenoma and, in patients with hormone-secreting tumors, a slow rate of hormonal normalization after radiotherapy and a small risk of secondary tumors in patients who undergo radiotherapy with long-term follow-up[5,11,17,18,31].

Stereotactic radiosurgery (SRS) has become an attractive treatment modality, often replacing external beam radiotherapy in selected patients with pituitary adenoma and has achieved favorable tumor growth control and functional preservation[13,19,29,34]. More recently, the CyberKnife (Accuray, Calif., USA), developed in 1997, has become a powerful instrument mounted on a highly maneuverable robotic manipulator which eliminates the need for skeletal fixation or rigid immobilization of the target through its use of real

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time image guidance[2,8]. This article reviews our 4 years clinical experiences in performing CyberKnife in patients with pituitary adenomas.

MATERIALS AND METHODS

Twenty-six patients with confirmed, previously resected pituitary adenomas underwent stereotactic radiosurgery with the CyberKnife (CKRS) between March 2004 and June 2008. A retrospective review of these cases was undertaken. Each patient was evaluated by the neuroendocrinologist and neuroophthalmologist before and after CKRS. A multidisciplinary team of neurosurgeons, radiation oncologists, and neuroradiologists evaluated each patient for treatment eligibility.

Selection criteria for CKRS and radiosurgical treatment planning

The selection criteria for CKRS were as follows : histological or MRI diagnosis of pituitary adenoma, recurrent or residual lesion after prior definitive therapy, no increased intracranial pressure, small volume tumor within sellar or cavernous sinus, poor candidates for microsurgery and patients refusing surgery. The lesions in each patient were evaluated on 1-25 mm contiguous slice, high-resolution computed tomography (CT) images with a GE Light Speed 8i unit. In most cases, thin-section magnetic resonance images (MRI) were also obtained. The image data were transferred to the CyberKnife workstation and the treating surgeon manually outlined the target volume and critical structures on the axial images using proprietary Multiplan and InView software. Simultaneous overlay of these contours on coronal and sagittal reconstructions were performed (Fig. 1).

Radiation dose selection

All treatment plans were designed using an inverse planning algorithm that involved setting dose constraints to minimize irradiation of specified structures such as the optic apparatus and maximize doses to the tumor. The neurosurgeon and radiation oncologist jointly determined the marginal, maximal doses and the number of sessions.

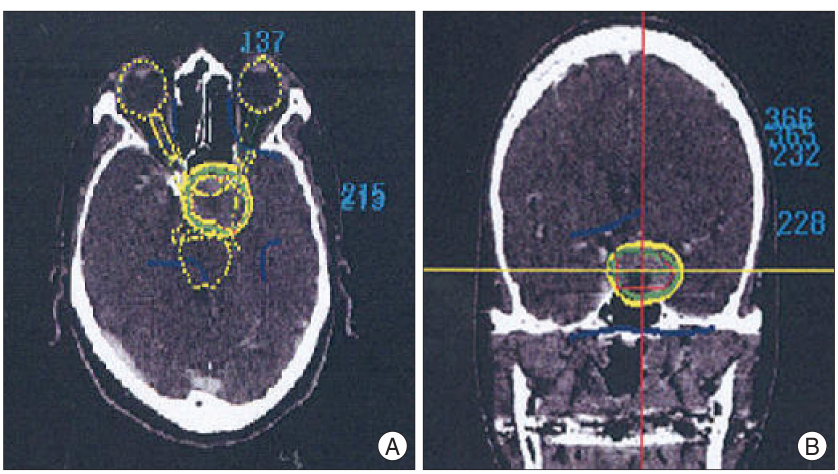

Fig. 1. Case 7. Axial computed tomography scan (A) and coronal reconstruction (B). Dose planning with the CyberKnife treatment planning software. Tumor margin, optic nerves, chiasm and tracts are delineated, and the radiation-sensitive optic apparatus is kept out of the high isodose areas. Red lines, tumor; yellow lines, vital structures; green lines, the 80% isodose.

Table 1. Guidelines Proposed by the Committee of the Brain Tumor Registry of Japan[35]

Parameter	Definition
Complete response (CR)	Gd-enhanced area disappears, and no regrowth is recognized at least four weeks after treatment
Partial response (PR)	Gd-enhanced area is reduced by more than 50%, and maintains this state at least four weeks after treatment
Minor response (MR)	Gd-enhanced area is reduced from 25% to 50%, and maintains this state at least four weeks after treatment
No change (NC)	Less than 50% reduction or less than 25% growth of Gd-enhanced area, maintained at least four weeks after treatment
Progressive disease (PD)	More than 25% growth of Gd-enhanced area

The control rates were calculated by CR+PR+MR+NC/CR+PR+MR+NC+PD

Postoperative evaluation

The change in the tumor volume, visual acuity and field, hormonal function, and complications by CKRS were analyzed in each case by a team consisting of neurosurgeons, radiation oncologists, neuroendocrinologits, neuroophtalmologists, and neuroradiologists. Post-radiotherapeutic states were assessed by serial clinical examinations and MRI at 3, 6, and 12 months during the first year, and every 6 months thereafter. The therapeutic response as measured by the size of the tumor was classified as follows, according to guidelines proposed by the Committee of the Brain Tumor Registry of Japan[35] (Table 1). Visual acuity and visual field test were performed at 6-month intervals for 2 years, then once every year. Endocrinological improvement is defined as a decline in the measured hormonal level of more than 50% from the pre-CKRS hormonal levels. For prolactin (PRL) and growth hormone (GH) producing tumors, the criteria for hormonal normalization was a serum PRL level

Table 2. Summary of cases

Case no.	Age	Sex	Pre-CKRS Visual symptom	Type	Prior operation history	Total dose (cGy)	Target volume (cm^3)	No. of Fractionation	Follow up period (months)
1§	31	M	No	GH	TSA* × 2	1,400	0.782	1	47
2‖	50	M	Yes	Non	TSA	1,500	7.886	1	47
3§	41	M	Yes	Prolactin	TSA	1,400	3.169	1	47
4§	34	M	No	GH	TSA × 2	2,400	2.827	3	46
5§	57	F	Yes	Non	TSA × 2	2,100	0.202	3	42
6§	55	F	Yes	GH	TSA	2,000	4.028	3	42
7‖	51	F	Yes	Non	TSA	2,000	7.357	1	41
8†	60	M	Yes	Non	Non	2,100	0.472	3	40
9†	51	F	Yes	Non	Non	2,000	4.443	3	39
10‖	39	F	No	Prolactin	TSA	2,000	1.616	3	38
11‖	38	M	Yes	Non	TSA	2,000	6.152	3	37
12§	43	M	No	Prolactin	craniotomy	1,900	0.514	3	36
13†	62	F	Yes	Non	Non	1,800	3.17	3	33
14§	38	M	No	Non	TSA × 2	1,800	1.187	3	29
15‡	34	M	No	GH	Non	2,000	0.235	3	29
16§	43	F	No	GH	TSA	2,000	0.281	1	29
17‖	57	F	Yes	Non	TSA	1,900	3.872	3	27
18§	50	F	Yes	Non	TSA	2,200	1.971	3	26
19§	55	M	Yes	Non	TSA	1,900	3.558	3	24
20§	40	M	Yes	GH	TSA	2,100	1.769	3	18
21§	57	F	Yes	Non	TSA	1,800	1.068	3	16
22‖	55	F	Yes	Non	TSA	1,900	2.627	3	14
23†	43	M	Yes	Non	Non	1,900	2.776	3	13
24‖	62	M	Yes	Non	TSA	2,000	1.747	3	11
25§	69	M	Yes	Non	TSA	2,000	2.014	3	11
26§	47	F	Yes	Non	TSA	1,800	1.979	3	7

*Transsphenoidal approach with tumor removal, †patients refusing microsurgery (n=4), ‡failure of microsurgery due to massive venous bleeding (n=1), §recurrent mass after microsurgery (n=14), ‖residual mass after microsurgery (n=7)

below 20 ng/mL and a serum GH level below 5 mIU/L.

RESULTS

Patient characteristics

Twenty-six patients with pituitary adenomas received stereotactic CKRS. The follow-up periods ranged from 7 months to 47 months (mean±standard deviation (SD) : 30±12.7 months). The patient characteristics are summarized (Table 2). The patients consisted of 17 with non-functioning adenomas, 3 with prolactinomas and 6 with acromegaly. Patient age ranged from 31 to 69 years (mean±SD : 48.5±10.0 years). Fourteen patients (53%) were male, and 12 (47%) were female. Before CKRS, 22 patients had undergone tumor removal operation through transsphenoidal or transcranial approach and 4 patients had no operation.

Radiation doses and fractionation

The total irradiation dose ranged from 1400 cGy to 2400 cGy (mean±SD : 1919.2±222.7 cGy). The mean irradiation dose of non-functioning adenomas and functioning adenomas were 1,923 cGy and 1,911 cGy, respectively. Single fraction was performed in 5 cases, three fractions were performed in 21 cases.

Tumor growth control

The pre-CKRS volume of the tumors ranged from 0.20 cm^3 to 7.89 cm^3 (mean±SD : 2.60±2.08 cm^3). The mean pre-CKRS volumes of the non-functioning and functioning adenomas were 3.08 cm^3 and 1.69 cm^3, respectively. The post-CKRS volume of the tumors ranged from 0 cm^3 to 7.65 cm^3 (mean±SD : 2.30±2.04 cm^3). The mean post-CKRS volumes of the non-functioning and functioning adenomas were 2.78 cm^3 and 1.40 cm^3, respectively. The overall tumor control rate was 92.3% based on guidelines proposed by the Committee of the Brain Tumor Registry of Japan[35]. In case 6, Gadolinium enhanced coronal and sagittal MRI obtained 12 months after CKRS demonstrated decreased size of pituitary adenoma at suprasellar portion compared with MRI at pre-CKRS (Fig. 2).

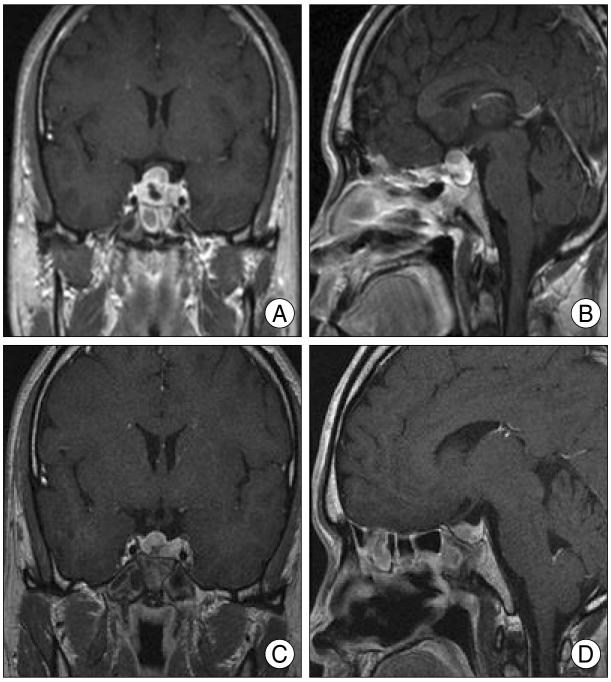

Fig. 2. Magnetic resonance (MR) images obtained in case 6. Gadolinium enhanced coronal (A) and sagittal (B) MR images obtained at the CyberKnife radiosurgery (CKRS), Gadolinium enhanced coronal (C) and sagittal (D) MR images obtained 12 months after CKRS showing decreased size of pituitary adenoma at suprasella portion.

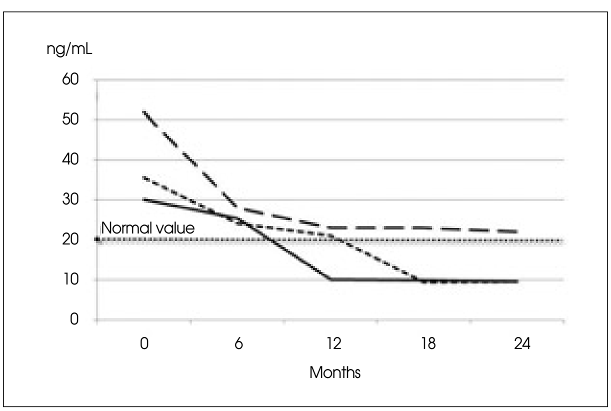

Fig. 3. Post- CyberKnife hormonal changes in prolactinoma (n=3).

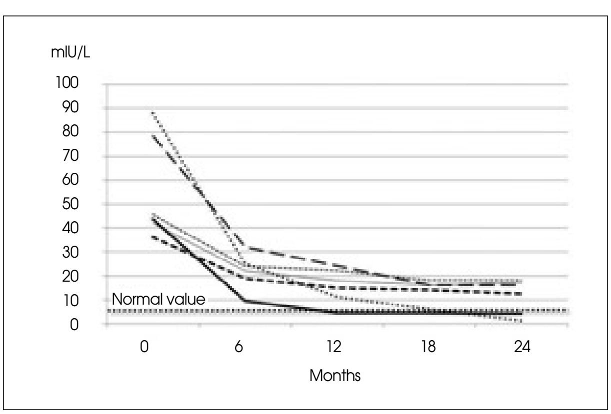

Fig. 4. Post- CyberKnife hormonal changes in acromegaly (n=6).

Visual function

Seventeen patients had visual dysfunction before CKRS. Visual acuity remained unchanged in 15 patients with pretreatment visual dysfunction. However, in two patients, visual acuity worsened due to cystic enlargement of the tumor after CKRS and an additional resection were performed. In the other 9 patients with no visual impairment before CKRS, visual function was preserved.

Hormonal function

Hormonal level improved in all of the 9 (100%) functioning adenomas after CKRS. Hormonal normalization was observed in 4 of the 9 (44%) patients with a mean duration of 16 months (Fig. 3, 4). No patient developed hypopituitarism after CKRS.

Complications

There were no incidences of pituitary dysfunction. However, two patients (7.6%) developed visual disturbances after CKRS.

Case 5 : A 57-year-old female who had a non-functioning adenoma developed a disturbance of visual acuity 40 months after CKRS (Fig. 5).

Case 7 : A 51-year-old female who had a non-functioning adenoma developed a disturbance of visual acuity 36 months after CKRS (Fig. 6).

DISCUSSION

The term 'Radiosurgery' was made by the Swedish neurosurgeon Lars Leksell in 1951 to delineate the procedure used to administer high doses of radiation in a single session to a small, critically located intracranial volume without opening the skull. The goal of radiosurgery is the destruction of cells in order to hold the growth or reduce the volume of tumors.

Radiosurgery has become an important treatment alternative to surgery for a variety of intracranial lesions. Radiosurgery techniques have evolved quickly with the development of new technologies, enabling more complex yet more efficient treatment plans. The current radiosurgery systems include the Gamma Knife, manufactured by Elekta based in Sweden; Novalis, manufactured by BrainLabs based in Germany; and CyberKnife, manufactured by Accuray based in the United States. Our institute has used CyberKnife since 2003.

CyberKnife is the name of a frameless robotic radiosurgery system invented by John R. Adler, a Stanford University Professor of Neurosurgery and Radiation Oncology[2)]. The current configuration of the system includes a small 6 MV LINAC mounted on a robotic arm, two diagnostic X-ray

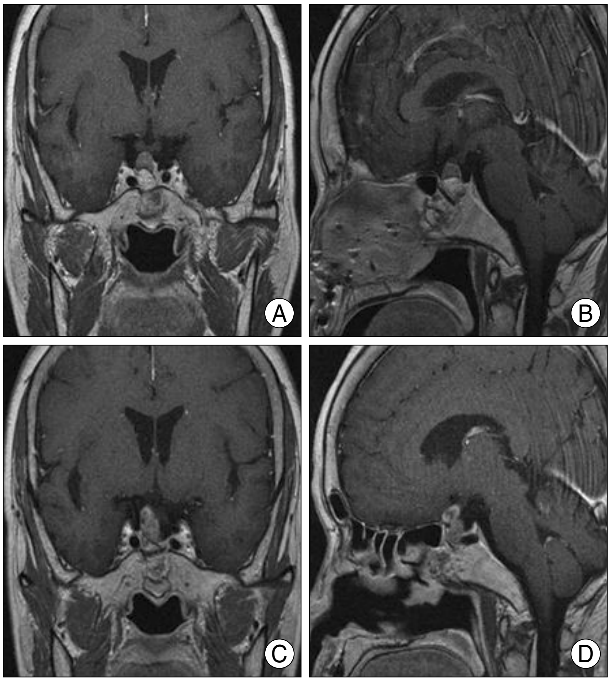

Fig. 5. Magnetic resonance images obtained in case 5. Gadolinium enhanced coronal (A) and sagittal (B) MR images obtained 24 months after CyberKnife (CKRS), Gadolinium enhanced coronal (C) and sagittal (D) MR images obtained 40 months after CKRS showing aggravation of optic nerve involvement due to superior extension of pituitary adenoma.

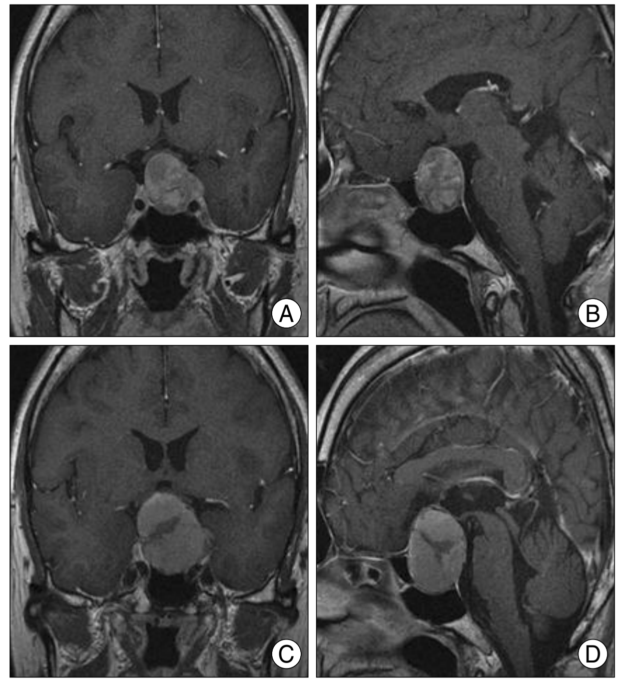

Fig. 6. Magnetic resonance (MR) images obtained in case 7. A : Gadolinium enhanced coronal (A) and sagittal (B) MR images obtained 6 months after CyberKnife, Gadolinium enhanced coronal (C) and sagittal (D) MR images obtained 36 months after CyberKnife showing increased size of pituitary adenoma at suprasellar portion.

sources attached to digital image collectors placed orthogonally to the patient to provide real-time treatment guidance, and a table that can move around different axes and thus adjust the position of the patient.

One of the most widely known stereotactic radiosurgery systems is the Gamma Knife. Disadvantages of Gamma Knife compared with CyberKnife are as follows. The Gamma Knife requires Cobalt reload and a head frame to be bolted onto the skull of the patient, and is only capable of treating cranial lesions. It has major drawbacks when treating patients with multiple, large or non-spherical tumors. The accuracy of Gamma Knife is only dependent upon the frame placement, and has no real time imaging capability.

Microsurgery is the gold standard for treatment of sellar lesions. It provides the advantages of pathological confirmation, rapid reduction of hormone oversecretion and decompression of the optic apparatus. Transsphenoidal resection is currently the most widely used approach for pituitary adenomas. However, microsurgery alone provides long-term tumor control rates of only 50 to 80%[7,15,24]. In all groups of hypersecreting tumors, a failure rate and a recurrence rate following surgery have been reported as high as 50%[6,15,36]. Because it is very difficult to resect completely due to location adjacent to critical neurovascular structures, extension beyond the pituitary fossa, or invasion into the dura[37]. Therefore, additional therapy after operation is often necessary. For such cases, conventional external radiation has been known to be effective, but it takes several years to achieve endocrinological remission and also carries a significant risk for panhypopituitarism or visual disturbances[20,25,26]. Radiosurgery can be a first choice of treatment, achieving both growth control and hormonal remission with minimum neurological complications, which is equivalent to conventional radiation therapy but with much less risk of radiation injury to the surrounding structures. One of the best indications for radiosurgery of pituitary adenomas is residual or recurrent tumor that is not safely removable when using microsurgical techniques.

We performed multisession CKRS in 21 of 26 patients. The selection of this treatment protocol (total dose, number of sessions, and dose per session) was based on the knowledge of optic nerve tolerance to single-session radiosurgery[22,23,27,28] and experience treating the anterior optic pathways and other cranial nerves with multisession radiosurgery[1,9,32]. The aim of fractionated stereotactic radiosurgery is to reduce radiation injury to the surrounding structures and to be able to make radiation field be broader. Gamma knife radiosurgery (GKRS) has traditionally been used for the single session irradiation procedure because of the inconvenience of stereotactic frame fixation. However, single session radiosurgery is not always recommended in perioptic lesions because it may be difficult to deliver an effective dose to the lesion while maintaining a dose to the optic apparatus. Therefore, CKRS can apply the advantages of multisession radiosurgery for perioptic lesions easily due to no need of stereotactic frame fixation. This is one of the greatest advantages of CyberKnife.

In fractionated radiation, the tumor control rate ranges from 76% to 97%[14,33]. Therefore, CKRS compares favorably with fractionated radiotherapy. According to the literature, the tumor control rate for the pituitary adenomas following GKRS ranges from 93.3% to 94%[16]. The results reported here (tumor control rate : 92.3%) are similar.

The improvement rate of endocrinopathies after GKRS has been reported to be 77.7% to 93%, and the normalization rate has ranged between 21% and 52.4%[16,30]. In fractionated radiation, endocrinological improvement ranges from 38% to 70%[33,39,42]. Thus, the current results of CKRS (endocrinological improvement : 100%, endocrinological normalization : 44%) are similar to that of GKRS and a little superior to that of fractionated radiation.

Complication rates for GKRS and fractionated radiation have ranged from 0% to 12.6% and from 12% to 100%, respectively[14,40]. Visual loss has been the most common complication[40]. Our complication rates (Visual disturbance : 7.6%) are similar to that of GKRS and much superior to that of fractionated radiation. The fact that there were no incidences of pituitary dysfunction is probably due to the multisession radiosurgey.

CONCLUSION

The present investigation confirms that stereotactic CKRS seems to be a safe and effective treatment for pituitary adenomas. Longer-term follow-up with a larger group of patients is required to fully evaluate the safety and effectiveness of this treatment modality.

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