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CyberKnife Radiosurgery in the Multimodal Management of Patients with Cushing Disease

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■ BACKGROUND: Surgery is the primary treatment for Cushing disease. When surgery is unsuccessful in normalizing hypercortisolism, adjuvant radiation, such as stereotactic radiosurgery, may be useful to improve biochemical control.

■ METHODS: This retrospective study included a cohort of consecutive patients treated with CyberKnife (CK) radiosurgery for active Cushing disease at Stanford Hospital and Clinics.

■ RESULTS: As first-line treatment, all patients underwent transsphenoidal surgery with histologic demonstration of an adrenocorticotropic hormone—producing pituitary adenoma. CK was performed as adjuvant therapy for persistent or recurrent disease. The median time between surgery and CK was 14 ± 34 months. Before CK, median maximal diameter of tumors was 9 mm (range, 7—32 mm), with cavernous sinus invasion in all patients (100%) and abutment of the optic chiasm in 1 patient (14.2%). With an average follow-up of 55.4 months, normalization of hypercortisolism was achieved in 4 patients (57.1%): 2 patients (28.5%) achieved normalization of the hypothalamic-pituitary-adrenal axis without glucocorticoid replacement, and 2 patients developed hypoadrenalism (28.5%). The median time to biochemical remission was 12.5 months. Hypopituitarism occurred in only 1 patient (14.2%), and no patients had visual complications. Time between surgery and radiotherapy of <14 months was associated with a significantly improved biochemical remission rate (P = 0.02).

■ CONCLUSIONS: In a cohort of patients with Cushing disease, we demonstrate that CK is an effective treatment with rare complications.

INTRODUCTION

Cushing disease (CD) refers to hypercortisolism resulting from an adrenocorticotropic hormone (ACTH)—producing pituitary adenoma and accounts for 70% of cases of Cushing syndrome.[1-3] Approximately 40% of patients have a microadenoma or no visible tumor at presentation.[4] The Endocrine Society Clinical Guidelines[5] recommend surgery as initial treatment, but failure to achieve surgical remission is common (60% in macroadenomas),[6] and patients with recurrent or residual disease often require additional treatment. Adjuvant therapeutic options in both adult and pediatric patients include repeat transsphenoidal (or open) surgery, radiotherapy, medical therapy, and bilateral adrenalectomy.[7]

Use of stereotactic radiosurgery (SRS) in recurrent or residual CD has increased, but experience is still limited.[8,9] Several small series of patients with CD treated with Gamma Knife (GK) (Elekta AB, Stockholm, Sweden) SRS have reported biochemical remission rates of 17%—87%.[10,11] GK SRS was complicated by hypopituitarism in approximately 30% of patients and optic neuropathy in selected cases.[10,12,13] CyberKnife (CK) (Accuray Inc., Sunnyvale,

California, USA) robotic SRS is a frameless image-guided stereotactic device that was first described by Adler et al.[14] in 1997 and is increasingly incorporated into treatment regimens for recalcitrant pituitary tumors. CK appears to be an efficacious adjuvant treatment option in clinically nonfunctioning pituitary adenomas.[5] Similar to other forms of SRS, CK may be associated with complications, including visual field deficits and hypopituitarism.[13] At the present time, there are virtually no data on outcomes of patients with CD treated with CK. This study aims to review the outcomes and complication profile of the first cohort of patients treated with the CK at Stanford Health Care.

MATERIALS AND METHODS

Patient Selection
Following institutional review board approval, a retrospective review of all patients with pituitary adenomas who underwent CK treatment between 2000 and 2016 at Stanford Health Care was performed. This article conforms to the STROBE (STrengthening the Reporting of OBservation studies in Epidemiology) guidelines. Patients met the study inclusion criteria if they had histologically confirmed diagnosis of an ACTH-staining pituitary adenoma, confirmed residual or recurrent tumor based on imaging and evidence of hypercortisolism, and availability of biochemical and imaging follow-up before and at least 6 months after the CK procedure. After surgery, evidence of recurrence of residual pituitary adenoma was found in all patients by a dedicated pituitary magnetic resonance imaging protocol with and without contrast enhancement.

Demographic and CK treatment variables were collected and included patient age, symptoms, tumor target volume, number of fractions of radiation delivered, tumor maximum dosimetry (Dmax), and left or right optic nerve Dmax. Given the range of marginal prescribed doses and number of fractions, the biologically effective dose (BED) and the 2 Gy equivalent dose were calculated. Pituitary adenomas were considered late responding tissue, and therefore an α/β ratio of 4 was used to calculate BED as follows: $Gy_3 = nd \ (1 + d/(\alpha/\beta))$, where "n" is equal to the number of fractions, and "d" is the dose. The 2 Gy equivalent dose was calculated as: $2 \ Gy \ equivalent \ dose = BED/(1 + 2/(\alpha/\beta))$.[15-17] Functional outcomes, defined using the modified Rankin Scale score, at discharge and at last clinical follow-up were included. Radiation side effects, including visual deficits, were noted.

Biochemical Follow-Up
The primary outcome was the resolution of hypercortisolism after CK treatment. Patients underwent annual evaluation for assessment of adrenal function as well as hypopituitarism. Remission was defined by both normalization of adrenal function and achievement of hypoadrenalism. Normalization of the hypothalamic-pituitary-adrenal axis was defined as normal 24-hour free urine cortisol excretion and/or normal plasma cortisol response to overnight 1-mg dexamethasone test without the requirement of glucocorticoid replacement. Hypoadrenalism was defined as a low morning plasma cortisol ($<5 \ \mu g/dL$) alone or in association with an insufficient response to an ACTH stimulation test (peak cortisol $<18 \ \mu g/dL$) with normal or low ACTH levels.[5] Active disease was defined as persistent

hypercortisolism (elevated 24-hour free urine cortisol excretion, elevated serum basal cortisol without suppression after overnight 1-mg dexamethasone test, or late night salivary cortisol) as per current diagnostic guidelines.[5]

The secondary outcome was the presence of hypopituitarism (defined as a deficiency in at least 1 hormonal axis). Hypopituitarism was defined as follows: growth hormone deficiency by low sex-matched and age-matched serum insulinlike growth factor-I, in association with insufficient response to a growth hormone stimulation test (growth hormone-releasing hormone and arginine or insulin-induced hypoglycemia); hypothyroidism by low free plasma thyroxine with normal or low plasma thyroid-stimulating hormone levels; and hypogonadism by low plasma total testosterone in the presence of low or inappropriately normal serum luteinizing hormone and follicle-stimulating hormone in men and by amenorrhea or by low or normal luteinizing hormone and follicle-stimulating hormone in women in menopausal age as per current guidelines.

Imaging Follow-Up
Magnetic resonance imaging was routinely completed at 3 months after initial surgery or CK treatment and thereafter at yearly intervals. Significant change in tumor size was defined as increase or decrease in greatest diameter by $>25\%$.

Statistical Analysis
Study data were collected and managed using REDcap (Research Electronic Data Capture) tools hosted at Stanford University.[18] Data were expressed as mean (SD). Means were compared using an unpaired Student t test and single-variable linear regression when data had a normal distribution and Wilcoxon-Mann-Whitney tests when data were nonnormal in distribution. Categorical data were analyzed using Fisher exact tests, and continuous nonnormal data were analyzed using Kruskal-Wallis tests. Single-variable logistic regression was used. We did not complete multiple variable regression owing to the small sample size. $P < 0.05$ was considered statistically significant. Analysis was performed with GraphPad Prism Version 6.7 (GraphPad Software, Inc., La Jolla, California, USA). Survival curves were performed with R Version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria) using the survival package.[19]

RESULTS

Patients
Inclusion criteria were met by 7 patients (2 men and 5 women) with active CD. Age range was 18−67 years (median 35.2 ± 18.7 years) (Table 1). At diagnosis, in addition to typical signs and symptoms of CD, 2 patients (28.5%) presented with visual impairment, and 4 patients (57.1%) presented with headaches. No patients presented with diabetes insipidus. Radiologic evaluation at diagnosis showed an intrasellar location of the tumor in 1 (14.2%) patient, suprasellar extension in 2 (28.6%) patients, and extension into the sinus cavernosus in 5 patients (71.4%). The tumor contacted the optic chiasm in 2 patients (28.6%) and abutted the anterior cerebral artery in 1 patient (14.2%).

After achievement of eucortisolism following transsphenoidal surgery, 2 patients (28.5%) experienced recurrence of CD after 5 and

Patient	Age (Years)/Sex	Recurrence After Surgery or Residual	Time from Surgery to CK (Months)	Hypopituitarism Before CK	Maximum Adenoma Dimension (mm)	Target Volume (cm³)	Fractions	Prescribed Dose (Gy)	BED (Gy)	OC Dmax (Gy)	Brainstem Dmax (Gy)	Hypopituitarism After CK	Follow-Up (Months)	Outcome
1	67/F	RCD	85	—	9	0.44	1	22	143	3.8	9.2	—	26.7	Active disease
2	26/M	R	14	G + T	20	6.40	5	30	75	24	15.6	G + T + GHD	149.5	Remission
3	32/F	R	63	G + T + GHD	11	0.27	1	25	181	0	0	G + T + GHD	10.3	Active disease
4	33/F	R	2	—	32	9.25	5	35.5	96	28.5	24.3	—	9.9	Remission
5	18/M	RCD	3*	GHD	8	0.50	1	25	181	6.1	8	GHD	35.7	Remission
6	27/F	R	3	—	7	1.18	1	25	181	4.5	7	T	54.0	Remission
7	18/F	R	15	—	9	1.45	3	21	75	8.6	0	—	101.6	Active disease

Table 1. Patient Characteristics

CK, CyberKnife; BED, biologically effective dose; OC, optic chiasm; Dmax, maximum dosage; F, female; RCD, recurrent Cushing disease after initial remission; M, male; R, residual tumor after surgery; G, hypogonadism; T, hypothyroidism; GHD, growth hormone deficiency.
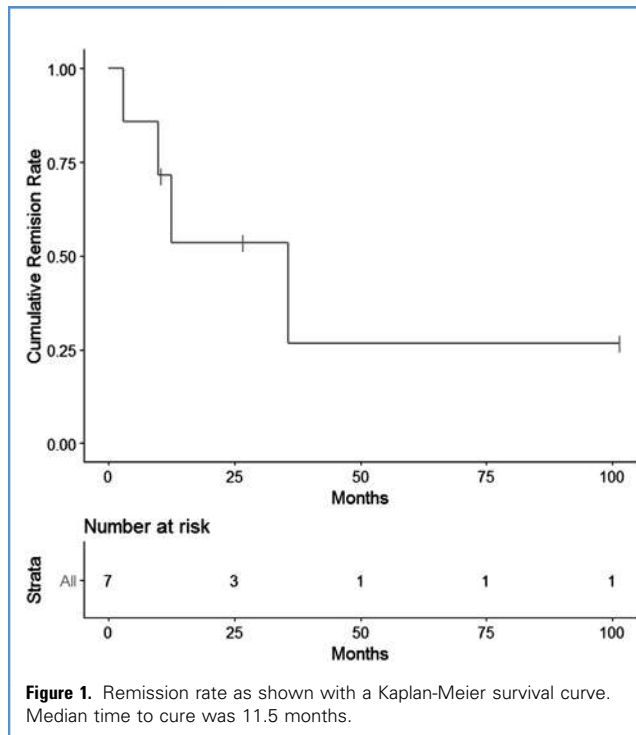*After second pituitary surgery.

Figure 1. Remission rate as shown with a Kaplan-Meier survival curve. Median time to cure was 11.5 months.

7 years, respectively. The remaining 5 patients (71.5%) underwent CK owing to residual disease after initial transsphenoidal surgery. Among them, 1 patient underwent 2 additional surgeries but had persistent hypercortisolism. Pituitary hormone deficiency was identified in 3 patients (42.8%) after surgery (Table 1). In 2 patients (28.5%), medical therapy was initiated (ketoconazole) before CK. Radiologic evaluation before CK showed sinus intercavernosus extension in all 7 patients (100%). The tumor abutted the optic chiasm in 1 patient (14.2%) and the anterior cerebral artery in the same patient (14.2%). No patients had prior conventional external-beam radiation therapy or prior radiosurgery.

CK Characteristics

The median maximal diameter of tumors before CK treatment was 9 mm (range, 7–32 mm) with an average target volume of 1.18 cm³ (range, 0.27–3.4 cm³). The median number of fractions delivered was 1; 4 patients received 1 fraction. Two patients received 5 fractions, and 1 patient received 3 fractions (Table 1). The average BED was 131 (53.9) Gy (median 143 Gy), and the average 2 Gy equivalent dose was 87.2 (35.9) Gy (median 95.3 Gy). The median prescribed treatment dose was 25 Gy (range, 21–35.5 Gy). The median Dmax to the optic chiasm was 6.1 Gy (range, 0–28.5 Gy). The median Dmax for the left and right eye was 4.2 Gy (range, 0–24.5) and 9.2 Gy (range, 3.8–25 Gy), respectively, and the median Dmax for the brainstem was 9.2 Gy (range, 0–24.3 Gy).

Biochemical Follow-Up

The average duration of follow-up after CK was 55.4 (52.1) months (median 35.7 months; range, 9–159 months). Two

Table 2. Comparison with Previous Studies

	Sheenan et al., 2013[31]	Grant et al., 2014[30]	Wilson et al., 2014[33]	Present Study
SRS	**GK**	**GK**	**LINAC**	**CK**
Number of cases	96	15	36	7
Prior surgery	94 (98)	NA	36 (100)	7 (100)
Prior RT	6 (6.2)	NA	0	0
Tumor location				
Sinus intercavernosus	41 (43)	NA	12 (33)	7 (100)
Suprasellar component	19 (20)	NA	6 (17)	2 (28.6)
Chiasmal involvement	NA	NA	1 (3)	1 (14.2)
ACA involvement	NA	NA	NA	1 (14.2)
Target volume, cm^3, mean (range)	1.8 (0.2—12.4)	5.69 (7.21)*	0.7 (0.19—13.5)	1.18 (0.27—3.4)
Prescribed dose, Gy, mean (range)	22 (3—30)†	35 (14.4—87.7)†	20 (17—25)	25 (21—35.5)
Fractions				
1	NA	NA	36 (100)	4 (57.1)
2	NA	NA	NA	0
3	NA	NA	NA	1 (14.2)
5	NA	NA	NA	2 (28.5)
BED, Gy	NA	NA	NA	130.8 (53.9)
Equivalent dose, 2 Gy	NA	NA	NA	87.2 (35.9)
Follow-up, months, median (range)	48 (12—209.8)	40	NA	55.4 (9—159)
Visual deterioration	5 (5.2)	0 (0)	NA	0
Tumor control	94 (98)	15 (100)	30 (83)	7 (100)
Hypopituitarism	35 (36)	6 (40)	NA	1 (14.2)
Remission criteria	24-hour UFC and morning serum cortisol level in normal range	24-hour UFC in normal range or hypoadrenalism	24-hour UFC ≤276 nmol/L or morning serum cortisol ≤140 mmol/L	24-hour UFC and/or normal response to overnight 1-mg dexamethasone test without requirement of GC replacement or hypoadrenalism
Biochemical remission	67 (70)	11 (73)	22.2/5.6 (UFC/serum)	4 (57.1)
Time to remission, months, median (range)	16.6 (1—165.7)	11.7 (4.4—19.1)	27	18.5 (9—35)
Recurrence	NA	4 (26.6)	NA	0

Data are expressed number (percentage) or mean (range).

SRS, stereotactic radiosurgery; GK, GammaKnife; LINAC, linear accelerator; CK, CyberKnife; NA, not applicable; RT, radiotherapy; ACA, anterior cerebral artery; BED, biologically effective dose; UFC, free urine cortisol excretion; GC, glucocorticoid.

*SD.

†Mean marginal dose.

patients were followed for <2 years. The median time between surgery and CK was 14 (33.5) months (range, 3—85 months). The median time to remission was 12.5 months with a biochemical remission rate approaching 78% at 5 years (**Figure 1**). At last follow-up, there was resolution of CD in 4 patients (57.1%); 2 patients achieved normalization of cortisol levels without the requirement of glucocorticoid replacement, and the remaining 2 patients achieved hypoadrenalism (28.5%). Three patients had persistent active disease after CK at last

follow-up. In patients with <14 months between surgery and CK, there was a significantly improved biochemical remission rate (P = 0.02). All 4 patients treated with CK <14 months after surgery achieved remission of CD. One patient (14.2%) with multiple pituitary deficits developed an additional deficit after CK. Only 1 patient (14.2%) with normal pituitary function at baseline developed a new deficit, hypothyroidism, at last follow-up. All the other patients with preexistent pituitary deficits remained stable.

Radiologic Follow-Up

At final radiologic follow-up, local control was 100%, with no growth of any of the tumors. No patients experienced visual deterioration after CK, and all patients had a stable modified Rankin Scale score compared with pretreatment. All data are shown in **Table 1**. No significant differences in biochemical response were observed among patients differing with respect to sex, age, tumor dimension, BED, presence of pituitary deficit, use of medical therapy with ketoconazole before CK, or previous normalization of hypothalamic-pituitary-adrenal axis after surgery.

DISCUSSION

In the treatment guidelines for CD, SRS is recommended as a therapeutic option for patients who have failed surgery and/or medical therapy.[5] In our initial cohort of patients with CD, we found that CK resulted in biochemical remission in 78% at 5 years in patients who had persistent histologically confirmed CD following initial surgery. This study shows the value of CK as an adjunct treatment in such patients. Only 1 other study has reported the results of CK in 2 patients with CD.[20] In this study, an 11-year-old girl was treated for CD (no further biochemical data were reported) with a prescribed dose of 27 Gy delivered in 3 fractions to a tumor volume of 0.20 cm³, resulting in local control with follow-up of 50 months but with panhypopituitarism. The second patient, a 63-year-old woman, was treated with 25.3 Gy in 3 fractions to a tumor volume of 0.69 cm³ and still had active disease after 27 months. In this patient, no side effects, such as hypopituitarism or visual deterioration, were noted.[20] Comparing this study with ours would not be meaningful, given the small sample and the presence of 1 pediatric patient.

The use of GK SRS in CD has been studied in greater detail, with 14 studies comprising 429 patients.[11-13,21-31] These studies, recently summarized by Minniti et al.,[32] report a wide range of rates of biochemical control of 17%–87%.[10,11] Similarly, the incidence of significant side effects varied across studies: hypopituitarism ranged from 0%[10] to 66%,[12] and visual field loss ranged from 0%[12] to 5.5%.[25] Several factors may explain the variable response rates to GK SRS in patients with CD. The use of different criteria to define biochemical remission, study attrition rates, variation in surgical and medical therapy before SRS, SRS dose, selection bias, and different follow-up durations (range, 6–180 months) may contribute to the different findings.[11-13,21-31,33] Outcome data for the most recently published GK SRS studies are summarized and compared with the present study in **Table 2**. The largest series of the group[31] reported the results of 96 patients treated with GK SRS and showed tumor control and biochemical remission rates of 98% and 70%, respectively, with a mean time to normalization of 16.6 months. These numbers are comparable to values from our study (mean time to normalization of 12.5 months). New or worsened hypopituitarism occurred in 36% of patients, and progressive or new cranial neuropathy occurred in 5.2% of patients, with a median follow-up of 48 months. Our study suggests that CK is comparable to GK SRS for treatment of CD in terms of biochemical control, timing to control, and tumor control after a similar duration of follow-up. We had a favorable incidence of hypopituitarism (14.2%) with no visual defects. However, any conclusions should be drawn with caution owing to the small size of the cohort. Grant et al.,[30] in a small study of patients with a larger tumor volume and higher radiation dosage, did not find a change in biochemical remission but did note a greater risk of complications (hypopituitarism) (**Table 2**).

We report an intriguing finding related to timing of CK after surgery. A time interval of <14 months between surgery and CK was associated with a significantly greater remission rate (P = 0.02). The reason for this finding is unclear. Confirming such a finding in a larger study would be useful to guide clinical practice following persistent CD after surgery.

The study has the limitations inherent in the retrospective observational cohort design. Although this is the largest report on the outcome of patients with CD treated with CK, the sample size remains small, and thus significant findings must be interpreted with caution and confirmed in larger studies. However, given the rarity of the condition, clinical practice is likely to be guided by small reports for the foreseeable future.

CONCLUSIONS

We described the efficacy and complication profile of CK in the treatment of CD. Our study suggests that CK is a safe and effective treatment for CD, allowing excellent local control and remission of the disease in more than half of patients. The shorter time between surgery and CK appears to result in a higher rate of remission. In this small cohort of patients, biochemical control was achieved without visual complications and only rarely new pituitary deficiency.

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