CyberKnife Radiosurgery in the Multimodal Management of Patients with Cushing’s Disease
(Poster ID 41733)

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I acknowledge my continuing obligation to disclose to AANS/NREF/NPA, promptly and in writing, any change in my circumstances.

I further acknowledge that if there is any case where my private interest conflict with the interests of AANS/NREF/NPA, I will indicate that I may have a conflict and abstain from any vote, speaking engagement, planning related to that issue.
METHODS

Patients
Following Institutional Review Board (IRB) approval, a retrospective review of all patients with pituitary adenomas who underwent CK treatment between 2000 and 2016 at SHC was performed. The manuscript conforms to the Strengthening the reporting of observation studies in Epidemiology (STROBE) guidelines. Patients met the study inclusion criteria if they had a histological 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. Following surgery, evidence of recurrence of residual pituitary adenoma was found in all patients by a dedicated pituitary magnetic resonance imaging (MRI) protocol with and without contrast enhancement.
METHODS

Statistical analysis

Study data were collected and managed using Redcap electronic data capture tools hosted at Stanford University. Data were expressed as mean ± standard deviation (SD). Means were compared using an unpaired Student’s t-test and single-variable linear regression when data had a normal distribution and Wilcoxon-Mann-Whitney tests when the data was non-normal in distribution. Categorical data was analyzed using Fisher’s exact tests, and continuous non-normal data was analyzed using Kruskal-Wallis tests. Single-variable logistic regression was used. We did not complete multiple variable regression due to the small sample size. Values of p < 0.05 were considered statistically significant. Analysis was performed with GraphPad Prism statistics software (version 6.7 GraphPad Software, Inc., USA). Survival curves were performed with R statistic software (version 3.4.1) using the survival package.
RESULTS

After achievement of eucortisolism after transsphenoidal surgery, two subjects (28.5%) experienced recurrence of CD after 5 and 7 years respectively. The remaining five patients (71.5%) underwent CK secondary to residual disease after initial transsphenoidal surgery. Among them, one patient underwent two additional surgeries, but had persistent hypercortisolism. A pituitary hormone deficit was identified in three patients (42.8%) following surgery. In two patients (28.5%) medical therapy was initiated (ketoconazole) prior to CK. Radiological evaluation before CK showed intracavernous sinus extension in all seven patients (100%). The tumor abutted the optic chiasm in one patient (14.2%) and in this patient also the anterior cerebral artery (14.2%). No patients had prior conventional external beam radiation therapy, or prior radiosurgery.

<table>
<thead>
<tr>
<th>Gender</th>
<th>value</th>
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</tr>
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<tbody>
<tr>
<td>Male</td>
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<td></td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

| Age (years) | 35.2 ± 18.7 | (18-67) |

<table>
<thead>
<tr>
<th>Tumor Characteristics at Diagnosis</th>
<th>value</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Intrasellar</td>
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<td>14.2%</td>
</tr>
<tr>
<td>Suprasellar</td>
<td>2</td>
<td>28.6%</td>
</tr>
<tr>
<td>Intracavernous</td>
<td>5</td>
<td>71.4%</td>
</tr>
<tr>
<td>Optic chiasm compression</td>
<td>2</td>
<td>45.40%</td>
</tr>
<tr>
<td>Anterior artery compression</td>
<td>1</td>
<td>9%</td>
</tr>
</tbody>
</table>

Table A. At diagnosis, in addition to typical signs and symptoms of CD, two patients (28.5%) presented visual impairment, and four patients (57.1%) headaches. None of them presented with diabetes insipidus.
**CK characteristics**

The tumors median maximal diameter prior to CK treatment was 9 mm (7- 32 mm) with an average target volume of 1.18 cm$^3$ (0.27- 3.4 cm$^3$). The median number of fractions delivered was 1, which occurred in 4 patients. Two patients were treated with 5 fractions and 1 patient received 3 fractions (Table 1). The average BED was 131 Gy (±53.9, median 143 Gy) and the average EQD2 was 87.2 Gy (±35.9, median 95.3 Gy).

The median prescribed treatment dose was 25 Gy (21-35.5 Gy). The median Dmax to the optic chiasm was 6.1 (0-28.5). The median Dmax for the left and right eye was 4.2 (0-24.5) and 9.2 (3.8 - 25) respectively, while the median Dmax for the brainstem was 9.2 (0-24.3).
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 patients were followed for less than two 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. At last follow up, there was resolution of CD in four patients (57.1%): among them, two patients achieved normalization of cortisol levels without the requirement of glucocorticoid replacement and the remaining two patients achieved hypoadrenalism (28.5%). Three patients had persistent, active disease following CK administration at last follow up. In subjects with less than 14 months between surgery and CK, there was a significantly improved biochemical remission rate (p=0.02). All four patients treated with CK less than 14 months after surgery achieved remission of CD. One patient with multiple pituitary deficits (14.2%) developed an additional deficit following CK. Only one patients with normal pituitary function at baseline developed a new deficit, hypothyroidism, at last follow up (14.2%). All the other patients with preexistent pituitary deficits remained stable.
Radiological Follow up

At final radiological follow up, local control was 100%. No patients suffered visual deterioration following CK and all patients had stable mRS when compared to pretreatment. All data are shown in Table 1. No significant differences in biochemical response were observed among patients differing with respect to gender, age, tumor dimension, BED, presence of pituitary deficit, use of medical therapy with ketoconazole before CK or previous normalization of HPA 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. In our initial cohort of patient 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 a adjunct treatment in such patients.

Only one other study has reported the results of CK in two patients with CD. [20] In this study an 11-year-old girl was treated for CD (no further biochemical data was reported) with a prescribed dose of 27 Gy delivered in 3 fractions to a tumor volume of 0.20 cm³, resulting in local control at a follow up of 50 months, but with panhypopituitarism. The second patient, a 63 years old female, 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. Comparing this study to ours would not be meaningful, given small sample and the presence of one pediatric patient.
The use of GK SRS has been studied in greater detail in CD, with 14 studies, including a total of 429 patients. These studies, recently summarized by Minniti et al., report rates of biochemical control ranging widely from 17% to 87%. Similarly, the incidence of significant side effects varied across studies: hypopituitarism ranged from 0% to 66% and visual field loss ranged from 0% to 5.5%. Several factors may explain the variable response rates to GK SRS in CD patients. The use of different criteria to define biochemical remission, study attrition rates, variation in surgical and medical therapy prior to SRS, SRS dose, selection bias and different durations of follow up (6 to 180 months) may contribute to the different findings. The largest series of the group reports 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 with those from our study (mean time to normalization 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 time follow up of 48 months. Our study suggests that CK is comparable to GK SRS for the treatment of CD in terms of biochemical control, timing to control, and tumor control after a similar duration of follow up.
We report an intriguing finding relating to timing of CK after surgery. A time interval of less than 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 in order to guide clinical practice following persistent CD after surgery. Use of ketoconazole therapy in one subject of our cohort did not affect the remission rate, which contrasts with was findings reported by Sheenan et al.

**Limitations**

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

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 the patients. The shorter time between surgery and CK appears to result in a higher rate of remission. In this small cohort of subjects, biochemical control was achieved without visual complications and only rare new pituitary deficit.