Fractionated CyberKnife Stereotactic Radiotherapy for Perioptic Pituitary Adenomas

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OBJECTIVE: **Stereotactic radiosurgery (SRS) is the reference standard for radiotherapy for pituitary adenomas but has been limited to lesions with sufficient distance (i.e., >3 mm) from the optic apparatus. We used marginless, fractionated (i.e., 25–28 fractions) stereotactic radiotherapy and the CyberKnife to treat pituitary adenomas that were not eligible for SRS. We present the clinical outcomes, including local control, endocrine function, and toxicity from modern fractionated radiotherapy.**

METHODS: **A total of 53 patients were treated for pituitary adenomas within 3 mm of the optic apparatus. The primary endpoint was tumor control with the secondary endpoints of vision and pituitary function preservation and endocrine control in hormone-secreting tumors.**

RESULTS: **The tumor control rate as measured on magnetic resonance imaging as either stable or decreased in size was 98.1% (52 of 53) at a mean follow-up of 32.5 months (range, 3–77). All patients experienced preservation or improvement of their preexisting vision status. No change in pituitary function was noted in 52 of the 53 patients (98.1%). One patient experienced worsening of pituitary function secondary to pituitary apoplexy that occurred 4 months after treatment. The endocrine control rate in hormone-secreting tumors was 75% (6 of 8).**

CONCLUSIONS: **Marginless, fractionated CyberKnife radiotherapy demonstrated excellent local tumor control and endocrine control rates, comparable to those with SRS, with preservation of vision in patients with adenomas in close proximity to the optic pathway.**

INTRODUCTION

Pituitary adenomas comprise 10.5%–20% of intracranial tumors and can be hormonally active or nonsecreting "null cell" adenomas.[1] The nonsecreting adenomas comprise ~30% of all adenomas.[1] As the lesion progresses, patients can present with pituitary hormonal dysfunction, symptoms of hormone excess, or visual disturbance secondary to compression of the optic apparatus.

The standard treatment has been surgical extirpation, which can often be curative. However, complete resection will not always be feasible. Recurrence after surgery has been reported in 24%–80%, with greater rates in hormonally active tumors and more aggressive subtypes (i.e., null cell subtype III).[2,3] The most common anatomic locations for recurrence have been within the cavernous sinus and along the optic apparatus.

Radiotherapy represents an option for inoperable or recurrent pituitary adenomas. Multiple radiotherapy modalities are available for the treatment of pituitary adenomas, including single fraction stereotactic radiosurgery (SRS), often delivered via the Gamma Knife (Elekta, Stockholm, Sweden), or fractionated radiotherapy delivered with traditional linear accelerators or specialized treatment devices such as the CyberKnife (Accuray Inc., Sunnyvale, California, USA). The choice of treatment modality has often been defined by the proximity of the tumor to the optic pathway and by whether SRS can be performed without significant risk of optic nerve injury. For tumors encasing or in close proximity to the optic pathway, fractionated radiotherapy uses the advantage of the disparate biology of neoplastic and normal tissue. It has typically been delivered in 25–30 fractions to a dose of 45–50.4 Gy.[4-6] Traditional linear accelerators will have intra- and interfraction uncertainty that necessitates a planning target volume (PTV) expansion, which will increase the treatment volume, delivering a dose to a larger component of the optic pathway and brain.[5,7]

The CyberKnife system is a frameless linear accelerator-based radiosurgical technology attached to a robot arm with kV imag-

Key words
- CyberKnife
- Fractionated
- Perioptic
- Pituitary adenoma
- Stereotactic radiosurgery

Abbreviations and Acronyms
ACTH: Adrenocorticotropic hormone
CI: Conformity index
GTV: Gross tumor volume
MRI: Magnetic resonance imaging
PTV: Planning target volume

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ing used to assess intrafraction patient motion. It delivers a conformal radiation dose with a steep dose dropoff similar to that of the Gamma Knife (Elekta).[8-10]

At our institution, we have used the CyberKnife for treatment of perioptic pituitary adenomas to the tumor alone without a PTV margin, similar to SRS. In the present series, we report the retrospective results of a marginless approach for recurrent and residual pituitary adenomas.

METHODS

Study Design, Setting, and Participants

We performed a retrospective review of prospectively collected data from 53 patients with pituitary adenomas who had undergone traditional fractionated CyberKnife radiotherapy at our institution from June 2008 to January 2018. All clinical information was collected within the guidelines approved by the institutional review board.

Variables

All patients treated with the fractionated CyberKnife scheme had had tumors within 3 mm of the optic apparatus as measured on magnetic resonance imaging (MRI). The primary endpoint was local tumor control. The secondary endpoints of vision preservation, worsening of pituitary function, and hormone control in the hormonally active lesions were assessed.

The treatment parameters assessed included treatment isodose line, tumor coverage, and maximum radiation dose to the optic apparatus. The conformity index (CI) is the ratio of the treatment volume to the target volume.

Data Sources and Measurements

Tumor control was assessed by an independent radiologist at 3 months and 1 year after treatment, followed by annual follow-up examinations thereafter. The tumor response to treatment was grouped into 3 possible outcomes: stable, decreased, and increased in size.

All patients underwent formal ophthalmologic evaluation using the Humphrey Visual Fields examination before treatment and annually after treatment. Endocrine function was assessed by an independent endocrinologist with annual follow-up examinations and assessment of the pituitary axis. Clinical follow-up examinations were performed at 3 months and 1 year after treatment and annually thereafter. All variables were recorded in the Epic electronic medical record system (Epic Systems, Verona, Wisconsin, USA) and retrospectively reviewed.

The gross tumor volume (GTV), CI, new CI, isodose line, tumor coverage, and maximum radiation dose to the optic apparatus were calculated using Accuray software (Accuray, Inc.).

Stereotactic Fractionated Radiotherapy

Each patient underwent fractionated CyberKnife radiotherapy (Accuray Inc.).[11] All the patients had undergone computed tomography simulation with a thermoplastic mask and mold-care cushion with and without intravenous contrast, with 1-mm slice thickness acquisition. This was registered with the diagnostic MRI scan, specifically the T1-weighted, contrast-enhanced fat-saturated and T2-weighted sequences, for target delineation. The gross tumor volume (GTV) was equal to the PTV and was determined from MRI scan and contrast-enhanced computed tomography scan. An inverse planning method was used to create each treatment plan. The CI and new CI were calculated for each treatment plan. The total dose to the optic chiasm was measured for each patient.

Study Size and Bias

The present study included consecutive patients who had been evaluated at our institution, had received this treatment paradigm, and who had met the inclusion criteria ($n = 53$). Although we performed a retrospective review of previously treated patients, the data had been collected prospectively to minimize misclassification and information bias and to better control the exposure and outcome assessment variables.

Statistical Analysis

The data were entered into an electronic spreadsheet (msExel [Microsoft, Redmond, Washington, USA]) and uploaded for analysis. The frequencies and percentages were used to describe all categorical variables. For patients with hormone-secreting tumors, if the post-treatment target hormone levels were not available, the patient was excluded from that analysis but was included in the tumor control analysis.

RESULTS

Participants

At treatment, the mean patient age was 55.4 years (range, 28–83). Of the 53 patients, 28 were women and 25 were men. Of the 53 patients, 51 (96.2%) had undergone previous surgical resection. The 2 patients who had not undergone previous surgical resection had had multiple medical comorbidities and were deemed poor surgical candidates. Both patients had nonfunctional adenomas and received the treatment paradigm as their primary treatment. Three patients had undergone previous stereotactic radiosurgery with the Gamma Knife (Elekta).

Of the 53 patients, 12 had hormonally active tumors: 5 with adrenocorticotropic hormone (ACTH)-secreting, 2 with prolactinoma, 3 with growth hormone-secreting, and 2 with gonadotroph-secreting tumors. The remaining 41 patients had nonfunctional adenomas, of which 6 were silent subtype III, a newly reported more aggressive tumor subtype.[12] Thirty-nine patients (95.1%) with nonfunctional adenomas had undergone previous resection and had radiologic tumor progression found on follow-up imaging studies.

Stereotactic Fractionated Radiotherapy

Of the 53 patients, 51 had received 25 fractions and 2 had received 28 fractions to a mean total dose of 46.7 Gy (range, 45–50.4). The mean isodose line was 74% (range, 54%–91%). The median GTV treated was 6.2 cm^3 (mean, 10; range, 0.2–68.6). The mean tumor coverage was 95.6% (range, 65.5%–100%). The mean CI was 1.30 (range, 1.07–1.83), and the mean new CI was 1.36 (range, 1.08–1.92). The mean total dose administered to the optic apparatus was 43.6 Gy (range, 18.4–56.2y). All tumors were within 3 mm of the optic apparatus. A summary of the patient data is provided in Table 1.

Table 1. Baseline and Treatment Characteristics of Patients Undergoing Fractionated CyberKnife Radiotherapy for Perioptic Pituitary Adenomas

Characteristic	Value
Sex	
Male	25 (47.1)
Female	28 (52.9)
Age (years)	
Mean	55.4
Range	28–83
Follow-up (months)	
Mean	32.5
Range	3–77
Previous surgery	51 (96.2)
Previous radiation	3 (5.6)
Tumor type	
Nonsecreting	41 (77.4)
ACTH	5 (9.4)
Prolactin	2 (3.8)
Growth hormone	3 (5.6)
Gonadotroph	2 (3.8)
Pretreatment visual deficit	22 (41.5)
Pretreatment pituitary dysfunction	14 (26.4)
Gross tumor volume (cm^3)	
Mean	10.0
Range	0.2–68.6
Prescribed dose (Gy)	
Mean	46.7
Range	45–50.4
Percentage of prescribed dose	
Mean	74
Range	54–91
Fractions	
25	51 (96.2)
28	2 (3.8)
Conformity index	
Mean	1.30
Range	1.07–1.83
New conformity index	
Mean	1.36
Range	1.08–1.92
Coverage (%)	
Mean	95.6
Range	65.5–100
Maximum dose to optic apparatus (Gy)	
Mean	43.6
Range	18.4–56.2

ACTH, adrenocorticotropic hormone.

Tumor Control

The tumor control rate as measured on MRI as either stable or decreased in size was 98.1% (52 of 53) at a mean follow-up of 33.3 months (range, 3–77; Figure 1). One patient with a prolactinoma experienced tumor progression at 31 months after treatment and received temozolomide. At the last follow-up examination, the tumor had stabilized.

Vision Outcome

Before treatment, 25 of the 53 patients (41.5%) had a documented visual deficit found on visual field examination by an ophthalmologist. At the mean follow-up point, all the patients had experienced preservation of their preexisting vision status, and 2 patients had reported improvement in their vision, based on a repeat formal visual field examination by an ophthalmologist. No patient had worsening of vision.

Endocrine Outcome

Fourteen patients (26.4%) had preexisting pituitary dysfunction before undergoing radiotherapy. At the mean follow-up point, no change in pituitary function was noted in 98.1% of the patients (52 of 53). One patient experienced worsening of pituitary function secondary to pituitary apoplexy that occurred 4 months after treatment.

Twelve patients had hormonally active tumors, of whom 8 had undergone serial measurements of the target hormone. Of these 8 patients, 6 (75%) had experienced endocrine control of the target hormone (4 of 4 ACTH-secreting, 1 of 2 growth hormone secreting, and 1 of 2 prolactinomas). Endocrine control was determined for ACTH-secreting tumors by normalization of the 8:00 AM cortisol or normal ACTH level, and for the growth hormone-secreting tumors, by an insulin-like growth factor 1 level at or below the age-adjusted normal. For the prolactinomas, endocrine control was determined by the normalization of prolactin levels. The mean interval to endocrine control was 31 months (range, 3–65).

Complications

One patient experienced an apoplectic event at 4 months after radiotherapy. He had not undergone previous surgery and had had normal pituitary function before treatment. His vision remained stable, but he required anterior pituitary supplementation thereafter.

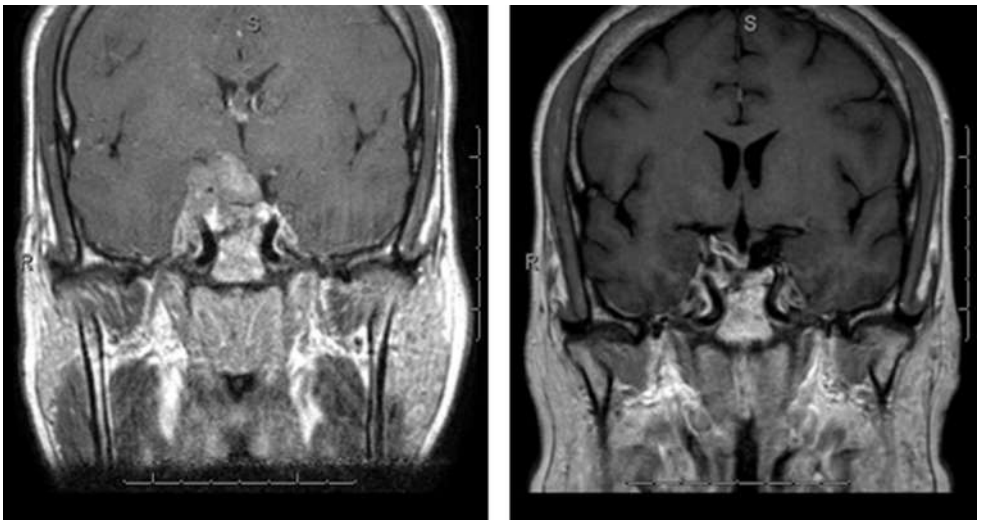

Figure 1. Residual perioptic pituitary adenoma. T1-weighted magnetic resonance image with gadolinium contrast. (**Left**) Pretreatment magnetic resonance image demonstrating residual tumor involving the right cavernous sinus and displacing the optic apparatus superiorly. (**Right**) Magnetic resonance image 6 years after treatment showing a significant decrease in tumor volume and decompression of the optic apparatus.

DISCUSSION

The primary treatment for pituitary adenomas has been surgical resection through either a transsphenoidal or transcranial approach. These tumors recur at a rate of 24%–80% after surgical resection, and the second-line therapy is radiotherapy.[2,3]

The use of stereotactic radiosurgery has been the reference standard and allows for a high-dose of conformal radiation to be delivered to the mass with a steep dose drop-off and relative sparing of surrounding tissue. The use of the Gamma Knife (Elekta) has been well established with ≤10 years of reported follow-up data available.[2,3,7,13-17] A single-fraction modality, such as the Gamma Knife (Elekta), is limited, however, within 2–3 mm of the optic apparatus, which has a single fraction dose tolerance of 8–10 Gy (fractionated dose tolerance, 55–60 Gy).[6,7,9,18-20]

Fractionated radiotherapy takes advantage of the therapeutic ratio between the tumor and normal tissue. In the past 2 decades, the CyberKnife (Accuray Inc.) has been used for the treatment of pituitary adenomas because it provides a similar dose distribution to the Gamma Knife (Elekta) and has the advantage of not requiring a stereotactic frame. Thus, it is amenable to fractionation.[8,9,21-23] Because of its evaluation of patient inter- and intrafraction positioning, we have been treating patients without a traditional PTV margin, limiting the treatment volume to the tumor alone, which might lower the risk of post-treatment complications and long-term radiation-induced neoplasia that can occur with fractionated CyberKnife (Accuray Inc.) treatment.[24]

Single-fraction treatment with the Gamma Knife (Elekta) has resulted in local tumor control rates of 93%–100% at ≤10 years of follow-up.[2,3,13,14,25] In contrast, the single-fraction treatment scheme has been associated with a 6%–30.3% rate of worsening of pituitary function and a 3%–9% rate of vision decline.[2,3,13,14,25] In particular, these rates have been greater for larger tumors, with 1 series by Starke et al.[14] demonstrating that tumors with a GTV >5 cm^3 have been associated with a greater likelihood of tumor growth.

Traditional fractionated radiotherapy has had a local tumor control rate similar to that with Gamma Knife surgery (Elekta) at 83%–100%.[4,5,16,17,26,27] The rate of worsening of pituitary function has been 18%–40%.[4,5,16,17,26,27] The relatively high rate of pituitary dysfunction was likely secondary to the 2-mm margin of error necessary for this paradigm, which increases the risk to the surrounding structures.

Recently, hypofractionation schemes (i.e., 3–5 fractions to a total dose of 20–25 Gy) have been used with CyberKnife (Accuray Inc.) for the treatment of perioptic lesions. Killory et al.[9] first described a small series of 20 patients with perioptic pituitary adenomas treated with hypofractionated CyberKnife (Accuray Inc.) with good vision preservation (100%). Since then, numerous studies have been reported of hypofractionated CyberKnife (Accuray Inc.) schemes with comparable results to those with the Gamma Knife (Elekta) and fractionated radiotherapy with respect to local control (90%–100%) and vision preservation (91%–100%).[8,9,23,24,28,29]

The marginless fractionated CyberKnife (Accuray Inc.) treatment plan used in our series demonstrated a tumor control rate similar to that of the Gamma Knife (Elekta) at 98.1% at a mean follow-up of 30.6 months. The rate of complications was much lower, however, with only a single patient experiencing worsening of pituitary function, and no patients experiencing a decline in vision. One difference was the GTV treated (6.2 cm^3), which was larger than the volume of adenomas previously reported to have the greatest risk of recurrence and complications with single-

fraction treatment.[14] Our proposed treatment scheme allows for successful local control of large adenomas and can contour the dose to the margins of the tumor and spare the nearby optic apparatus.

Functional adenomas are more difficult to treat and require a higher dose (25–30 Gy vs. 15–18 Gy for nonfunctional adenomas).[2,15] These lesions are notoriously difficult to treat with radiotherapy when the goal is hormone control. Gamma Knife (Elekta) treatment has a reported hormone control rate of 25%–82%, with the typical interval to hormone normalization ~24 months.[3,13-15] The limited data for hypofractionated CyberKnife treatment showed a hormone control rate of 40%–54%.[9,24,30] Minniti et al.[19] suggested a hormone control benefit results from a single-fraction, high dose of radiation delivered to the functional adenomas, such as seen with the Gamma Knife (Elekta).[26] Our series has demonstrated a hormone control rate on the high end of the spectrum near that of Gamma Knife (Elekta) dosing,[3,13-15] albeit with limited follow-up. It will be important to determine the durability of hormone control. This suggests that a higher total dose delivered in a fractionated manner to the tumor, in contrast to a hypofractionated scheme, might be of benefit for cases in which the tumor is adjacent to the optic apparatus and, therefore, a poor single-fraction candidate. Additional follow-up and a greater number of patients are necessary for confirmation.

It could be contended that the follow-up in the present study was not long enough to detect complications such as vision decline, and, thus, we did not detect future vision decline in our follow-up interval. However, Adler et al.[8] reported the results for 3500 patients who had undergone radiotherapy for perioptic masses. They found that all vision decline had occurred within the first 24 months after treatment.[8] Thus, it would be expected that any vision decline in our series would have been detected early after fractionated treatment. It is possible that the length of follow-up in the present series was not long enough to detect hypopituitarism. Traditional external beam radiotherapy and stereotactic radiotherapy and radiosurgery have been associated with a rate of hypopituitarism of 30%–100% and 30%–70% at 10 years, respectively.[31] As the follow-up period increases, we would expect the rate of hypopituitarism to increase as a result of treatment. Given the conformality of the dosing and the tissue benefits of fractionation, we would expect the rate to be comparable to that with radiosurgical techniques.

Study Limitations

The present study had limitations inherent to retrospective studies, including selection bias for patients who would likely benefit from fractionated radiotherapy, the lack of long-term follow-up beyond 3 years for all patients, and information bias from tumor volume assessment on MRI. Our study was also a single-institution study and the findings might not be generalizable to all populations.

Future Directions

Our study has demonstrated favorable outcomes with traditional fractionation of stereotactic radiotherapy for perioptic pituitary adenomas. An increase in the number of patients, longer follow-up, and multi-institutional cooperation are potential future directions.

CONCLUSION

Overall, a marginless fractionated stereotactic CyberKnife treatment scheme for perioptic pituitary adenomas demonstrated local tumor control comparable to that of reported Gamma Knife (Elekta) outcomes, with a lower rate of complications and greater rate of vision preservation. The results are similar to the reported hypofractionated schemes with the possible benefit of a greater rate of endocrine control in hormonally active tumors. The treated lesions in the present series were larger than those in other reported series. Fractionated CyberKnife (Elekta) radiotherapy is a safe, highly effective treatment paradigm and should be considered in the treatment of these challenging lesions.

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