Craniohypophyseal tumors are benign extraaxial epithelial tumors that arise from squamous epithelial remnants of the Rathke pouch, near the pituitary gland. These cells may extend from the nasopharynx to the tuber cinereum and may arise within the sphenoid bone, the sella, or the suprasellar region. Although craniopharyngiomas are rare, they are the most common suprasellar tumor in the pediatric age group, accounting for as many as 5% of all intracranial tumors or up to 10% of pediatric brain tumors. The incidence of craniopharyngioma has been estimated to be approximately 1.5 per million people per year, but may be considerably higher in specific ethnic groups, such as Japanese children (5.25 per million). Craniopharyngiomas have a bimodal age distribution, generally appearing in young patients between the ages of 5 and 14 years and in adults between 50 and 74 years.

Although they are histologically benign, craniopharyngiomas can cause severe and often permanent damage to nearby hypothalamic, visual, and endocrine apparatus. The presentation of these tumors may include symptoms related to endocrine derangement of the hypothalamic-pituitary axis, with severity dependent upon location, size, and rate of growth. Mass effect from hypothalamic-pituitary axis dysfunction may result in increased intracranial pressure presenting as headache, nausea, and vomiting. Cases with large mass lesions may also present with hydrocephalus (noted more commonly in children than in adults) as a result of the obstruction of the cerebral aqueduct or the interventricular foramina. Compression of the nearby optic chiasm typically results in VFDs such as hemianopia and papilledema. Endocrine disruption often manifests as amenorrhea, hypothyroidism, and diabetes insipidus.

The structural composition of these tumors may include solid, cystic, mixed solid and cystic, or calcified components. Traditionally, craniopharyngiomas have been separated into either the adamantinomatous or papillary variety. More commonly observed in the pediatric population, the adamantinomatous type is characterized as calcified with mixed composition. Papillary craniopharyngiomas observed in adults are often more solid. Current treatment strategies for craniopharyngiomas include cystic drainage, intracavity chemotherapy, limited resection or GTR, and radiation therapy. These strategies are often combined into a patient-specific treatment plan based on age at presentation, tumor size, relation to optic chiasm and third ventricle, presence of hydrocephalus.

The role of radiosurgery in the treatment of craniopharyngiomas

Anand Veeravagu, M.D.,1 Marco Lee, M.D., Ph.D., F.R.C.S.,1,2 Bowen Jiang, B.S.,3 and Steven D. Chang, M.D.1

1Department of Neurosurgery, Stanford University School of Medicine, Stanford, California; 2Department of Neurosurgery, Santa Clara Valley Medical Center, San Jose, California; 3Stanford University School of Medicine, Stanford, California

The treatment of craniopharyngiomas is composed of an intricate balance of multiple modalities. Resection and radiotherapy have been combined to synergistically control tumor growth while preventing undue harm to crucial neurovascular structures. Although a craniopharyngioma is a benign lesion pathologically, it may induce severe neurological injury due to its location and rate of growth. More recently, the advent of targeted, fractionated radiotherapy has allowed for more aggressive tumor control while reducing the necessity for large resections. Initial studies have demonstrated significant tumor control in patients who are treated with resection combined with radiation therapy, versus surgery alone, with a lower rate of treatment-associated neurological deficits. In this review, a detailed account of the current studies evaluating the role of stereotactic radiosurgery in the management of craniopharyngiomas is presented. The authors also provide a short account of their experience to aid in defining the role of CyberKnife radiosurgery. (DOI: 10.3171/2010.2.FOCUS09311)

Key Words • craniopharyngioma • radiosurgery • CyberKnife • Gamma Knife

Abbreviations used in this paper: BED = biologically equivalent dose; CGE = cobalt Gy equivalent; GK = Gamma Knife; GTR = gross-total resection; PFS = progression-free survival; SRS = stereotactic radiosurgery; STR = subtotal resection; VFD = visual field deficit.
lus, and degree of pituitary endocrinopathy. If total excision can be safely performed with minimal risk to these structures, then surgery remains the treatment of choice because it allows rapid decompression, minimizes recurrence, and provides a histological diagnosis. However, judgment of minimal risk is often unclear as some favor STR coupled with adjunctive therapy to achieve similar outcomes.\(^9,18,34,35,38,43,80,82,92\) Although surgical approaches are often curative, they can produce high treatment-related morbidity and even death due to the close proximity of crucial neurovascular structures. Recurrent craniopharyngiomas must be considered separately, because secondary surgery is associated with a higher risk of complications and a lower cure rate.\(^5,8,18,21,29,57,87\) More recently, SRS techniques have become increasingly used as either a primary or secondary treatment for patients with craniopharyngioma.

**Surgical Outcomes**

Complete resection of craniopharyngiomas is a primary objective and has curative potential. In a recent patient series studied by Shi et al.,\(^77\) 284 patients (58 children) were treated surgically with no adjunctive therapy between 1996 and 2006. Gross-total resection, STR, and partial removal of the tumors was achieved in 237 (83.5%), 34 (12.0%), and 13 patients (4.5%), respectively. Upon follow-up, 23 patients (14.1%) experienced recurrence (83.5%), 34 (12.0%), and 13 patients (4.5%), respectively. The delay to recurrence ranged from 1 to 180 months (mean 42 months, median 12 months). In this study, 13% of patients in whom a GTR was achieved experienced tumor recurrence; 33% with STR experienced recurrence; and 69% with partial removal suffered a recurrence of tumor. Radiotherapy was not systematically administered and was only reserved for cases of recurrence. The surgical mortality rate was 4.2%. In another 25-year retrospective study by Van Effenterre and Boch,\(^85\) 122 patients underwent either GTR (59%), STR (29%), or partial resection (12%). During the follow-up period, 29 patients (24%) experienced 1 or more recurrences. The actuarial 10-year survival rate was 95% at 2 years, 91% at 5 years, and 83% at 10 years.

The comparison of surgical complications for craniopharyngiomas across various patient series produces a variable picture. Most of the recent large patient series report a GTR rate of 59 to 90%.\(^18,33,85,89\) The 10-year recurrence-free survival rates have been reported as 74 to 81% for GTR,\(^19,87\) 41 to 42% after partial removal,\(^21,69\) and 83 to 90% after a combination of surgery and radiotherapy.\(^32,69\) Surgical mortality rates in these series vary between 1.1 and 4.2%.\(^18,76,85,89\) It is well documented that recurrent tumors are associated with significantly higher risk and poorer outcome, with overall mortality rates reported to be between 10.5 and 40.6%.\(^18,89\) Pituitary dysfunction may occur in 50 to 100% of patients, with diabetes insipidus as the most common dysfunction. Visual deterioration may occur in up to 50% of patients undergoing GTR for craniopharyngiomas.\(^85\)

**Radiation Therapy**

Although surgical drainage or resection of craniopharyngiomas may be the initial step in management, the rate of complete obliteration is low using only 1 modality. The fine balance between further neurological deficit and complete tumor resection has led to the use of various noninvasive forms of therapy. Radiation therapy is often applied during the postoperative course in the event of STR or tumor recurrence. Frequently, external radiation therapy is the preferred strategy, but in recent years endocavitary/intracavitary radiation and SRS have also demonstrated efficacy in tumor control.

**Proton Beam Radiotherapy**

Proton beam radiotherapy, a specific form of conformal external beam therapy, is used as an adjuvant and/or salvage treatment modality for craniopharyngiomas, particularly those in the pediatric population. In a retrospective study by Luu and colleagues,\(^53\) 16 patients (ages 7–34 years) were treated with proton beam radiation. A daily dose of 1.8 CGE was used for a total CGE of 50.4 to 59.4. Local tumor control was achieved in 14 patients with few acute side effects. The authors reasoned that if the dose to the optic pathway was below 36 CGE, the rate of complication would be < 10% with minimal damage to the optic apparatus. In a similar study by Fitzek et al.,\(^22\) 15 patients with craniopharyngioma were treated with combined proton-photon irradiation at a median dose of 56.9 CGE. The actuarial 10-year survival rate was 72% and the 10-year local control rate was 85%. Two patients suffered visual defects (hemianopia and total loss of vision) after receiving doses of 64 and 55.3 CGE, respectively, to their optic chiasm.

**Endocavitary Radiation Therapy**

Endocavitary/intracavitary irradiation with a beta-emitter (\(^{186}\)Re, \(^{32}\)P, \(^{198}\)Au, or \(^{60}\)Y) or an antitumoral antibiotic (bleomycin) can be used to treat purely cystic, or cystic components, of craniopharyngiomas.\(^15\) This treatment modality requires the use of stereotactic technique to achieve intracystic instillation of radioactive agents. In a recent retrospective study of endocavitary irradiation (\(^{186}\)Re) treatment by Derrey et al.,\(^15\) complete cystic resolution was achieved in 17 (44%) of 48 patients treated and partial resolution in another 17 patients (44%). Visual function improved in 12 patients while baseline endocrine function was preserved. Similarly, Julow and colleagues\(^42\) observed an 80% reduction in 47 patients and complete disappearance of the cyst in 27 patients within 1 year after treatment with intracystic colloidal \(^{60}\)Y. Across several studies, the response rate of tumors to endocavitary/intracavitary irradiation is 71 to 88%.\(^67,88\) However, because intracavitary irradiation is limited to cystic tumors, recurrence and survival rates using only this type of therapy are considered inferior to those of surgery or external radiotherapy.\(^56,88\) Additionally, the risk of visual deterioration is considerable, possibly due to unpredictable radiation dose to the optic pathway and radiation damage from leakage. In a review by Cáceres,\(^7\) the numbers of patients experiencing no change or improvement in visual acuity

---

**Endocavitary Radiation Therapy**

Endocavitary/intracavitary irradiation with a beta-emitter (\(^{186}\)Re, \(^{32}\)P, \(^{198}\)Au, or \(^{60}\)Y) or an antitumoral antibiotic (bleomycin) can be used to treat purely cystic, or cystic components, of craniopharyngiomas.\(^15\) This treatment modality requires the use of stereotactic technique to achieve intracystic instillation of radioactive agents. In a recent retrospective study of endocavitary irradiation (\(^{186}\)Re) treatment by Derrey et al.,\(^15\) complete cystic resolution was achieved in 17 (44%) of 48 patients treated and partial resolution in another 17 patients (44%). Visual function improved in 12 patients while baseline endocrine function was preserved. Similarly, Julow and colleagues\(^42\) observed an 80% reduction in 47 patients and complete disappearance of the cyst in 27 patients within 1 year after treatment with intracystic colloidal \(^{60}\)Y. Across several studies, the response rate of tumors to endocavitary/intracavitary irradiation is 71 to 88%.\(^67,88\) However, because intracavitary irradiation is limited to cystic tumors, recurrence and survival rates using only this type of therapy are considered inferior to those of surgery or external radiotherapy.\(^56,88\) Additionally, the risk of visual deterioration is considerable, possibly due to unpredictable radiation dose to the optic pathway and radiation damage from leakage. In a review by Cáceres,\(^7\) the numbers of patients experiencing no change or improvement in visual acuity...
Radiosurgery in the treatment of craniopharyngiomas

after intracavitary irradiation ranged from 42 to 99% of the different series, whereas 31 to 58% experienced deterioration in visual function.

External Radiation Therapy

Fractionated radiation therapy improves craniopharyngioma control and survival and is the standard treatment for residual or recurrent tumor. Most patient series demonstrate that when combined with STR, adjuvant radiotherapy allows for greater tumor control and survival than surgery alone. In a study by Varlotto et al., an 89% tumor control rate was noted in patients who received both STR and external beam irradiation. Stripp and colleagues examined the records of 121 patients and subdivided the patients into 4 treatment categories: GTR, GTR with radiotherapy, partial removal, and partial removal with radiotherapy. The recurrence-free survival rate was 100% at 10 years in the GTR only and GTR with radiotherapy groups, 38% in the partial removal group, and 77% in the partial removal with radiotherapy group.

When using radiotherapy, the risk of neurotoxicity from radiation injury should be considered alongside gains in potential tumor control. Doses of 50–60 Gy are most commonly used. Conventionally fractionated focal radiation therapy around the sellar-suprasellar region is also associated with risks similar to surgery. Disruption of the hypothalamic-pituitary axis may result in diabetes insipidus, panhypopituitarism, hypogonadism, hypothalamic obesity, or sleep disturbance. The normal optic apparatus is particularly sensitive to radiation; optimized dose and fractionation regimes carry a 3% risk of optic neuropathy. There is also considerable discussion about the effect of radiation on cognitive function, an issue particularly pertinent in the pediatric population. Additionally, radiation itself carries the risk of secondary malignancies, radiation necrosis, and vasculopathy, which also have secondary neurodegenerative effects.

Typically, craniopharyngiomas are treated with radiation doses between 45 and 55 Gy in 1.8 to 2 Gy fractions to prevent growth of tumor and minimize injury to the visual pathways. Long-term (10-year) local control ranges from 31 to 42% with surgery alone compared with 57 to 89% with surgery and radiotherapy. However, there are limitations, as the wide treatment field includes irradiating many structures, such as the optic apparatus, pituitary gland, hypothalamus, and medial temporal lobe. The risk may only manifest itself after a long delay, but this issue is particularly important because benign conditions such as craniopharyngiomas confer favorable long-term survival and have a predilection for the pediatric population. Another limitation of radiation therapy is that when conventional radiotherapy fails, it almost inevitably precludes further radiotherapy treatment to the recurrent tumor. Finally, although of minor importance, conventional fractionated radiotherapy usually takes place over a 6-week course, which is less attractive to patients when compared with other shorter treatment courses. For these reasons, radiosurgery (particularly multisession radiosurgery) may present a more practical option, especially for treating those tumors surrounding the optic apparatus.

Stereotactic Radiosurgery

Stereotactic radiosurgery is a relatively recent therapeutic option for craniopharyngioma that has significantly improved the effectiveness of, and morbidity associated with, radiation therapy. With SRS, 1 to 5 radiation treatments are used to treat residual or recurrent lesions. The application of stereotaxis for target localization, treatment planning, and daily treatment immobilization allows for a more precise delivery of radiation dose, with a steeper dose gradient between tumor and parenchymal tissue to prevent further neurological deficit. The radiation dose can be delivered using either a multiple cobalt-60 gamma radiotherapy-emitting source such as the GK or a modified linear accelerator (CyberKnife). Most stereotactic systems can deliver a radiation beam to within approximately 1 mm of the lesion. Historically, SRS for craniopharyngiomas was limited to tumors 3 cm or less in size that were 3 to 5 mm away from the optic chiasm and nerves. In the case of single-session SRS, the optic chiasm becomes a limiting anatomical structure capable of only receiving 8 to 10 Gy per session before the incidence of optic neuropathy increases. More recent multisession SRS using image-guided radiosurgical techniques has allowed for treatment of craniopharyngiomas immediately adjacent to the anterior visual pathways. In the current literature, several studies have reported safe and effective long-term results with the application of SRS using the GK for the treatment of craniopharyngiomas. Kobayashi et al. published the largest treatment and outcomes series, involving 98 cases. At a mean marginal dose of 11.5 Gy and a mean tumor size of 3.5 cm³, these authors observed a tumor control rate of 79.6%, with a complete response in 19.4% and partial response in 67.4% of the cases. The actuarial 5- and 10-year survival rates were 94.1 and 91%, respectively, with respective PFS rates of 60.8 and 53.8%. Also within the last year, Yomo and colleagues demonstrated the outcomes in 18 patients with residual or recurrent craniopharyngioma who were treated using the Leksell GK Model C. Tumor growth was controlled in 17 cases (94%), and volume reduction was attained in 13 cases (72%). Mean tumor volume was 1.8 cm³ and the mean marginal radiation dose was 11.6 Gy. No new endocrinopathy was observed and 3 patients experienced substantial improvement of visual functions following shrinkage of the neoplasm. In another study by Chung et al., tumor control was achieved in 87% of the 31 patients in the study, and 84% demonstrated fair to excellent clinical outcomes. Minniti et al. completed a large meta-analysis of 8 published studies that included 252 patients who underwent either fractionated radiosurgery or GK therapy, demonstrating a tumor control rate of 69%. Taken together (Table 1), the published studies on GK therapy for craniopharyngiomas...
demonstrate an average control rate of 90% for solid tumors, 88% for cystic tumors, and 60% for mixed tumors. Tumor control was achieved with a mean marginal dose of 12 Gy and recurrence of tumor was observed in 85% of cases that received a marginal dose < 6 Gy.

Given the current advances in image-guided radiosurgical technology, the principle of multisession delivery of SRS can be incorporated with the anatomical precision and conformality of radiosurgery. This incorporation allows for the precise delivery of potentially safer radiation doses than encountered in single session radiosurgery, while exploiting the volume effect by applying higher and more effective doses than was possible using conventional radiation therapy. The multisession delivery approach is particularly pertinent in treating craniopharyngiomas, which are often located near delicate neurovascular structures. The tolerance of these critical structures to radiation depends on the amount of radiation received, volume of tissue irradiated, previous insult, and prior radiotherapy. Due to the proximity of the tumors to the optic apparatus, only a single dose of 8 to 10 Gy is tolerable to avoid damage to the nearby structures. Higher doses to optic nerves are associated with increasing rates of deficit. Leber et al. reported that optic neuropathy occurred in 22 patients (26.7%) who received 10 to 15 Gy and 13 patients (78%) who received > 15 Gy, whereas 31 patients who received < 10 Gy were without optic insult. Likewise, Stafford and colleagues observed radiation optic neuropathy in 1.7% of patients who received < 8 Gy, in 1.8% of patients who received 8–10 Gy, and in 6.9% of patients who received > 12 Gy after treatment with the GK for benign tumors of the sellar or parasellar region.

**Cyberknife SRS: Our Experience**

The CyberKnife (Accuray, Inc.) consists of a miniature lightweight linear accelerator mounted on a robotic arm with 6° of freedom of movement. This configuration allows unobstructed access to the entire body and a photon beam can be targeted with submillimeter accuracy (Fig. 1). The CyberKnife employs an image-guided control loop with target tracking capabilities, thus it can adjust for patient movement and obviates the use of invasive frames to stabilize the patient. Patients do wear a thermoplastic mask that can be used for multisession SRS (hypofractionation) in patients with tumors near eloquent structures, allowing higher doses of radiation to be delivered over a longer period of time.

In a study by Lee et al., 11 patients with residual craniopharyngiomas within 2 mm of the optic apparatus or pituitary gland were treated using the CyberKnife SRS system. The clinical presentation, surgical history, radiation received, and outcome of these 5 male and 6 female patients with an average age of 34.5 years are documented in Table 2. A mean marginal dose of 21.6 Gy prescribed to a mean isodose line of 75% was applied over multiple sessions. The mean maximum dose was 29.9 Gy and the mean target volume was 6 cm³ (Table 3). Patient outcomes were quantified using MR imaging and formal Goldman visual field assessments at 6-month intervals for 2 years, then once every year (Table 4). Prior to CyberKnife therapy, 10 patients suffered from a degree of visual loss, while 5 had endocrine abnormalities requiring hormonal replacement. Ten patients had operative reports documenting an STR with radiological confirmation, and 1 underwent a complete resection with follow-up MR imaging demonstrating recurrence 1 year after surgery. Residual tumor was most often located in the suprasellar region, and in 10 cases was found to be against or displacing the optic nerve or chiasm. The pituitary stalk only was compressed in 1 patient.

The mean follow-up time was 15.4 months (range 4–64 months). All 10 patients with visual field or acuity problems either improved or remained stable after CyberKnife radiosurgery. In this series, treatment plans were designed to keep the dose experienced by the optic apparatus to < 5 Gy during any single session. The volume of the optic apparatus that received 80% of the prescribed dose was < 0.05 cm³, whereas the volume that received 50% of the dose was < 0.5 cm³. Therefore, the actual volume of the optic segment that received 5 Gy would be small relative to the total volume of the optic apparatus. Preservation of baseline visual function is supported by our previous work, which showed that the risk...
### TABLE 1: Summary of published series of patients who underwent SRS for craniopharyngioma*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Study Country</th>
<th>Intervention</th>
<th>No. of Patients</th>
<th>Mean Marginal Dose (Gy)</th>
<th>Mean Tumor Size (cm³)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miyazaki et al., 2009</td>
<td>Japan</td>
<td>CyberKnife</td>
<td>13</td>
<td>22.7</td>
<td>NA</td>
<td>tumor shrinkage achieved in 6 of 13 patients, tumor control in another 5; 2 patients had cystic enlargement of the residual tumor followed by microsurgical resection</td>
</tr>
<tr>
<td>Yomo et al., 2009</td>
<td>Japan</td>
<td>GK</td>
<td>18</td>
<td>11.6</td>
<td>1.8</td>
<td>tumor growth controlled in 17 cases (94%), &amp; volume reduction attained in 13 cases (72%); in 3 patients significant shrinkage of the neoplasm after radiosurgery was accompanied by improvement of the visual functions</td>
</tr>
<tr>
<td>Kobayashi, 2009</td>
<td>Japan</td>
<td>GK</td>
<td>98</td>
<td>11.5</td>
<td>3.5</td>
<td>complete response 19.4%, partial response 67.4%, tumor control rate 79.6%, &amp; progression rate 20.4%; patient outcome excellent in 45 cases, good in 23, fair in 4, poor in 3; 16 patients died &amp; deterioration of visual &amp; endocrinological functions were found as side effects in 6 patients (6.1%)</td>
</tr>
<tr>
<td>Lee et al., 2008</td>
<td>US</td>
<td>CyberKnife</td>
<td>11</td>
<td>21.6</td>
<td>5.9</td>
<td>tumor shrinkage achieved in 7 of 11 patients, tumor control in another 3; 1 patient had cystic enlargement of the residual tumor; overall, control or shrinkage of tumor was achieved in 91% of patients, w/ no visual or neuroendocrine complications</td>
</tr>
<tr>
<td>Minniti et al., 2007</td>
<td>UK</td>
<td>SCRT</td>
<td>39</td>
<td>50</td>
<td>10.2</td>
<td>3- &amp; 5-year PFS was 97 &amp; 92%, respectively, &amp; 3- &amp; 5-year survival was 100%; 2 patients required further debulking surgery; 12 (30%) had acute clinical deterioration due to cystic enlargement of craniopharyngioma following SCRT &amp; required cyst aspiration, 1 w/ severe visual impairment prior to radiotherapy had visual deterioration following SCRT; 7 of 10 patients w/ a normal pituitary function before SCRT had no endocrine deficits following treatment</td>
</tr>
<tr>
<td>Combs et al., 2007</td>
<td>Germany</td>
<td>FSRT</td>
<td>40</td>
<td>52.2</td>
<td>13.3</td>
<td>local control 100% at both 5 &amp; 10 years; overall survival rates at 5 &amp; 10 years were 97% &amp; 89%, respectively; complete response observed in 4 patients &amp; partial responses noted in 25 patients; 11 presented w/ stable disease during follow-up</td>
</tr>
<tr>
<td>Giller et al., 2005</td>
<td>US</td>
<td>CyberKnife</td>
<td>3</td>
<td>42</td>
<td>1.14</td>
<td>tumor regression w/o visual changes achieved in all 3 patients at 29, 39, &amp; 40 months after treatment; dose to the optic apparatus was &lt;8 Gy for all patients treated w/ a single dose or w/ hypofractionation (3–5 doses); dose to the brain stem &lt;10 Gy in all single dose &amp; hypofractionation treatments</td>
</tr>
<tr>
<td>Albright et al., 2005</td>
<td>US</td>
<td>GK</td>
<td>5</td>
<td>NA</td>
<td>6.5</td>
<td>no morbidity or mortality from GKS, which achieved tumor stabilization or shrinkage in 4 of 5 cases</td>
</tr>
<tr>
<td>Amendola et al., 2003</td>
<td>US</td>
<td>GK</td>
<td>14</td>
<td>14</td>
<td>3.7</td>
<td>all patients alive &amp; w/o evidence of recurrent disease 6–66 mos after treatment; only 2 patients required retreatment</td>
</tr>
<tr>
<td>Selch et al., 2002</td>
<td>US</td>
<td>FSRT</td>
<td>16</td>
<td>55</td>
<td>7.7</td>
<td>3-year actuarial overall survival = 93%, rate of survival free of any imaging evidence of progressive disease = 75%; 3-year actuarial survival rates free of solid tumor growth or cyst enlargement = 94 &amp; 81%, respectively</td>
</tr>
<tr>
<td>Ulfarsson et al., 2002</td>
<td>Sweden</td>
<td>GK</td>
<td>21</td>
<td>3–25</td>
<td>7.8</td>
<td>5 of 22 tumors were reduced in size, 3 unchanged, 14 increased; 11 (85%) of 13 tumors that received a dose &lt;6 Gy to the margin increased in size, whereas only 3 (33%) of 9 tumors that received 6 Gy increased; in 5 of 6 tumors that became smaller after GKS, there were no recurrences w/ a mean follow-up period of 12 years; 9 (82%) of 11 tumors in children ultimately increased after GKS, compared with 5 (50%) of 10 in adults; in 8 patients there was a deterioration of visual function, 4 patients developed pituitary deficiencies</td>
</tr>
<tr>
<td>Chiou et al., 2001</td>
<td>USA</td>
<td>GK</td>
<td>10</td>
<td>16</td>
<td>1.7</td>
<td>7 of 12 tumors became smaller or vanished within a median of 8.5 mos; prior visual defects objectively improved in 6 patients; 1 patient w/ prior visual defect deteriorated further &amp; lost vision 9 months after radiosurgery</td>
</tr>
<tr>
<td>Yu et al., 2000</td>
<td>China</td>
<td>GK</td>
<td>46</td>
<td>8–18</td>
<td>13.5</td>
<td>tumor control rate = 90% in solid tumors, 85.7% in mixed tumors, 92.1% in the solid segment, 89.5% in total</td>
</tr>
</tbody>
</table>

*continued*
of visual loss with multisession radiosurgery appears to be low for perioptic tumors. Radiation-induced optic neuropathy is a known entity that tends to present over the course of several years, but the short follow-up duration of our study prevents making definitive conclusions regarding the effect of multisession therapy.

There were no new neuroendocrine problems and the 5 patients with endocrine derangement remained stable, with no new deterioration after CyberKnife treatment. Tumor shrinkage was observed in 7 patients, with 3 of these tumors remaining the same at 2 years after treatment, resulting in a 91% tumor control rate. One patient developed a cystic enlargement of the residual tumor without any worsening symptoms or signs. Irradiation of cystic craniopharyngiomas may result in cystic enlargement, which does not represent tumor recurrence and may later regress. In our series, the patient’s symptoms remained stable, but rigorous clinical and radiological assessment is critical, including visual and neuroendocrine assessment. We believe that multisession treatment regimens minimize the risk to the optic apparatus and pituitary gland while delivering an appropriate amount of radiation for disease control.

There are several assumptions that contributed to doseimetry calculations for stereotactic radiation delivery. In a review by Timmerman et al., the authors outlined 3 requirements necessary for a successful treatment: 1) the ability to describe the location of the target; 2) the ability to shape the prescription isodose surface to the surface of the target volume; and 3) the ability to construct radiation dose distributions with very rapid fall-off dose to spare surrounding healthy tissue. In calculating dosimetry, the best approach is to have multiple beam directions, which allows for attenuation of the primary beam outside of the targeted areas using multileaf collimators.

**Radiosurgical Dosing**

Several factors influence the choice of radiosurgical dose, including the pathology of the lesion, the nature of the adjacent tissues, and the volume of both of these structures. Much of what we know about the tolerance of normal brain structures came from studies using conventional radiation therapy and single fraction radiosurgery. As discussed, the CyberKnife, with its frameless platform, allows for multisession schedules. Multisession radiation allows sublethal injury to normal tissue, which can repopulate between fractions; other advantages include achieving higher tumor cell death by reoxygenation of hypoxic cells, and reassortment of cells into sensitive phases of the cell cycle.

To estimate the BED of different fractionation schemes, the linear quadratic model of cell survival from radiation is used. Multifraction treatments were converted to a single-fraction BED using the linear quadratic model:

$$\text{BED} = n[d + \frac{d}{\alpha/\beta}]$$

where \(n\) represents the number of fractions, \(d\) represents dose per fraction, and \(\alpha/\beta\) represents the alpha/beta ratio. The ratio of \(\alpha/\beta\) reflects the radiosensitivity of the cell

---

**TABLE 1: Summary of published series of patients who underwent SRS for craniopharyngioma**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Study Country</th>
<th>Intervention</th>
<th>No. of Patients</th>
<th>Mean Marginal Dose (Gy)</th>
<th>Mean Tumor Size (cm³)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chung et al., 2000</td>
<td>Taiwan</td>
<td>GK</td>
<td>31</td>
<td>12.9</td>
<td>8.1</td>
<td>tumor control achieved in 87% of patients &amp; 84% had fair to excellent clinical outcome in an average follow-up period of 36 mos; 2 patients with uncontrolled tumor progression noted in 4 patients; only 1 patient found to have a mildly restricted visual field; no additional endocrinological impairment or neurological deterioration could be attributed to the therapy; no treatment-related mortality</td>
</tr>
<tr>
<td>Mokry, 1999</td>
<td>Austria</td>
<td>GK</td>
<td>23</td>
<td>10.8</td>
<td>7.0</td>
<td>volume reduction of the residual tumor in 74% of the cases; smaller tumors &amp; targets more likely to shrink; 5 patients with large multicystic residual tumors showed further progression</td>
</tr>
<tr>
<td>Prasad et al., 1995</td>
<td>USA</td>
<td>GK</td>
<td>9</td>
<td>13</td>
<td>decrease in the solid component of tumor noted in 5 patients &amp; no change in 2; 1 patient had increase in solid tumor component; clinical improvement noted in 6 of 8 cases</td>
<td></td>
</tr>
</tbody>
</table>

* FSRT = fractionated stereotactic radiotherapy; GKS = Gamma Knife surgery; NA = not available; SORT = stereotactically guided conformal radiotherapy.
Radiosurgery in the treatment of craniopharyngiomas

being exposed; the higher the $\alpha/\beta$ ratio, the more radiosensitive the cell. Various studies have shown that cranial nerve neuropathies occurred in 1 to 3% of cases when the brainstem was irradiated to 12 to 13 Gy. We have chosen to use a fractionation scheme when the single fraction dose exceeds 13 Gy to more than 20% of the brainstem, as is often encountered in craniopharyngiomas. In addition, we limit the single fraction dose to the optic apparatus to < 10 Gy by utilizing a fractionation scheme of 2 to 5 fractions and limiting the exposure to the optic apparatus to < 5 Gy per fraction. Using these parameters, we have been able to preserve preradiation visual function in 94% of cases involving perioptic lesions.1

The exact $\alpha/\beta$ ratio of craniopharyngiomas is unknown, but others have used a ratio of 2. By assuming an $\alpha/\beta$ ratio of 2, we can calculate that a radiation schedule of 25 Gy in 5 sessions estimates a single-dose equivalent of 12.3 Gy, a dose that approaches our intended target.

Conclusions

Optimal management of craniopharyngiomas remains controversial. The often peculiar location of a...
3. Albright AL, Hadjipanayis CG, Lunsford LD, Kondziolka D, 8 therapy following primary STR and also as a primary treatment of craniopharyngiomas, both as an adjuvant strategy that multisession therapy may prevent unintended consequences to surrounding optic structures and provide significant disease control. Although further long-term studies are required to fully evaluate clinical outcome, current evidence suggests beneficial results of radiotherapy for craniopharyngiomas.

Disclosure

Dr. Chang is a shareholder of Accuray, Inc., and is supported in part by a research gift from Robert C. and Jeannette Powell.

Author contributions to the study and manuscript preparation include the following. Conception and design: A Veeravagu, M Lee, SD Chang. Acquisition of data: A Veeravagu, M Lee, SD Chang. Analysis and interpretation of data: A Veeravagu, M Lee, B Jiang, SD Chang. Drafting the article: A Veeravagu, M Lee, B Jiang, SD Chang. Critically revising the article: A Veeravagu, B Jiang, SD Chang. Reviewed final version of the manuscript and approved it for submission: A Veeravagu, SD Chang. Statistical analysis: A Veeravagu, SD Chang. Administrative/technical/material support: A Veeravagu, SD Chang. Study supervision: A Veeravagu, SD Chang.

References

31. Haupt R, Magnani C, Pavanello M, Caruso S, Dama E, Garré

A. Veeravagu et al.
Radiosurgery in the treatment of craniopharyngiomas


A. Veeravagu et al.