Evaluation of the role of Gamma Knife surgery in the treatment of craniopharyngiomas

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✓The management of craniopharyngioma involves balancing adequate reduction in tumor volume and prevention of recurrence while minimizing damage to delicate surrounding structures. Because of the lesion's proximity to the optic chiasm and its relationship to the hypothalamic-pituitary axis, morbidity rates following treatment can be high. Gamma Knife surgery (GKS) is now being considered as a viable method of providing tumor control while ensuring minimal side effects. The authors conducted a literature review of 10 studies in which GKS was used to treat craniopharyngioma; some lesions had been previously treated and some had not. The mean marginal dose ranged from 5 to 16.4 Gy (mean 12.3 Gy). Tumor control was achieved in 75% of cases overall and varied with tumor subtype (cystic, solid, mixed). Control was seen in 90% of solid, 80% of cystic, and 59% of mixed tumors. The overall morbidity rate resulting from radiosurgery was 4% and the overall mortality rate was 0.5%. These results suggest that GKS may provide a favorable benefit-to-risk profile for many patients with craniopharyngiomas.
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KEY WORDS • craniopharyngiomas • Gamma Knife • radiosurgery

CRANIOPHARYNGIOMAS are tumors of the parasellar region that arise from residual epithelial cells of the Rathke pouch. They may be solid, cystic, or mixed in nature and are commonly calcified. Up to 60% of craniopharyngiomas have both cystic and solid components.^{7,28} Craniopharyngiomas occur in a bimodal age distribution, generally appearing in young patients between the ages of 5 and 14 years and in older patients between 50 and 74 years. According to an international meta-analysis of > 10,000 individuals, craniopharyngiomas account for ~ 7.8% of pediatric brain tumors.³¹ Because the tumor is relatively rare and generally benign, the results of demographic studies in adults are inconclusive.

Although histologically benign, the resulting clinical sequelae can be severe. Neurological symptoms can be divided into those resulting from mass effect and those resulting from dysfunction of the hypothalamic-pituitary axis. Mass effect can result in increased intracranial pressure presenting as headache, nausea, and vomiting. Obstruction of the aqueduct of Sylvius or the foramina of Monro may result in hydrocephalus in cases with large mass lesions.¹⁰ Hydrocephalus is a more common presenting sign in children than in adults.¹⁵ Due to its location in the sellar and parasellar areas, compression of the optic chiasm typically results in bitemporal hemianopsia. Visual disturbance can also include central visual defects, optic atrophy, and papilledema. Headache and visual field defects are the most common presenting symptoms.^{2,18,20} Endocrine disruption is

often suppressed, manifesting as amenorrhea, hypothyroidism, orthostatic hypotension, and diabetes insipidus, which occurs in as many as 15% of craniopharyngioma patients.^{9,15} In children, growth hormone deficiency may result in delayed puberty and short stature.^{1,22}

Treatment options for craniopharyngioma include total or subtotal resection, external-beam radiation therapy, stereotactic radiation therapy, intracavitary radiation, or a combination of treatment modalities. More recently, GKS has been utilized as either a primary or secondary treatment for craniopharyngioma patients. Given the spectrum of treatments available for this tumor, proper management remains controversial. In this paper, we evaluate the current role of Gamma Knife radiosurgery in the neurosurgical treatment armamentarium for craniopharyngioma patients.

Clinical Materials and Methods

In this study we review the trends in treatment of craniopharyngiomas for both pediatric and adult populations. Ten major studies of outcomes after GKS for craniopharyngioma were evaluated. Case studies were not included. Studies were evaluated for age at presentation, prior resection, concurrent treatment with intracavitary irradiation or bleomycin, follow-up duration, marginal radiation, mortality and morbidity rates, tumor control, and tumor progression (Table 1).

Results

Population Characteristics

The patient populations each ranged from 5 to 98 cases

Abbreviations used in this paper: CN = cranial nerve; GKS = Gamma Knife surgery; GTR = gross-total resection.

TABLE 1
Summary of 10 studies involving GKS for craniopharyngioma*

Authors & Year	Study Period	No. of Patients/ Tumors	Mean Age (yrs)	Prior Tumor Resection	Treatment (%)				Mean Value											
					Intracavitary Isotope		Bleomycin		Follow- Up (yrs)	Marginal Dose (Gy)	Tumor Size (cm ³)	Tumor Control Rate (%)				Tumor Prog Rate (%)	Further Treatment		Rates (%)	
					Pre-GKS	Post-GKS	Pre-GKS	Post-GKS				Sol	Cyst	Mix	Total		GKS	Resection	Morbidity	Mortality
Kobayashi et al., 2005	1993- 2005	98	38 < 15 60 > 15	100	0	0	3	0	5.5	11.5	3.5	93	79	61	79.6	20.4	14	1	6	5
Chung et al., 2000	1993- 1999	31	32	74	6.5	0	0	3	3	12.2	8.94	100	100	75	87.2	12.8	10	3	3.2	0
Ulfarsson et al., 2002	1968- 1995	21/ 22	11 < 15 10 > 15	56	19	23		0	13.6	5	8	57	100	21	36	67	14	0	19	0
Mokry, 1999	1992- 1998	23	31.4	39	0	0	43	4	2	7.8- 9.7	7 ± 8.3	—	74	—	74	26	13	4	0	0
Barua et al., 2003	1966- 2001	7	NA	100	NA	NA	NA	NA	4.2	14.2	NA	NA	NA	NA	100	0	NA	NA	71†	0
Chiou et al., 2001	1988- 1998	10/ 12	14.5	50	30	10	0	0	5.65	16.4	1.74	100	—	37.5	58	42	0	10	10	0
Prasad et al., 1995	1989- 1994	9	38.1	67	44	11	0	0	NA	12.9	10	100	—	50	62.5	37.5	0	22	0	0
Amendola et al., 2003	1994- 2000	14	11.5	86	8	0	0	0	3.3	14	3.7	NA	NA	NA	86	14	14	0	0	0
Albright et al., 2005	1983- 2004	5	13	0	80	0	0	0	2.4	NA	6.5	—	—	80	80	20	0	0	0	0
Yu et al., 2000	1996- 1999	46	39	61	72	6.5	0	0	1.33	8-18‡	13.5	90	—	86	89	12	0	0	0	0

* Cyst = cystic-type tumor; mix = mixed-type tumor; NA = not available; Prog = progression; sol = solid-type tumor; — = none.

† Not included in overall evaluation of morbidity due to ambiguity in the cause of new symptoms and the effects of concurrent surgical manipulation.

‡ Study provided only the range of values.

Radiosurgery for craniopharyngiomas

and included both children and adults. The average age of patients was 25.6 years (range 13–39 mean age). In 2 studies, tumor outcome was evaluated based on the number of tumors, as opposed to the number of patients. Kobayashi et al.¹⁹ and Ulfarsson et al.³⁶ did not report mean age, but patients > 15 years of age comprised 61 and 48% of these respective studies. Of the 10 studies reporting follow-up durations, the mean follow-up time was 4.6 years (range 1.33–13.6).

Treatment Prior to GKS

On average, in 63% (range 0–100%) of cases, prior resection had been performed (either subtotal or complete). An average of 29% of patients underwent intracavitary radiotherapy prior to GKS. Patients in 2 studies were treated with bleomycin prior to GKS, 3% in the study by Kobayashi et al.¹⁹ and 43% in the study by Mokry.²⁷

Radiosurgical Dose

On average, the mean marginal dose was 12.3 Gy (range 5–16.4 Gy). Mokry²⁷ reported a mean marginal dose of 7.8–9.7 Gy, and Yu et al.³⁸ reported a range of doses from 8–18 Gy (mean dose not available).

Tumor Control and Progression

All studies defined tumor control as a stable or decreased size of the tumor following GKS. Preoperative tumor sizes ranged from 1.74 to 13.5 cm³ (mean 7 cm³) and the mean size was not reported in 1 study. The mean tumor control rate was 75% (range 36–100%). Solid tumors were treated in 6 studies and their mean control rate was 90% (range 57–100%); cystic tumors were treated in 4 studies and their mean control rate was 88% (range 74–100%); and mixed tumors were treated in 7 studies and their mean control rate was 58.6% (range 21–86%). Tumor progression was observed in ~ 25% of cases (range 0–67%).

Further Treatment After GKS

An average of 4% of patients underwent intracavitary radiotherapy following GKS. Chung et al.⁶ and Mokry²⁷ treated patients with bleomycin following GKS to control cysts in 3 and 4% of patients, respectively. An average of 4% of patients (range 0–22%) required an additional resection in an attempt to control tumor progression. An average of 7% of patients (range 0–14%) underwent an additional treatment with GKS.

Morbidity and Mortality Rates

Assessment of morbidity included both endocrinological and visual deterioration resulting from GKS. Overall morbidity rates were low at 4% (range 0–19%). Death was only observed in 1 study and was reported as 5% of the population, giving an average mortality rate of 0.5% across all 10 studies. In 50% of the studies investigators reported no morbidity or mortality associated with GKS. Barua et al.³ reported a high incidence of morbidity, but this series was omitted from tabulation due to ambiguity in the underlying cause of the complications.

Discussion

Resection for Craniopharyngiomas

Traditional treatments for tumors of the sellar and parasellar regions include resection alone or resection coupled with radiosurgery or radiotherapy as an adjuvant treatment when complete resection is not possible. The proximity of craniopharyngiomas to the optic nerves, optic chiasm, oculomotor nerve, and carotid arteries, often precludes total resection. Although GTR is sometimes possible and should be the goal, it is often difficult and one must take into account the size, consistency (solid, cystic, or mixed), and location of the tumor in preoperative planning. Midline tumors with an origin below the diaphragm may be removed via a transsphenoidal route, either partially or completely. However, the transsphenoidal approach does not necessarily minimize postoperative endocrinopathy.^{8,35}

Morbidities associated with resection of craniopharyngiomas include visual deterioration and endocrine dysfunction. Visual deterioration is estimated to occur in an average of 19% of surgical cases, and it has been reported in as many as 35% of cases.⁴ Endocrine dysfunction results from damage to the hypothalamic–pituitary tract and is a major deficit following resection of craniopharyngiomas. Diabetes insipidus has been reported as the most common abnormality, seen in 59–93% of cases.³³ Honegger et al.¹³ have reported an increased incidence of diabetes insipidus from 16.1% preoperatively to 59.4% following resection. Many patients undergoing radical resection require long-term treatment for diabetes insipidus and additional hormone replacement therapy.⁴ Panhypopituitarism has been reported to occur in as many as 75–100% of patients undergoing resection.³⁴

In a review of surgical series in which patients were treated for craniopharyngioma, Brada and Thomas⁴ reported a mean mortality rate of 12% (range 2–43%) and a mean severe morbidity rate of 30% (range 12–61%). A striking 40% (range 30–57%) of the patients experienced hypothalamic morbidity. Authors at St. Jude's Children's Research Hospital found an increased incidence in both visual deterioration and endocrine dysfunction in the surgery-treated group compared with patients in whom more limited surgery and adjunctive radiotherapy were performed.²⁵ In a large-scale retrospective analysis of 309 patients treated by a single neurosurgeon, Shi et al.³² concluded that despite advances in imaging that have improved outcomes, morbidity related to hypopituitarism is still a major problem of craniopharyngioma surgery. This same study also reported a 3.9% mortality rate associated with extirpation. Mark et al.²⁴ reported a 10% mortality rate at 5 years and a severe surgical morbidity rate of 16%. These authors further reported that all patients who had undergone complete resection had worsened functional status after surgery and that all patients in whom resection was attempted had worsened pituitary function.

In addition to the increased morbidity associated with tumor resection, tumor recurrence and the need for reoperation may arise despite an initial GTR.²⁴ Prasad et al.³⁰ reviewed results of surgical treatment for craniopharyngioma published between 1966 and 1994 and reported that only 35.5% of these surgical series for craniopharyngioma achieved a radical resection of > 50% and that even when radical resection was accomplished, tumors recurred in

10–50% of cases. Although the utility of radiosurgery in treating craniopharyngiomas is still being analyzed in comparison to GTR, some studies have suggested that GTR is most strongly recommended in cases lacking hypothalamic involvement, whereas adjunctive or primary radiosurgery should be considered in other cases to decrease the rates of postoperative morbidity and mortality.¹

Inoue et al.¹⁴ observed that GTR for craniopharyngioma causes more hypothalamic–pituitary dysfunction than radiosurgery and that radiosurgery-treated patients may have preserved function without the need for hormone replacement postoperatively. In a pediatric series of 66 patients, growth hormone deficiency was documented in 100% of cases, gonadotropin deficiency in 80%, and hypothyroidism in 74% following either gross-total or partial craniopharyngioma resection.¹¹ Radiotherapy following surgery did not increase the incidence of endocrine abnormalities, suggesting that the most of dysfunction following craniopharyngioma management results from surgery itself.

Forms of Adjunctive Radiotherapy

Several options exist for cases not amenable to GTR. Subtotal resection may be followed by conventional radiotherapy, intracavitary irradiation, fractionated radiotherapy, and stereotactic radiosurgery. Radiotherapeutic techniques have also been performed as a primary treatment modality in patients with no history of resection.

Fractionated Stereotactic Radiotherapy. Fractionated stereotactic radiotherapy delivers conventionally fractionated radiation with some degree of precision, and it has been suggested to provide increased tumor control with low toxicity. It involves the use of computed tomography and/or magnetic resonance imaging for treatment planning. The delivery of radiation is more localized than that achieved with conventional radiotherapy. A 5-year progression-free survival rate of 92% has been reported for fractionated stereotactic radiosurgery compared with 80–90% for complete excision and only 50–60% for partial resection.²⁶ Despite its utility, fractionated stereotactic radiotherapy is still susceptible to several complications including vasculitis, neuropsychological changes, worsening of visual symptoms, and, rarely, an increased occurrence of secondary tumors.¹

Stereotactic Intracavitary Irradiation. Stereotactic intracavitary radiation with yttrium-90 or phosphorus-32 beta-emitting isotopes has been widely shown to be an effective primary treatment for multicystic or medium-sized monocytic tumors^{1,12,37} but not useful for solid tumors.¹² This type of therapeutic approach has been shown to control up to 96% of cystic tumors²³ and 88% when including all forms of partially cystic tumors.²⁹ Side effects include blindness, CN dysfunction, new-onset diabetes insipidus,²⁹ and panhypopituitarism.^{12,37} Vision may improve (48%) in some patients but can deteriorate in others (29%) following treatment.¹² An additional limitation is the progression of solid elements or secondary cyst formation, requiring further treatment.²³

Primary or Secondary GKS as a Treatment for Craniopharyngioma

Gamma Knife surgery involves stereotactic neuroimag-

ing-based planning to deliver a single, precise fraction of radiation with a steep dose fall-off. The Leksell stereotactic frame offers a superior degree of patient immobilization compared with other types of radiotherapy.¹⁷ The precision of the Gamma Knife typically allows for sparing of critical structures such as the hypothalamus and optic apparatus from damaging amounts of radiation. Several authors have reported that a therapeutic effect in craniopharyngiomas is seen with a marginal dose of 6 Gy, but the optimal dose, while not definitive, probably lies between 9 and 12 Gy.^{6,19,36} Ulfarsson et al.³⁶ noted that 2 patients with postoperative endocrine dysfunction had received marginal doses of 15 Gy. The optic apparatus is usually restricted to a dose of ≤ 8 Gy.³³ However, it has also been reported that up to 10 Gy may be tolerated.²¹ Other CNs within the cavernous sinus are thought to be more radioresistant than CN II.

Compared with other treatment modalities, GKS is associated with relatively few complications, avoiding the immediate complications of resection as well as some of the long-term problems associated with radiotherapy.³⁴ In the 10 series we have reviewed, the mean morbidity rate was 4%, which was considerably lower than the incidence of complications associated with resection and alternative forms of radiotherapy. Death was virtually absent and was only seen in a study by Kobayashi et al.²⁷ in 5% of the cases. In a study of residual or recurrent craniopharyngiomas treated with GKS, Chiou et al.⁵ reported visual deterioration in a single patient (10%).

Favorable quality of life outcome was most frequently demonstrated in patients with tumors that decreased in size following GKS.^{6,19} Tumor regression after either initial or adjuvant GKS has been shown in some patients with craniopharyngiomas. In a study of 5 pediatric patients, GKS was the primary treatment for the solid portion of mixed tumors after ³²P intracavitary irradiation was used to treat the cystic portion. Two patients experienced tumor regression, and 2 experienced tumor stability.¹ Studies in our review exhibited higher control rates in cases of single-type tumors, solid or cystic, than in mixed-type tumors. These results are consistent with the findings of Chung et al.⁶ who found that single-type tumors, either cystic or solid, responded more effectively than mixed-type tumors of a smaller volume.

Poor quality of life outcomes after GKS are associated with tumor progression.¹⁹ Mokry²⁷ found that larger tumor volume and multicystic tumors were predictive of poor outcome. The best outcomes in his study were seen in patients with monocystic tumors treated with stereotactic drainage and bleomycin, followed by GKS. Ulfarsson et al.³⁶ and Kobayashi et al.¹⁹ found that tumor progression after GKS tended to be a function of enlargement of the cystic rather than the solid component of the tumor. It has been suggested that tumors with large cysts treated with intracavitary irradiation may benefit from GKS after cyst size decreases.¹ It is thought that solid-type tumors and the solid portions of mixed-type tumors are less responsive than cystic tumors to intracavitary irradiation.¹⁶ Prasad et al.³⁰ have recommended that mixed-type tumors be treated with a combination of radioisotope instillation and GKS. The combined treatment of both GKS and intracavitary irradiation has been advocated as a primary therapy for mixed cystic–solid tumors.^{1,38}

Possible complications of GKS include hypothalamic

dysfunction resulting in changes in sleep and appetite, endocrine changes, visual defects, radiation necrosis, and malignant lesions. Complications resulting from radiation therapy vary depending on patient age, tumor size, and radiation doses.¹⁷ However, several authors have found that GKS provides excellent tumor control with minimal or no postoperative morbidity or mortality.^{1,2,5,6,19,27}

Risk associated with GKS is elevated when a large cystic volume obscures the visibility of other structures, such as visual pathways, or if there is tumor adherence to radiosensitive structures. Numerous authors have suggested the use of multimodal treatments in such cases because large cystic or mixed-type tumors can be reduced through cyst aspiration. Such volume reduction may reduce the risk of radiation-induced injury and allow more effective targeting of the solid portion of the tumor.^{6,27} Proper dose planning and avoidance of optic pathways becomes possible.⁶ In addition, an immediate improvement in a patient's condition can occur following aspiration of a cystic-type tumor, as compression of critical neural structures is relieved.

Conclusions

Gamma Knife surgery provides reasonable benefit-to-risk profile in the treatment of craniopharyngioma. In comparison to craniopharyngioma treated with resection alone, GKS appears to be associated with a decreased rate of morbidity and mortality. Due to great precision in tumor targeting, GKS may also be associated with fewer complications than other forms of radiation delivery. It can be used to treat residual or recurrent craniopharyngiomas after extirpation; it can also be used as an initial treatment option for some patients. Further studies will help to elucidate the role of GKS in the long-term management of craniopharyngioma in patients.

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