

Role of gamma knife radiosurgery in craniopharyngioma

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ABSTRACT

Craniopharyngiomas continue to be a challenge to manage, due to difficulty in complete excision and frequent recurrences. The management protocol remains controversial. They have a tendency to invade the normal brain tissues around them and due to their position in suprasellar region in close relationship with vital structures like optic apparatus, pituitary-hypothalamic axis, complete removal is often not feasible without causing serious morbidity and mortality. In this scenario, sub-total excision seems to be a better alternative, which is plagued by early and frequent recurrences. Radiotherapy has been used for increasing the progression free survival and to improve the overall quality of life. Recently Gamma knife radiosurgery has evolved as a promising technique of radiating the residual or recurrent tumor in a single session with great accuracy and precision. This helps in maximizing the radiation dose to the tumor with steep dose fall off to the surrounding tissue, and hence there is better control of the tumor and minimal radiation exposure to surrounding normal, vital brain tissues. We discuss the current strategies of Gamma knife treatment for craniopharyngioma and review the literature.

Key words: Craniopharyngioma, gamma knife, radiosurgery

INTRODUCTION

Craniopharyngiomas are usually slow-growing, extra-axial and often calcified cystic tumors arising from squamous epithelial remnants of the Rathke pouch.^[1] They are comparatively rare as compared to other intracranial tumors and account for about 7.8% of pediatric brain tumors^[2] and 1-4% of adult brain tumors. They have bimodal age distribution with peaks in childhood (5-14 years) and adulthood (50-70 years). Although craniopharyngiomas are benign, slow-growing tumors, they have a tendency to invade critical surrounding structures such as the pituitary stalk, hypothalamus, optic apparatus and adjacent vasculature, making their complete excision difficult. The treatment should be individualized according to the presentation and natural history of the disease for each patient. A number of treatment modalities are used either in alone or combination, including gross total resection (GTR), radiation therapy and chemotherapy (intracystic). While complete tumor resection is the best management option, in many cases, this is not possible due to adherence of

the tumor to important surrounding structures. Even with GTR, craniopharyngiomas often recur and require additional management. Sub-total removal followed by radiotherapy reduces post-operative morbidity, mortality as well as improves the progression free survival (PFS). Nowadays various modalities of radiation therapies are available including conventional external fractionated radiotherapy, 3D conformal radiotherapy, intensity modulated radiotherapy, intracavitary radiotherapy, proton beam therapy and the stereotactic radiosurgery (SRS).

Radiotherapy is the mainstay of multidisciplinary management of incompletely resected and recurrent craniopharyngioma. Advances in imaging and radiotherapy technology provide new alternatives with the principal aim of improving the accuracy of treatment and reducing the volume of normal brain receiving significant radiation doses. SRS has been used as a minimally invasive approach for the management of recurrent or residual craniopharyngiomas. SRS includes Gamma knife radiosurgery with primary source of radiation being the multiple radioactive Co⁶⁰ gamma emitting sources and Cyberknife using the modified linear accelerator as the radiation source.

GAMMA KNIFE RADIOSURGERY

Need for radiosurgery

Complete excision of the craniopharyngioma should be done whenever feasible so as to decrease the chances of recurrence. Several retrospective studies have reported

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that GTR in selected patients led to better local tumor control than did subtotal resection.^[3,4] Although surgical excision remains the initial gold standard treatment protocol for craniopharyngiomas, a complete resection is not always possible, without irreversible post-operative morbidity and mortality, due to the intimate relationship of the tumor with various important structures. Most of the series have reported a GTR rate of 27-90%.^[5-8] Even so, 8 out of 16 patients in Thompsons' series showed recurrence, even after complete resection.^[9] Shi *et al.*,^[10] in their study reported 14.1% and 64.9% recurrence in GTR and STR after a period of 1.0-3.5 years and 0.25-1.5 years respectively when no radiotherapy was given. Inoue *et al.*^[11] reported 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 recurrent cases, the surgical excision technique becomes challenging with mortality rates up to 40.6% (range 10.5-40.6%).^[5,8] Although with the addition of post-operative conventional external beam radiotherapy, local control rate can be increased from 42% to 84%^[12] (10 year control rate), the conventional radiotherapy has its local damaging effect on the optic apparatus, pituitary endocrine system, hypothalamus and cognitive functions, thereby diminishing the quality of life. With gamma knife radiosurgery, a large dose radiation can be delivered in a single shot to the residual or recurrent tumor with great accuracy and precision, so that complete excision and thereby, cure can be achieved without causing unnecessary morbidity. Changing the surgical pattern from overzealous GTR causing morbidity and mortality to subtotal resection followed by destruction of residual tumor with minimum doses of accurate radiation should be welcomed. Although consensus has yet to be reached in terms of optimal treatment modality for craniopharyngioma, maximum surgical resection that can be safely accomplished followed by SRS is increasingly being accepted as a viable management option.^[13-16]

Indications

Gamma knife radiosurgery is mostly used as an adjunctive procedure after the initial surgical excision of the tumor. It was first advocated by Backlund *et al.*,^[17] in 1965, as adjunctive or potentially definitive treatment of solid craniopharyngiomas. Surgical excision remains the gold standard treatment for the management of craniopharyngioma. However, for tumors which are invasive and involve surrounding critical structures, surgical removal involves a very high risk of causing irreversible visual loss, hypothalamic damage, diabetes insipidus and other endocrinopathies. In such cases, gamma knife radiosurgery can rarely be used as the sole treatment procedure. Niranjana *et al.*,^[18] in their series

of 46 patients, had 3 patients, in whom after initial stereotactic biopsy, gamma knife was offered as the primary treatment for the tumor. Saleem *et al.*,^[19] had reported a 33 month child, in whom 3.0 cm³ tumor was primarily and successfully treated with gamma knife radiosurgery [Table 1].

Previous treatment before gamma knife radiosurgery

Most of the patients who are a candidate for Gamma knife radiosurgery usually have had surgical resection of the craniopharyngioma. However, in purely cystic or largely cystic tumors, instead of open surgery, certain procedures are carried to decrease the size of the tumor before the gamma knife treatment. These include neuro-endoscopic fenestration and stereotactic aspiration of the cyst.^[19,20] In addition, ventriculo-peritoneal shunting (VP shunt), Ommaya reservoir placement are done to treat the hydrocephalus, associated with the tumor. Patients may present after undergoing conventional external beam radiotherapy, intracavitary P32 instillation and intracystic chemotherapy with Bleomycin.

Gamma knife technique and dose planning

All children <14 years of age should receive gamma knife under general anesthesia. An imaging-compatible stereotactic Leksell head frame, which provides better degree of patient immobilization, is fitted to the patients' head. A high-resolution magnetic resonance imaging (MRI) comprising Gadolinium-enhanced axial T1-weighted and T2-weighted MRI and computed tomography scans are acquired in 1-mm slices to define the target volume. The imaging data are imported to treatment-planning computers. The enhancing tumor margin serves as the radiosurgical target. The main concern is to limit the dose to optic apparatus to less than 8 Gy. However, Leber *et al.*,^[21] reported that the visual pathway may tolerate up to 10 Gy. He observed that optic neuropathy occurred in 22 patients (26.7%) who received 10-15 Gy and 13 patients (78%) who received >15 Gy, whereas 31 patients who received <10 Gy were without any damage to optic pathways. Similarly, Stafford *et al.*,^[22] observed radiation induced 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 gamma knife for benign tumors of the sellar or parasellar region.

Table 1: Indications for gamma knife radiosurgery in craniopharyngioma

Small residual or recurrent craniopharyngiomas of size equal or less than 3cm
Tumors situated more than 3mm from the optic apparatus
As primary treatment in small tumors in which surgical excision carries a very high risk of morbidity and mortality

In theory, satisfactory surgical extirpation is required to create adequate distance between tumor and the optic apparatus, which would allow for escalating marginal dose to solid component of the tumor and lead to better local control, without causing further damage to already compromised optic pathway.^[20] The target of the radiation should be either solid tumor or the cystic and solid components of the tumor. But if there is a large cystic part of the tumor closely encroaches the optic chiasm, then only the solid part of the tumor should undergo radiosurgery.

Gamma knife uses multiple isocenters to deliver the radiation. Whenever it is required and necessary, selected beam channels within each collimator should be plugged to shift the peripheral isodose curves away from the optic nerve, chiasm, or tract. Chiou *et al.*,^[23] used 50% isodose curve in 8 of their 12 tumors, 60% isodose in three tumors and one at 70% isodose. They utilized Leksell Gamma Knife to deliver radiation in a single session, using 1-9 isocenters (median, 2.5 isocenters) of different beam diameters with a median dose of 16.4 Gy (range, 12.5-20 Gy) for the tumor margin. Kobayashi^[13] used a conformal dose plan, using lower isodoses (e.g. 30-35%) to cover the entire tumor margin and even the portion close to the optic chiasm. A lower marginal dose (10 Gy) was prescribed to this lower prescription isodose to keep the marginal dose low, but maintain a high central dose and avoid potential adverse radiation effects. Niranjana *et al.*^[18] covered most of the tumor with 50% isodose line, leaving only a small rim of tumor, near the optic apparatus, which was covered with a lower isodose such as 30-40% so that, a larger tumor volume receives a greater dose and only a small segment near the adjacent critical structure receives a lower dose. In the series by Ulfarsson *et al.*,^[24] 11 (85%) of 13 tumors received a dose of less than 6 Gy to the margin, increased in size, whereas only 3 (33%) of nine tumors that received 6 Gy increased and this difference was statistically significant ($P = 0.01$). Several authors have reported that a therapeutic effect in craniopharyngiomas is seen with a marginal dose of 6 Gy but the optimal dose, probably lies between 9 and 12 Gy.^[24-26]

OUTCOME ANALYSIS BY FOLLOW-UP

All the patients who undergo Gamma knife radiosurgery should meticulously undergo serial follow-up MRIs, neurosurgical, neuro-ophthalmological and neuro-endocrinological evaluations to detect any change in the tumor morphology, neurological, ophthalmological and endocrinological status. Overall aim of the follow-up is to ascertain the response of the tumor to radiosurgical

treatment as well as identify any complications arising out of it. Broadly, it can be divided into (1) tumor response and (2) clinical response.

Tumor response

Following radiotherapy, the original residual or recurrent tumor may show regression in size, remain stable with no further growth or it may increase in size or develop tumor recurrence at sites distant from radiosurgery. Tumor response can be classified according to the one described by Chung *et al.*,^[25] as

- Complete response: Residual tumor volume was <20%;
- Partial response: Residual tumor volume was 20-50%;
- No change: Residual tumor volume was 50-80%;
- Progression (PG): Tumor volume increased or was >80% of the initial volume.

In 12 tumors in 10 patients reported by Chiou *et al.*,^[23] 7 (58%) showed regression in tumor size or total disappearance, 3 (25%) exhibited no growth, while 2 (17%) cases developed distant recurrences. Immediately after the radiosurgery, some of the cystic tumors may rapidly increase in size to produce mass effect, which may require implantation of an Ommaya reservoir or cyst excision either through open craniotomy^[23] or via endoscopic surgery. Kobayashi^[13] divided his 46 patients, who underwent gamma knife radiosurgery into solid, cystic and mixed tumors containing both solid and cystic component. Solid and cystic tumors underwent complete coverage, whereas the mixed tumors underwent both complete coverage as well as coverage for solid component only. Out of 22 tumors with only solid component complete resolution was identified in five tumors, >50% reduction in 11 tumors, <50% reduction in 2 tumors and enlargement in 4 tumors. Among mixed tumors treated with complete coverage ($n = 14$) >50% reduction was noted in 6 tumors, <50% reduction in another 6 tumors and PG in 2 tumors. Among mixed tumors treated for solid component only ($n = 10$) >50% reduction of solid tumor was identified in 4 tumors, <50% reduction in another four tumors and enlargement in 2 tumors. Of patients with cystic tumors ($n = 5$), >50% reduction was identified in 4 patients. Cyst progression was noted in 1 patient with a cystic tumor (20%), 4 with mixed tumors treated with complete coverage and 7 with mixed tumors treated with SRS to only the solid component. He finally observed that the 5-year overall local control rate for solid, cystic, mixed solid and cystic tumors who were treated with complete radiosurgical coverage (77.5%, 100% and 64.3% respectively) was better than that for mixed solid and cystic tumors treated only for the solid component (51.9%). Complete tumor

coverage in the radiosurgical target volume resulted in improved PFS, in all his patients as well in mixed tumor group. Saleem *et al.*,^[19] observed marked regression of the tumor when the dose was approximately 10 Gy. Overall, reducing the tumor marginal dose results in decreased therapeutic response and increased tumor PG and recurrences, whereas the rate of visual and pituitary function loss decreases and *vice-versa*.

Clinical response

Hormonal function

Many patients with craniopharyngioma, who undergo surgical excision, usually present with hypo- or panhypopituitarism (including diabetes insipidus) even before the gamma knife radiosurgery. Following SRS these patients' hormonal deficit may remain stable, deteriorate or improve following radiosurgery. Kobayashi^[13] reported improvement in anterior pituitary dysfunction in one and worsening of anterior pituitary dysfunction to panhypopituitarism in another patient, out of 46 patients following gamma knife radiosurgery. Many other series have reported no deterioration of already existing pituitary endocrine status by gamma knife radiosurgery.^[19,25,27]

Visual function

Following gamma knife radiosurgery, the residual or recurrent tumor may continue to grow resulting in new onset visual deficits, if not present before the radiosurgery or may deteriorate the already existing visual deficits. Similarly, the tumor may diminish or completely disappear, causing improvement in vision. Out of 25 patients with normal visual function, Kobayashi^[13] observed visual deterioration in form homonymous hemianopia in 2 patients. 5 out of 19 patients who had pre-existing visual field defects (VFD) progressed and in 2, there was a resolution of defect. In the rest of the patients visual function continued to be same. Saleem *et al.*,^[19] reported 7 patients improving, 6 patients maintaining and only 1 patient deteriorating in visual function among their 14 patients who had visual deficit before gamma knife. No patient with normal visual function had deteriorated. Yomo *et al.*,^[27] in their reported substantial improvement of visual functions following shrinkage of the neoplasm in 3 their patients. Chung *et al.*,^[25] reported only one patient showing restriction of visual field out of his 31 patients.

POST GAMMA KNIFE TREATMENT

Purely cystic or predominant cystic tumors can increase in size due to expansion following gamma knife requiring further treatment. Multicystic varieties may not respond to the gamma knife therapy due to size constraint or radioresistance of cystic tumor. Saleem *et al.*,^[19] reported

stereotactic aspiration of the cyst contents in four patients, implantation of an Ommaya reservoir in two and VP shunt in two patients, to relieve hydrocephalus. Xu *et al.*,^[20] reported six patients undergoing surgical management for the enlargement of cystic component and another six patients receiving stereotactic cyst aspiration and/or P32 instillation, after the initial gamma knife treatment.

Overall bird's view of all studies on gamma knife radiosurgery for craniopharyngioma is presented as Table 2.

Advantages of gamma knife radiosurgery

1. Better coverage of tumor target due to highly specific and precise localization with the help of stereotactic technique.
2. Acute and long term complications of conventional external radiotherapy on surrounding structures can be prevented due to steeper dose gradient between tumor and surrounding normal brain tissue.
3. Entire radiation dose can be delivered through a single large or few multiple sessions in comparison to a large number of sessions in conventional radiotherapy.

Disadvantages of gamma knife radiosurgery

1. Expensive and not widely available.
2. The benefits of hypofractionation not available.
3. High dose in a single session gamma knife cannot be used safely in tumors very close to optic apparatus.
4. Cannot be used in children <3 years.

FACTORS CONTROLLING THE OUTCOME

Xu *et al.*^[20] had used eight covariates including gender (male vs. female); age (child vs. adult); number of prior surgeries (≤ 1 vs. ≥ 2); absence versus presence of VFD at diagnosis of craniopharyngioma; absence versus presence of VFD at gamma knife surgery (GKS) for craniopharyngioma; GKS treated tumor volume (≤ 1.6 cm³ vs. > 1.6 cm³); maximum dose (> 30 vs. ≤ 30 Gy); and marginal dose (> 14.5 vs. ≤ 14.5 Gy). After using multivariate analysis they observed the absence of VFD at the time of gamma knife, tumor volume less than or equal to 1.6 cm³ and marginal dose > 14.5 Gy were related to a longer in-field PFS. Niranjana *et al.*,^[18] reported that radiosurgical coverage for the whole tumor and no previous RT or phosphorus-32 implantation are associated with improved PFS following the radiosurgery. Chiou *et al.*,^[23] observed that the best outcomes are achieved in small-volume tumors. Both of their patients who had deterioration of vision following

Table 2: Published series on gamma knife treatment for craniopharyngioma

Authors	No. of patients	Marginal dose (Gy) (mean)	Tumour size (cm ³) (mean)	Tumor control	Clinical outcome	Visual outcome	Endocrinological outcome
Saleem <i>et al.</i> ¹ (2013)	35	11.5	12	Control/response rate 88.5%, 77%	Excellent 10, Good 17, fair 4, poor 4	Worsening 1, Improvement 7 patients	No patient developed hypopituitarism
Niranjan <i>et al.</i> ¹⁸	46	13	1.0	3, 5-year PFS 91.6%, Local control rate 91%, 81% and 68% at 1,3,5 years	Survival rate 97.1% at 5 years	2 new visual field deficits	No patient developed hypopituitarism
Xu <i>et al.</i> ²⁰ (2010)	37	14.5	3.24	3.5-year PFS 84.8%, 67%. Tumor volume <1.6 cc, marginal dose >14.5 Gy related to longer PFS	NA	3 new visual field deficits	NA
Yomo <i>et al.</i> ²⁷ (2009)	18	11.6	1.8	94% control rate, volume reduction in 72	NA	NA	No patient developed hypopituitarism
Kobayashi <i>et al.</i> ¹³ (2009)	98	11.5	1.8	complete response 19.4%, partial response 67.4%, tumour control rate 79.6%, and progression rate 20.4%;	Excellent 45, good 23, fair 4, poor 3. 16 patients died	Visual worsening in 6 patients	Endocrinological disturbances in 6 patients
Albright <i>et al.</i> ²⁸ (2005)	5	NA	6.5	80%	NA	NA	NA
Amendola <i>et al.</i> ²⁹ (2003)	14	14	3.7	85.7%	Good outcome in all patients	NA	NA
Ulfarsson <i>et al.</i> ²⁴ (2002)	21	3-25	7.8	36.3% control rate	82% tumors increased in size in children, 50% in adults	Visual worsening in 8	Hypopituitarism in 4
Chiou <i>et al.</i> ²³ (2001)	10	16.4	1.35	58.3	NA	Visual worsening in 1	
Yu <i>et al.</i> ³⁰ (2000)	46	8-18	13.5	90% in solid, 85.7% in mixed, 89.5% overall	NA	NA	NA
Chung <i>et al.</i> ²⁵ (2000)	31	9.5-16	9	87	84% good to fair outcome	Visual field deficits in 1	No patients had Hypopituitarism
Mokry <i>et al.</i> ³¹ (1999)	23	10.8	7	74. 5% patients with large multicystic tumors showed further progression	NA	NA	NA
Prasad <i>et al.</i> ³² (1995)	9	13	10	55.5%	Clinical improvement in 75%		

PFS – Progression free survival

radiosurgery had undergone previous P32 intracavitary radiation and one had undergone external beam irradiation. Kobayashi¹³ studied 9 factors, including gender, age, pediatric (≤ 17 years) or adult patient, partial removal or recurrence, mean tumor diameter, tumor type (solid or cyst), pathological types (squamous cell or adamantinoma), number of previous treatments and radiation dose to determine the prognostic factors for tumor recurrence, after the gamma knife radiosurgery of partially resected and recurrent craniopharyngiomas. Out of this they observed only the tumor diameter of <19 mm and a marginal dose of ≥ 13.2 Gy are favorable prognostic factors for the gamma knife radiosurgery.

CONCLUSIONS

Gamma knife radiosurgery is an effective and safe procedure, particularly in residual and recurrent small craniopharyngiomas for completely destroying the tumor in a single session. It avoids morbidity and mortality associated with conventional external radiotherapy. Literature review

till now shows that the clinical, tumor response is almost same as that of conventional radiotherapy, whereas the associated visual, endocrine deficits are much less. Along with surgical resection, it should now be strongly considered as the first line therapy for craniopharyngiomas situated at a particular distance from the optic pathway. Many other types of radio-therapy like fractionated stereotactic radiotherapy, proton beam therapy, intracavitary radiation are in up-coming phase for the treatment of craniopharyngioma and have to be compared with gamma knife radiosurgery for their superior efficacy in removing residual or recurrent craniopharyngiomas.

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