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Original Article

Volume-staged gamma knife surgery for the treatment of large skull base meningioma surrounding the optical apparatus: A snowman-shape design

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Abstract

Background: In cases of meningioma surrounding the optical apparatus, this study sought to reduce the incidence of radiation-induced optical neuropathy resulting from gamma knife surgery (GKS) by dividing the treatment volume into 2 or 3 fractions.
Methods: Four patients with a large skull base meningioma (1 male and 3 females; median age: 42 years; range: 33−43 yrs) were treated using volume-staged GKS. In stage I, the large basal part of the tumor (13.2 mL; range: 3.9−54.7 mL) was treated with a marginal dose of 13.5 Gy (range: 12−15 Gy). In stage II, treatment focused on the smaller upper portion of the tumor located close to the optical apparatus (4.3 mL; range: 1.5−16.2 mL), and the marginal dose was 9 Gy (range: 8−10 Gy).
Results: All patients tolerated the treatments well, and tumors regressed over a median follow-up period of 100.5 months (range: 42−122 mos). Specifically, a 34−46% reduction in tumor volume was observed. All four patients presented improvements in the neurological deficits observed prior to GKS treatment, albeit to varying degrees. No adverse effects of radiation or new visual deterioration were observed during the follow-up period. Furthermore, no evidence of new endocrine dysfunction or new cranial nerve neuropathy was observed within a follow-up period of 100.5 months.
Conclusion: The application of volume-staged GKS using snowman-shape design appears to be an effective approach to control tumor growth when treating benign meningiomas surrounding the optical apparatus. This approach enables the application of higher radiation dosages to facilitate tumor control while still preserving optic nerve function.

Keywords: Gamma knife; Meningioma; Optical neuropathy; Stereotactic radiosurgery

1. Introduction

Despite recent advances in the surgical treatment of skull base meningioma, this disease is still associated with high rates of morbidity.[1−5] In contrast, radiosurgery is able to control the growth of tumors in 80−100% cases of skull base meningioma,[6−10] and GKS can reduce morbidity rates among meningioma patients. For example, Kondziolka et al. reported long-term tumor control in 91% of 290 consecutive patients who underwent GKS for a meningioma between 1987 and 1997.[11] However, in cases where the tumor is large and close to the optical apparatus, surgeons face a clinical dilemma as high-dose radiation exposure can lead to optic neuritis and irreversible deterioration in visual function.

Vision can be preserved by limiting the maximum radiation exposure of the optic pathway to 8−10 Gy per stereotactic radiosurgery (SRS) session[12−15]; unfortunately, the minimum effective dose for the treatment of benign skull base meningioma is 11−13 Gy. To address this dilemma, we developed a

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volume-staged SRS strategy, referred to as the snowman-shape design, that enables tumor control while also protecting the optical apparatus from radiation damage. Using the technique, the basal portion of the tumor (distal to the optical apparatus) is first treated with a regular (high) dose of radiation, and the upper portion of the tumor (proximal to the optical apparatus) is treated at intervals of 3 months or more. This paper reports on four cases in which the snowman-shape volume-stage treatment was implemented. We provide a detailed account of the techniques employed as well as resulting treatment outcomes.

2. Methods

2.1. Patient population

Four patients with a benign meningioma at the base of the skull were subjected to volume-staged GKS (Elekta Instruments, Inc., Stockholm, Sweden) using the snowman-shape design between Nov. 2005 and Sep. 2012. The Institutional Review Board of the Buddhist Tzu Chi Medical Center approved the research protocol. Three female patients and one male patient met the criteria for inclusion in the study. The age range of participants was 33−43 years (median: 42 years). The tumors were located in either the tuberculum sellae, the cavernous sinus, the suprasellar or retrosellar region, the petroclivus, or in all of the aforementioned locations. In all cases, the optical apparatus was compressed or encased by the tumors. Preoperative neurological deficits are presented in Table 1. All patients underwent microsurgery prior to GKS, and all of their histologies presented WHO grade I meningioma.

2.2. Radiosurgery technique

Each treatment session began by fixing a rigid Leksell frame (Model G, Elekta Instruments, Stockholm, Sweden) to the head of the patient after local anesthesia had been applied to the scalp (5% bupivacaine and 2% xylocaine). The frame was tilted anteriorly approximately 30°, which aligned the frame parallel to the plane of the optic nerves and chiasm, thereby ensuring that the optic nerve and chiasm were positioned along the same plane in axial MR images. MR stereotactic images acquired using a fiducial system attached to the stereotactic frame were transported through a fiber optic Ethernet cable to a GammaPlan (Elekta Instruments) computer, where images were checked for distortion/accuracy. Axial MR images using coronal and sagittal reconstruction with a slice thickness of 1 or 2 mm were required for the planning of treatment. After optimizing the plan, the marginal and maximum doses were determined for the target. Radiosurgery was performed using a 201-source, cobalt-60 gamma knife, and both the head of the patient and the stereotactic frame were immobilized within a collimator helmet. The automatic positioning system (APS) automatically moves the stereotactic frame until the target is fully irradiated.

Table 1
Demography of the 4 patients who underwent volume-staged GKS for skull base meningioma close to the optic apparatus.

Case/ No.	Age (yrs)/ sex	Tumor location	Neurological deficits	Total tumor vol (ml)	Stage	Treated target vol (ml)	Marginal dose/ isodose	Fractional interval (mos)	Mean tumor dose (Gy)	Mean/max chiasm dose (Gy)	Tumor vol after treatment (ml)[b]	New endocrine dysfunction[c]	Follow-up period[a] (mos)
1	42/M	PC	Ataxia	69.4	I	54.7	15 Gy/50%	–	21.0	6.2/8.0	46.1 (−34%)	No	122
		C	R 2−5N Df		II	16.2	10 Gy/50%	6	13.6	5.0/9.5			
2	42/F	TS	L 2N Df	13.9	I	7.8	13 Gy/50%	–	16.8	4.0/5.1	8.4 (−40%)	No	105
		C + Orb			II	4.5	8 Gy/42%	4	12.0	2.2/7.0			
3	33/F	TS	Ataxia	21.5	I	18.5	14 Gy/50%	–	16.3	7.3/8.2	11.6 (−46%)	No	96
		PC + C	R 3−5N Df		II	4.0	8 Gy/50%	4	11.2	6.1/9.3			
4	43/F	TS	Bil 2N Df	5.3	I	3.9	12 Gy/50%	–	16.3	6.2/12.8	2.9 (−45%)	No	42
		C			II	0.38	10 Gy/50%	4	14.3	2.6/7.7			
					III	1.14	10 Gy/50%	8	13.8	2.1/11.3			

R = right, L = left, Bil = bilateral, N = cranial nerve, Pc = petroclival, C = cavernous sinus, Orb = orbit, TS = tuberculum sellae, Df = dysfunction.

[a] Follow up since the first GKS.

[b] The data also showed the percentage of tumor volume decrease.

[c] The basal endocrine function for adrenocorticotropic hormone, cortisol, thyroid-stimulation hormone, triiodothyronine (T3), tetraiodothyronine (T4), growth hormone, and prolactin.

2.3. Snowman-shape design in volume-staged GKS treatment

The snowman-shape design in volume-staged GKS treatment was developed to treat patients with a large and/or extensive skull base meningioma that involves the optical apparatus. In most cases with a large skull base meningioma, the upper mass of large tumors in this area compresses the optical apparatus superiorly, whereas the basal mass pushes the brain stem inferiorly. This results in a shape similar to that of a snowman with a fat abdomen, small head, and a delicate hat (Fig. 1). To ensure that the meningioma is treated with a sufficient dose of radiation, an optimal peripheral dose (e.g. 12 Gy or more) is first applied to the basal part of the tumor, and an 8 Gy isodose is applied at the border of the optical apparatus (Fig. 2). Thus, the basal portion of the tumor

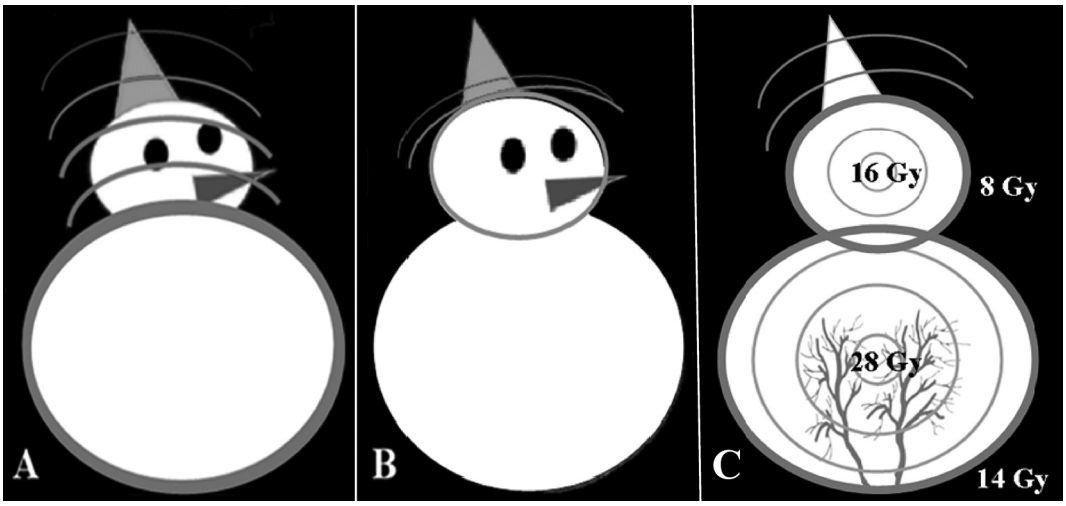

Fig. 1. Schematic diagrams illustrating the snowman-shape design (using data of illustrative Case 3 as the model): (A) stage I and (B) stage II. The basal mass of the meningioma is represented by the fat abdomen, the superior part of the tumor (touching the optical apparatus) is represented by the small head, and the optical apparatus is represented by the hat. In the 1st stage of GKS, the entire abdomen received the full marginal dose, whereas the small head (upper part of tumor) received a fall-off moderate dose and the hat (optical apparatus) received a dose of less than 8 Gy. In the 2nd stage of GKS, a moderate marginal dose was directed over the entire head area (upper portion of the tumor), such that the hat (optical apparatus) received a fall-off dosage. Image C illustrates the distribution of applied radiation and vascular supply as well as the degree to which the optical apparatus remained protected.

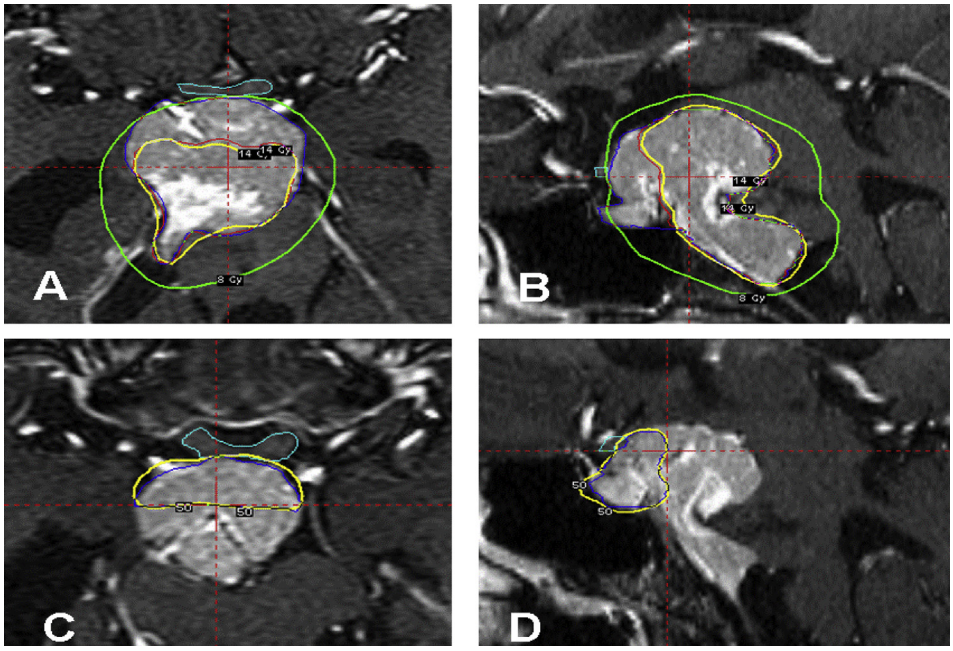

Fig. 2. Case 3. (A) Axial and (B) sagittal MR images showing the large basal mass encased by the 14 Gy isodose line (yellow) during the first stage of the snowman strategy, with the 8 Gy isodose line (green) just touching the chiasm (blue); (C) axial and (D) sagittal MR images showing the smaller, more anterior tumor treated with a less adequate dose in the first stage encased in the 8 Gy isodose line during the second stage of the snowman strategy, with the dose of the chiasm lower than 8 Gy as much as possible.

receives a full dose of radiation, whereas the small superior portion of the tumor (proximal to the optical apparatus) receives between 8 Gy and the marginal dose of the basal part of tumor (e.g. 11−13 Gy). At least 3 months after administering the first stage of GKS, a smaller dose of radiation is applied to the upper portion of the tumor (8−10 Gy), while maintaining exposure of the optical apparatus at less than 10 Gy. The upper part of the tumor is exposed to radiation twice: it receives a peripheral dose (8−12 Gy) and a central dose (8−10 Gy). SRS parameters, including tumor volume, radiation volume, marginal dose, maximal dose, and mean dose within the tumor as well as radiation exposure of optic nerve, chiasm, and tracts were recorded for the purpose of analysis (Table 1).

2.4. Follow-up examinations

Patients underwent follow-up examinations by a neurosurgeon and ophthalmologist. Follow-up MR imaging was performed at 6-month intervals in the first year following GKS and on an annual basis thereafter. The tumor volume was calculated from post-contrast T1-weighted images (T1 + C signal). Volumes were computed by numerical integration of tumors that had been segmented on a slice-by-slice basis. To avoid bias in computation, all follow-up MR images were imported into Gamma Plan® software and fused with pre-GKS MR images to facilitate contouring and the computation of volume. A decrease or increase in tumor size was determined by comparing post-treatment values with values measured at the time that GKS was first administered (Table 1).

3. Results

Three of the four patients underwent GKS treatment in two fractions, and one patient (Case 4) underwent GKS in three fractions. All intervals between fractions were 4−6 months. The median marginal dose for the first session was 13.5 Gy (range: 12−15 Gy) at the 50% isodose line, whereas the median marginal dose in the second session was 9 Gy (range: 8−10 Gy). The median tumor volume was 17.7 mL (range: 5.3−69.4 mL) at the initial presentation, whereas the median volume following the first session of treatment was 13.2 mL (range: 3.9−54.7 mL), which is approximately 3/4 of the initial tumor volume. The median volume following the second session of treatment was 4.3 mL (range: 0.38−16.2 mL), which means that the upper portion of the tumor (surrounding the optical apparatus) was exposed to 8−10 Gy. Case 4 underwent fractionated GKS three times over a 4-month period due to the presence of two separate tumor portions encasing the optic nerve inferiorly, anteriorly, and superiorly. In this case, we prescribed treatment with 10 Gy for each of the upper two parts of the tumor, which had volumes of 0.38 mL and 1.14 mL, respectively (Table 1).

For all patients, follow-up procedures were continued for at least 3.5 years, with a median follow-up time of 100.5 months after the initial GKS treatment (range: 42−122 months) (Table 1). All four tumors showed signs of regression, with tumor volume decreasing by 34−46% (median: 42.5%). Four of the patients who presented neurological deficits prior to GKS showed partial improvements, albeit to varying degrees. For example, Case 1 (large petroclival meningioma of 69.4 mL) showed improvement in the ataxia; however, dysfunction in the right 3rd−5th cranial nerves remained unchanged. Most importantly, none of the four patients presented signs of deterioration in their vision. This was true even for Case 4, where compression had rendered the optical apparatus particularly fragile. Specifically, visual acuity in the right eye remained at 0.09, whereas light perception was preserved in the left eye. Vision continued to show gradual improvement following surgical decompression, even after three treatments using GKS (Fig. 4).

3.1. Illustrative case

A 33-year-old female patient had been suffering from diplopia and dizziness for 2 months. Brain MRIs revealed a suprasellar and posterior fossa meningioma measuring 3.8 × 4.4 × 4.9 cm with invasion to the cavernous sinus and compression of the thalamus, optic nerve, and brain stem. A right presigmoid transpetrosal craniotomy with partial removal of the tumor was performed. Histological analysis confirmed

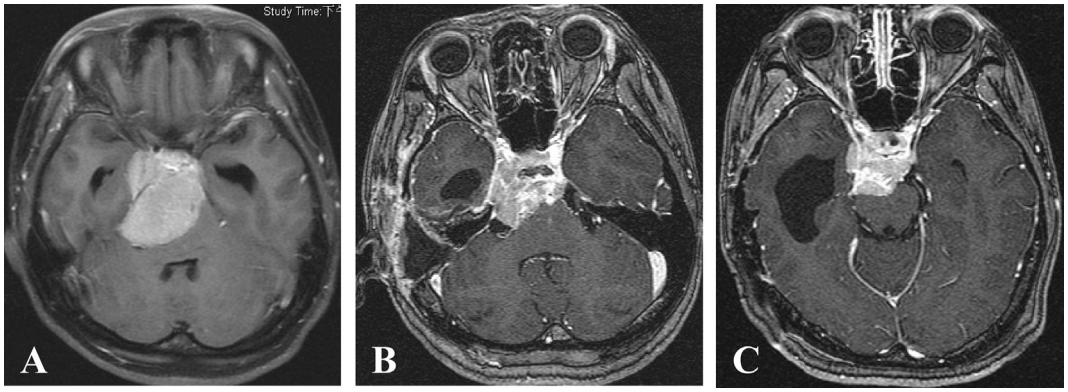

Fig. 3. Case 3. (A) Pre-operative and (B) post-operative contrast-enhanced axial MR images, showing meningioma invading the cavernous sinus and compressing the brain stem. Axial MR images reveal (B) the reduction in tumor volume following surgical decompression (C) and tumor shrinkage following 2 stages of GKS treatment after a 96-month follow-up period.

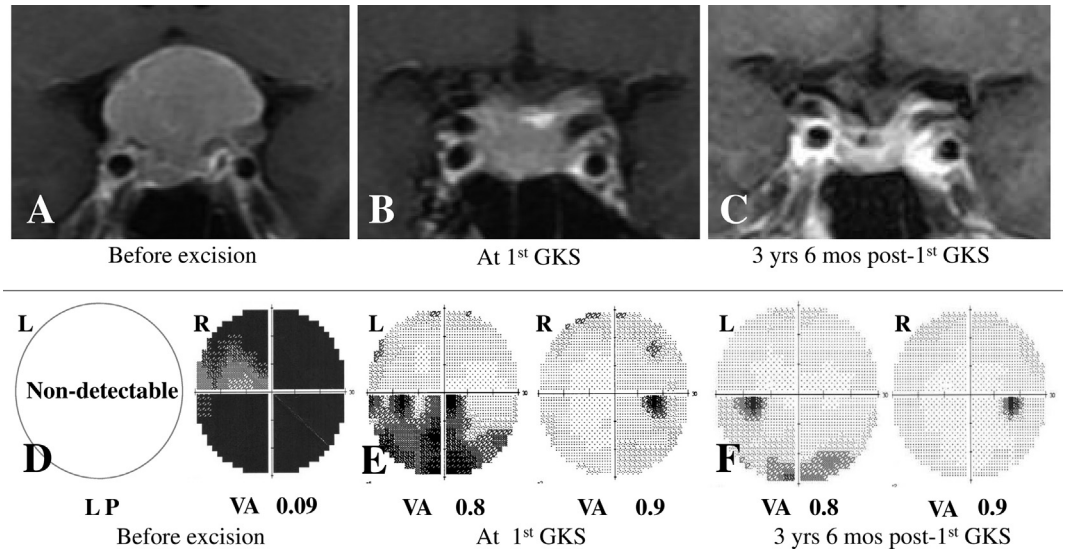

Fig. 4. Case 4. (A) 43-year-old female patient presented with bilateral visual field deficits. The patient underwent surgical resection to decompress the optic chiasm. Post-resection, the patient's vision improved, with only lower visual field deficits of the left eye remaining. The patient underwent 3 fractions of GKS according to the snowman strategy. MRI revealed tumor shrinkage 3.5 years post-GKS, and visual function had improved even further (L = left, R = right, LP = light perception, VA = visual acuity).

that the tumor was a WHO grade I meningioma. Following the operation, the residual tumor presented the shape of a snowman with a fat abdomen, small head, and delicate hat (Fig. 1). Meningioma patients require a minimum dose of radiation to control the main tumor mass; therefore, a peripheral dose of 14 Gy/50% isodose was first applied to the basal portion of the tumor, with a safe dose of 8 Gy isodose applied so that it was just touching the hat (optical apparatus) (Figs. 1C, 2A and B). Specifically, the basal tumor received a radiation dose of 14−28 Gy, whereas the small head received only 8−14 Gy and the optical apparatus received <8 Gy. Four months later, a lower dose of radiation (8 Gy at the periphery) was applied to the small head (Fig. 2C and D). Thus, the tumor received a dose of 8−16 Gy, whereas the chiasm received <8 Gy. The small head of the tumor received an additional 8−16 Gy when using the 50% isodose at the periphery. By the time of the last follow-up (96 months), the volume of the tumor had been reduced from 21.5 mL to 11.6 mL (Fig. 3 and Case no. 3 in Table 1). Furthermore, the patient's visual acuity improved to 1.0 (1.0 = 20/20 vision) and showed no visual field defects. Diplopia was completely recovered, and no new onset of cranial nerve deficit was found. Finally, the results of basal endocrine exams were within normal limit during the follow-up period, and the patient's vision was sufficient to allow for participation in daily activities, including driving a car.

4. Discussion

SRS has proven effective in the treatment of skull base meningioma, showing good tumor control.[6−10] In cases where the skull base meningioma is large or the tumor encases the optical apparatus, the dose limiting factor is determined by normal tissue tolerance to radiation. Fractionated radiotherapy may help avoid late complications involving the optic nerve and chiasm; however, SRS can require less time and reduce costs while providing an excellent dose fall-off gradient. In the case of single-fraction SRS, Tishler et al. did not observe the development of optic neuropathy in patients who received a maximal radiation dose (Dmax) of less than 8 Gy.[15] Leber et al. investigated the risk of optic neuropathy in 50 patients, the results of which demonstrated that a Dmax of less than 10 Gy is sufficient to avoid optic neuropathy when radiation is applied to the optic nerve or chiasm.[12] Moreover, Pollock et al. did not observe any cases of radiation-induced optic neuropathy among 62 patients undergoing GKS for nonfunctioning pituitary adenoma. For that study, the median Dmax applied to the optical apparatus was 9.5 Gy, and researchers reported using a dose constraint of <12 Gy when treating the optic structure.[13] In contrast, Shrieve et al. recommended that optimal treatment of benign meningioma required, at minimum, a single dose of 13.5−16.5 Gy radiation, which exceeds the clinical tolerance of the optic nerve and chiasm.[16] For meningioma patients who are candidates for stereotactic radiosurgery, hypofractionated radiosurgery is currently being promoted as a means to achieve the optimal treatment dose. Metha et al. previously employed image-guided stereotactic radiosurgery using a Cyberknife to treat lesions proximal to the anterior visual pathways. Radiation dosages were scheduled as follows: 25 Gy in 5 fractions, 21 Gy in 3 fractions, and 20 Gy in 2 fractions (with a 24-h interfractional interval). After a median follow-up time of 18 months (range: 12−54), four of the patients presented an improvement in vision, and no patients showed visual deterioration.[17] Hypofractionated radiosurgery therefore appears to have resolved the clinical dilemma caused by the close distance between tumors and the optical apparatus.

Several mathematical and biological models have been proposed to elucidate the relationships between dose schedule

and radiation-induced optic neuropathy. For example, Goldsmith et al. proposed a model with which to predict the cumulative radiation dose associated with optic nerve injury. In single-dose irradiation, the estimated Optic Ret dose is 8.9 Gy.[9,18] In contrast, a linear-quadratic model is well fitted for multiple-fraction therapy, with a fraction size <2 Gy; however, this model is unreliable when extrapolating from the fractionated dose range (1.8−2.0 Gy/fraction) to the single-fraction range.

The *snowman-shape design volume-staged radiation treatment*, which is based on the concept of fractionation, spares the optical apparatus exposure to unnecessary radiation, wherein an isodose of 8 Gy is delivered to the margin of the optical apparatus in the first fraction followed by another isodose of 8 or 10 Gy in the second and/or third fractions. This translates to a mean biologically effective dose (BED) ($\alpha/\beta = 3$ for optical apparatus) of 86 Gy [BED = D (1 + d/α/β) = 20 (1 + 10/3) = 86], compared to a BED of 90 Gy [BED = D (1 + d/α/β) = 54 (1 + 2/3) = 90] in conventional 2 Gy multi-session radiotherapy.[19] The *snowman strategy* allows higher maximum and cumulative radiation doses to be delivered while still reducing the amount of radiation that the optical apparatus is exposed to.

4.1. Radiation biology and tumor vascular anatomy of skull base meningioma

Application of the snowman strategy depends on the blood supply to parasellar/skull base meningiomas and the radiation biology of SRS. The blood supply of most parasellar/skull base meningiomas is provided by the external carotid artery (ECA) and the internal carotid artery (ICA), which are anastomosed to the lower part of skull base meningiomas. ECA circulation provides the primary supply of blood to the dura which is proximal to the meningioma,[20,21] with the middle meningeal artery (MMA) serving as the major supplier. The MMA follows a course anteriorly and posteriorly to supply the anterior dura and regions of the temporal bone as well as the middle fossa, the posterior fossa dura, and the lateral tentorium. Specifically, the MMA anastomosis with the ethmoidal arteries, the lacrimal artery, the posterior meningeal branch of the vertebral artery, and the artery of the inferior cavernous sinus. Most of these tumor feeders attach to the basal portion of the tumor. Feeders from the upper arachnoid or pia supplier including the meningohypophyseal trunk, McConnell's capsular arteries,[22] and even the ophthalmic artery are rarely observed. Thus, the basal portion of skull base meningiomas is the most important target in planning SRS treatment.

Handa et al.[23] and Yamaki et al.[24] used angiography to illustrate the derivation of the blood supply in the sphenoid ridge and the tuberculum sellae meningiomas, classifying vessels into anterior, lateral, and posterior groups. The anterior group includes branches of the ophthalmic and internal maxillary arteries as well as the MMA. This group supplies the dura of the sphenoidal plate, the tuberculum sellae, the anterior clinoid process, and the undersurface of the medial sphenoid ridge. The lateral group includes branches of the ophthalmic artery and the MMA, which supply the dura over the medial sphenoid ridge. Branches of the ICA as well as ophthalmic and accessory meningeal arteries, which supply the lateral wall of the cavernous sinus, are included in the posterior group.[24] From these angiographic studies, we identified very few feeders originating in the upper aspect of the tumor. This made it possible to apply the snowman-shape design using volume-staged SRS, in which the basal part of tumor was assigned the highest priority and the tumor vessel was eliminated (Fig. 1C). This approach also makes it possible to locate the hotspot either anteriorly, laterally, or posteriorly according to the vascularity of the individual tumor.

For decades, physicians have debated the precise biological effects of GKS radiation on benign intracranial tumors. GKS, which delivers single session irradiation at a high dose, is unlikely to meet the radiobiological principles such as the 4 Rs (Reoxygenation, Repair, Redistribution, Repopulation) for conventional fractionated radiotherapy. Song et al.[25] posited that the biological effects of GKS on intracranial benign tumors could be attributed to indirect cell death caused by vascular damage, which in turn resulted from hypofractionated irradiation (high dose per fraction). The role of tumor blood perfusion in the response of tumors to radiotherapy was first reported in 1936.[26] Ng and Fenton later reported that blood vasculatures in the inner regions of tumors are preferentially destroyed, compared with those in the tumor periphery.[27,28] Therefore, we believe that radiation doses which are high enough to deal with the basal mass can obliterate nutritive vessels in the upper portion of the tumor, and thereby contribute to tumor control (Fig. 1C). Following multiple stages of treatment, the basal portion of the tumor receives a full dose, the superior portion receives two moderate doses, and the optical apparatus receives two dosages below the upper tolerance limit.

4.2. Rationale for applying dose- and volume-staged SRS in the treatment of skull base meningioma

Staged SRS has proven to be as effective as single-session SRS and has lower complication rates.[29−35] In recent decades, the debate has continued as to whether volume-staged or dose-staged SRS is more beneficial. Many reports have recommended that dose-staged SRS be used to treat large intracranial lesions located close to critical neurovascular structures in order to prevent radiation-induced neuronal injury (e.g. traditional radiotherapy, Extend system® in GKS, or Cyberknife system®, fractionated GK, or Cyberknife). This approach is predicated on the fact that dose-fractionated SRS allows the delivery of higher maximum and cumulative radiation doses.[32] Kim et al. used a median marginal dose of 20 Gy to treat a tumor with an average volume of 4.1 cm^3 at isodose lines ranging from 46% to 50% in multisession GKS for benign perioptic lesions.[36] In comparison, a group from Stanford University delivered an average marginal dose of 20.3 Gy to treat a tumor with a mean volume of 7.7 cm^3 at isodose lines ranging from 70% to 90% using CyberKnife.[37] It therefore appears that dose-staged SRS is able to deliver doses

beyond the therapeutic margin without inducing complications.

However, in one recent systemic review, researchers investigated volume-staged and dose-staged SRS to compare the obliteration rate of intracranial arteriovenous malformations (AVMs). Their results revealed that the two treatment approaches are comparable with regard to safety; however, volume-staged SRS appears to produce higher obliteration rates.[38] In a comparison of volume-staged SRS and hypothetical single-session procedures, Pollock et al. discovered that volume-staging reduces exposure to radiation in the adjacent brain and critical neurovascular structure.[39] In a comparison of volume-staged radiosurgery and hypothetical hypofractionated stereotactic radiation therapy (HSRT), Fogh et al. determined that these two approaches were very similar in terms of sparing normal brain tissue from exposure to radiation. However, they found that HSRT applied a higher total dosage than what was calculated as an ideal dose in which efficacy and toxicity were balanced.[40] Based on these findings, it is reasonable to expect that volume-staged SRS (such as the snowman-shape design) should be ideally suited to the treatment of large lesions near the optical apparatus.

This is the first report to outline techniques used when implementing the concept of snowman shape in volume-staged GKS to treat a large skull base meningioma. Numerous reports have emphasized the importance of fractionated SRS (Extend system® in GKS, or Cyberknife system®) in the treatment of skull base meningioma; however, the snowman-shape design is the only method based on volume-staged SRS. This study demonstrated that the efficacy and safety of volume-staged SRS are comparable to those of dose-staged SRS for a large skull base meningioma.

4.3. Study limitations

The main limitation of this study is the fact that it was conducted retrospectively using a relatively small patient population, which limited the statistical power of the analysis. Furthermore, differences in inter-fraction intervals may have led to different histological changes and cellular regeneration patterns in tumors. Finally, selection bias and differences in radiosurgical techniques were unavoidable. Future studies should use a larger number of cases and a longer follow-up period to further validate the efficacy and safety of the snowman strategy in the treatment of skull base meningioma.

In conclusion, applying GKS to meningioma surrounding the optical apparatus presents a number of challenges. In this paper, we have reported four cases with a large skull base meningioma. GKS treatment was implemented using the novel snowman-shape design, which is a type of volume-staged SRS. Throughout the follow-up period, tumors were well controlled, and the function of the optic nerve was strongly preserved. We believe that the snowman-shape design is a highly feasible method for protecting the optical apparatus from radiation-induced injury. Nonetheless, long-term follow-up using a larger number of cases will be required to further evaluate the efficacy and to identify potential side effects.

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