Craniopharyngiomas are benign parasellar tumors that arise from residual epithelial cells of Rathke’s pouch. These tumors are characterized by a propensity to involve and densely adhere to surrounding vital neurovascular structures.  

Despite improvements in surgical outcomes with advances in microsurgical and endoscopic techniques, significant operative morbidity and mortality rates continue to pose formidable challenges to long-term remission from craniopharyngiomas.  

Therefore, adjuvant therapies, such as radiation therapy, have been considered since as early as 1904.  

Radiotherapy (RT) has emerged as a valuable ad-
juvenant treatment modality for recurrent or residual craniohypophyseal tumors. Several radiotherapeutic modalities, including conventional external-beam radiation therapy, intensity-modulated radiation therapy, single-fraction stereotactic radiosurgery (SRS) (e.g., Gamma Knife surgery [GKS]), fractionated stereotactic RT, and proton beam RT, have been used over the past decades and offer reasonable rates of tumor control. With advances in neuroimaging and RT modalities, dose delivery is more accurate and focused, resulting in decreased long-term complication rates over time. In this study, we reviewed a series of cases in which patients with craniopharyngioma were all treated by GKS. The long-term efficacy and safety of GKS were evaluated. Complications and prognostic factors were also analyzed. The goal of this report is to define the role of GKS in the current treatment of patients with craniopharyngioma.

Methods

A consecutive series of 137 patients with a craniopharyngioma underwent GKS at our institution between March 1993 and December 2012. Clinical data, including patient demographics, outcome of resection, adjuvant radiosurgical parameters, and imaging results, were retrospectively reviewed from an institutional review board–approved database.

The clinical survey of the patients with a craniopharyngioma included a meticulous neurological examination, a comprehensive hormone study, and ophthalmological evaluations, including formal visual acuity and visual field testing. Systemic endocrine studies, including obtaining the growth hormone, insulin-like growth factor–1, adrenocorticotropic hormone, serum cortisol, prolactin, triiodothyronine, thyroxine, free thyroxine, thyroxin-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, and estrogen (for female patients) or testosterone (for male patients) levels, were performed. Comprehensive hormone studies were performed for patients with a craniopharyngioma before and after their GKS.

Neuroimaging studies consisted of CT scans and MR images with and without contrast using thin slices and volume acquisition through the region of the sella turcica; an estimate of the volume of each tumor was established by MR volumetry. The sum of the areas was multiplied by the thickness of the MRI section, thus yielding the total tumor volume.39

GKS is intended to treat residual or recurrent craniopharyngiomas. In patients with mixed-type tumors, especially those with large cystic lesions adjacent to a solid nodular component, GKS has been reserved largely for treating only the solid portion in conjunction with the installation of radioisotopes for the cystic portion. In patients with a purely cystic craniopharyngioma, aspiration immediately before GKS was used for better tumor control.

Gamma Knife Technique

At Taipei Veterans General Hospital, a Leksell frame was placed for all adult patients under local anesthesia. Pediatric patients younger than 14 years were given general anesthesia for frame placement, which was main-
GKS for craniopharyngioma

years). The cohort consisted of 81 (59%) female patients. Before GKS, a combination of typical clinical features of craniopharyngiomas was found: visual field deficits (n = 127 [92.7%]), pituitary dysfunction (n = 118 [86.1%]), diabetes insipidus (n = 85 [62.0%]), other hypothalamic dysfunction (n = 32 [23.4%]), and other cranial nerve deficits (n = 10 [7.3%]). The median tumor volume was 5.5 ml (range 0.8–28.4 ml). A pure solid craniopharyngioma was present in 23 (16.8%) patients, a purely cystic craniopharyngioma in 23 (16.8%) patients, and a mixed-type craniopharyngioma in 91 (66.4%) patients. In terms of tumor location, 126 (92.0%) patients had a craniopharyngioma extending to the suprasellar region, 24 (17.5%) tumors extended into the third ventricle, 31 (22.6%) had cavernous sinus extension, and 4 (2.9%) extended to the retrosellar region (Table 1).

Resection such as craniotomy or transsphenoidal surgery was suggested as the first-line treatment for 94 patients (68.6%). For patients who had a purely cystic craniopharyngioma, biopsy (n = 3 [2.2%]) and aspiration (n = 28 [20.4%]) were performed. An alternative was the placement of Ommaya reservoirs for the intermittent aspiration of cysts that could not be completely resected (n = 21 [15.3%]). When repeated cyst aspirations were deemed inadvisable, intralesional RT or chemotherapy was used (n = 5 [3.6%]). Minimal excision combined with intermittent intralesional bleomycin through an Ommaya reservoir was used for children with cystic craniopharyngioma (n = 3). Another alternative for patients with a solitary or multicystic tumor was intracavitary irradiation via stereotactically applied radioisotopes (n = 2). Beta-emitting isotopes such as yttrium-90, rhenium-196, and phosphorus-32 were preferred because of the limited penetration of the emitted energy and the relative ease of handling (Table 1).

Treatment Parameters

A median margin dose of 12.0 Gy (range 9.5–16.0 Gy) was delivered to a median isodose line of 55% (50–78%). The median maximum dose was 21.8 Gy (range 15.4–32.0 Gy), and the median mean dose was 16.2 Gy (range 12.9–21.4 Gy) (Table 2).

Tumor Control

Nine (6.6%) of the 137 patients were lost to follow-up, and their post-GKS images were not available. The median neuroimaging follow-up time of the other 128 patients was 45.7 months (range 6–226 months). Follow-up times of at least 2, 4, and 6 years were obtained for 87, 56, and 34 patients, respectively. At the last follow-up, a decrease in tumor volume was observed in 69 patients (53.9%), and 2 patients (1.6%) were in stable condition after GKS (Table 3).

However, 21 (16.4%) of 128 patients had tumors that had enlarged despite GKS, 19 (14.8%) patients had initial tumor shrinkage followed by delayed growth, 6 (4.7%) patients had new lesions that were outside the previous GKS field (outfield recurrence), and 11 (8.6%) patients had only cyst enlargement without tumor growth. A discrepancy between tumor and cyst growth, which was treated by simple aspiration or bleomycin injection (Table 3), sometimes occurred after GKS. The detailed numbers and percentages of tumor response in the 3 groups of patients are listed in Table 4 to compare the efficacy of GKS with regard to different features of their craniopharyngiomas. Good tumor control was achieved in 72.7%, 73.9%, and 66.3% for patients with purely solid tumors, purely cystic tumors, and mixed solid and cystic tumors, respectively (Table 5).

The actuarial progression-free survival rates plotted by the Kaplan-Meier method were 70.0% and 43.8% at 5 and 10 years after radiosurgery, respectively (Fig. 1). The overall survival rates in this group of patients were 91.5% and 83.9% at the 5- and 10-year follow-ups, respectively (Fig. 2). Images from 2 patients with a craniopharyngioma who had excellent tumor response are shown in Figs. 3 and 4.

Prognostic factors were analyzed using univariate and multivariate analysis by logistic regression (Table 6). A smaller tumor volume before GKS was associated with successful GKS treatment (p = 0.050 [univariate analysis] and 0.011 [multivariate analysis]) (Fig. 5). Other factors such as age, sex, margin dose, maximum dose, mean dose, tumor extension, previous visual field deficits, pathological classification, and the extent of resection were not associated with the tumor control outcome (Table 6).

Neurological and Endocrinological Results

The median neurological and endocrinological follow-up time was 52.6 months (range 6–226 months). Of the 137 patients, 127 (92.7%) were found to have visual field deficits before GKS, and 13 of them (9.5%) showed subjective and objective improvement at the last follow-up; 118 patients (86.1%) had preexisting hypopituitarism, and none discontinued their hormone replacement treatment after GKS. At the last follow-up, only 1 of 10 patients with cranial nerve dysfunction had shown improvement. Three patients with diabetes insipidus who needed medications before radiosurgery were able to discontinue their medications, and their quality of life was much improved (Table 7).

Most patients had stable neurological results, but a few had neurological and endocrinological deterioration, mostly related to tumor growth. For example, visual field progression was present in 28 patients, 2 of whom were without tumor growth. Seven patients suffered cranial nerve palsy, 1 of whom had no tumor recurrence. Neurological deficits without tumor growth may be results of radiation injury and, thus, were considered to be complications of GKS. The mortality rate in this series was 8.8% (Table 7).

Complications

Hypopituitarism. A pre-GKS loss of 1 or more pituitary axes was present in 118 patients (86.1%). New-onset or worsened pituitary deficiencies were detected in 8.0% (n = 11) of the patients and were seen in the thyroid axis (n = 8), cortisol axis (n = 8), growth hormone axis (n = 3), and gonadotroph axis (n = 2). Two patients developed panhypopituitarism after GKS. The median time to de-
Development of a new pituitary hormone deficiency was 37 months (Table 8).

Other Complications. Two patients had adverse radiation effects that appeared on MRI studies 18 months after GKS; however, these patients were asymptomatic. There were 2 patients without tumor growth who suffered worsened visual field deficits, and 1 patient without tumor growth who developed new-onset third cranial nerve palsy. Fifteen patients (10.9%), together with the patients with new-onset hypopituitarism, may have suffered radiation injury and, hence, were included as those who experienced complications of GKS (Table 8).

### TABLE 1: Characteristics of 137 patients with a craniopharyngioma who underwent GKS*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>age at diagnosis (yrs)</td>
<td>median</td>
<td>27.1</td>
</tr>
<tr>
<td></td>
<td>mean</td>
<td>28.6</td>
</tr>
<tr>
<td>age at GKS (yrs)</td>
<td>median</td>
<td>30.1</td>
</tr>
<tr>
<td></td>
<td>mean</td>
<td>30.3</td>
</tr>
<tr>
<td>sex (F/M ratio)</td>
<td></td>
<td>81:56</td>
</tr>
<tr>
<td>median tumor vol (ml)</td>
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<td>5.5</td>
</tr>
<tr>
<td>classification</td>
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<td></td>
</tr>
<tr>
<td>solid</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>cystic</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>mixed</td>
<td></td>
<td>91</td>
</tr>
<tr>
<td>no. of tumors w/ suprasellar extension</td>
<td></td>
<td>126</td>
</tr>
<tr>
<td>no. of tumors w/ 3rd ventricle extension</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>no. of tumors w/ cavernous sinus invasion</td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>no. of tumors w/ retrosellar extension</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>no. of patients w/ 5 previous resections</td>
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<td>94</td>
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<tr>
<td>resections</td>
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<td>1</td>
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<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
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<td>1</td>
</tr>
<tr>
<td>no. of patients w/ previous biopsy</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>no. of patients w/ previous cyst aspiration</td>
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<td>28</td>
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<tr>
<td>no. of patients w/ previous Ommaya reservoir placement</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>no. of patients w/ previous intracavity Tx (RT or chemo)</td>
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<td>5</td>
</tr>
<tr>
<td>no. of patients w/ previous VP shunt placement</td>
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<td>88</td>
</tr>
<tr>
<td>no. of patients w/ previous RT</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>no. of patients w/ previous chemo</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>pre-GKS visual field deficits</td>
<td></td>
<td>127</td>
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<tr>
<td>pre-GKS hypopituitarism</td>
<td></td>
<td>118</td>
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<tr>
<td>pre-GKS diabetes insipidus</td>
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<td>pre-GKS hypothalamic dysfunction</td>
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<td>32</td>
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<tr>
<td>pre-GKS CN deficits</td>
<td></td>
<td>10</td>
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</table>

* chemo = chemotherapy; CN = cranial nerve; TV = tumor volume; Tx = treatment; VP = ventriculoperitoneal.

† No. of patients with GTR of tumor. Only 6 patients had GTR, in most of whom the GTR was achieved in the first or second resection.

### TABLE 2: Treatment parameters of the patients with a craniopharyngioma

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median Value</th>
<th>Range</th>
</tr>
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<tbody>
<tr>
<td>radiation vol (ml)</td>
<td>7.2</td>
<td>0.5–34.0</td>
</tr>
<tr>
<td>margin dose (Gy)</td>
<td>12.0</td>
<td>9.5–16.0</td>
</tr>
<tr>
<td>maximum dose (Gy)</td>
<td>21.8</td>
<td>15.4–32.0</td>
</tr>
<tr>
<td>mean dose (Gy)</td>
<td>16.2</td>
<td>12.9–21.4</td>
</tr>
<tr>
<td>isodose level (%)</td>
<td>55.0</td>
<td>50–78</td>
</tr>
<tr>
<td>no. of isocenters</td>
<td>12</td>
<td>2–29</td>
</tr>
</tbody>
</table>
Additional Management After GKS

Among patients with tumor growth (n = 21) after GKS, 16 underwent resection and 5 were observed. Among the 16 patients who underwent resection, 5 received adjuvant RT and 4 received repeated GKS. Of the patients who had initial tumor shrinkage followed by delayed regrowth (n = 19), 11 underwent repeated GKS, 7 underwent resection, 2 underwent RT. Observation was not an option of management. Of the patients with an out-of-field recurrence (n = 6), 5 received repeated GKS and 1 underwent craniotomy plus RT. For these patients, a wait-and-see approach was not an option. All the patients with isolated cyst enlargement underwent aspiration, and 6 of them received an Ommaya reservoir implantation. After aspiration of the cyst, 5 patients received repeated GKS, 4 received conventional RT, and 1 patient began bleomycin injection. A craniotomy for cyst removal was performed in 2 cases (Table 3). In each of the patients who required resection, histological results indicated either an adamantinomatous or a papillary subtype of craniopharyngioma. No changes in diagnosis were made.

The tumor control rates in the patients with a craniopharyngioma after a single GKS were 75% at 3 years, 70% at 5 years, 54% at 8 years, and 44% at 10 years GKS (Fig. 6). The rates were higher with repeated GKS: 82% at 3 years, 77% at 5 years, 64% at 8 years, and 61% at 10 years. The difference was statistically significant (p = 0.003).

Discussion

Surgical results for craniopharyngiomas have shown that a complete resection rate of 45%–90% can be achieved,6,27,37,38,41,48 with a reported 5-year tumor control rate of 70%–90%.11,15,41 Similar tumor control and recurrence rates were achieved for patients who underwent transsphenoidal surgery.6,11 However, recurrence rates of up to 85% were observed for partially resected craniopharyngiomas.11,37,38,41,48 Mortality rates in patients with a partially resected craniopharyngioma have ranged from 0% to 4%.11,37,41 In contrast, a dramatic increase in mortality rates to 10%–17% was demonstrated when aggressive resection was attempted to achieve total resection.41 Its associated morbidity (e.g., pituitary dysfunction, hypothalamic dysfunction, and visual and neurocognitive deficits) rate has ranged from 20% to 80%.22,11,15,16,41

Gamma Knife surgery results for patients with a craniopharyngioma have been reported in 14 previously published reports.2–4,7,8,18,22,23,30,32,34,40,44,46,47 In 4 reports with long-term follow-up periods, the 5-year progression-free survival rates were 52%–68%, with 5-year overall survival rates of 86%–97% (Table 9). In a series of 37 patients who underwent GKS for a craniopharyngioma, the 5-year overall survival and in-field progression-free survival rates were 75.6% and 67%, respectively. Hasegawa et al.13 reported 5- and 10-year progression-free survival rates of 62% and 52%, respectively, in 100 patients with a craniopharyngioma, Niranjan et al.32 reported a 97.5% overall survival rate 5 years after GKS and a 91.6% 5-year progression-free survival rate among 46 patients with long-term follow-up (mean 62.2 months). A possible explanation for the discrepancies in overall survival and progression-free survival rates among the different craniopharyngioma radiosurgical series may be the relatively smaller number of patients and shorter follow-up periods in these studies compared with those in reports from conventional RT series.

In the Xu et al. series,44 prognosis factors associated with the in-field progression-free survival rate were an absence of visual field deficits before GKS, a solid tumor volume of less than 1.6 ml, and a margin dose greater than 14.5 Gy The magnitude of the margin dose depends considerably on tumor volume and its proximity to critical structures.9,13 Higher margin doses seem to be associated with prolonged progression-free survival. Additional factors associated with a favorable response to GKS, as shown in previous reports, were noncystic tumor composition, fewer previous interventions, and lower tumor volume. For patients with significant tumor recurrence,
Cytoreductive surgery may be considered before treatment with GKS.\textsuperscript{8,44}

With repeated GKS, tumor control rates can be improved by 7%, 7%, 10%, and 17% at the 3-, 5-, 8-, and 10-year follow-ups, respectively (Fig. 5). We believe that repeated radiosurgery plays an important role in preventing tumor enlargement, especially for small tumors distant from the optic apparatus.

Cyst Development and Enlargement During Radiation Therapy

The cystic component of a craniopharyngioma commonly presents a problem for radiation therapy and radiosurgery. Cyst reaccumulation is not equivalent to tumor recurrence, and shrinkage of the tumor’s solid component is not always accompanied by cyst regression. The solid component of the tumor can usually be controlled by radiation. In contrast, the cystic component may require surgical decompression. Tumor growth and cyst enlargement can be independent. On the basis of this principle, several approaches can be taken in the management of patients with a cystic craniopharyngioma either at initial presentation or at recurrence. Of these approaches, the following treatments are commonly used to decrease cyst size: intermittent aspiration by stereotactic puncture or placement of an Ommaya reservoir, sclerosis of the cyst wall by chemotherapeutic drugs, and internal irradiation (i.e., brachytherapy) with implanted radioisotopes.

Percutaneous aspiration of cyst contents has been used to alleviate cyst-related symptoms, and intermittent aspiration may be recommended for patients who are poor surgical candidates. An alternative is the placement of an Ommaya reservoir for the intermittent aspiration of a cyst that cannot be completely resected. Recently, several case reports indicated that stereotactic cyst aspiration in conjunction with same-day SRS achieved good tumor control (Fig. 3).\textsuperscript{14,26,33}

Debates

Although the beneficial effect of radiation in the treatment of craniopharyngiomas has been well recognized, 2 critical issues remain sources of significant controversy: 1) the merits of GTR versus subtotal resection followed by irradiation given the surgical morbidity and mortality rates associated with aggressive resection and 2) the role of RT immediately after resection without first monitoring for tumor progression and the role of RT in the absence of resection (up-front or salvage treatment).

On the basis of the complications associated with aggressive resection and the proven efficacy of radiation for craniopharyngiomas, several authors have recommended subtotal resection and RT as an acceptable alternative to total resection. Although clinicians can often mitigate the

### Table 5: Imaging outcomes of 128 patients with a craniopharyngioma after GKS based on features of the tumor\textsuperscript{*}

<table>
<thead>
<tr>
<th>Tumor Control</th>
<th>Solid (n = 22)</th>
<th>Cystic (n = 23)</th>
<th>Mixed (n = 83)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>good (%)†</td>
<td>16 (72.7)</td>
<td>17 (73.9)</td>
<td>55 (66.3)</td>
<td>88 (68.8)</td>
</tr>
<tr>
<td>poor (%)‡</td>
<td>6 (27.3)</td>
<td>6 (26.1)</td>
<td>28 (33.7)</td>
<td>40 (31.3)</td>
</tr>
</tbody>
</table>

* The 2 × 3 chi-square test showed no differences between tumor control and tumor types (p = 0.710).
† Good tumor control included shrinkage, stability, new lesion development, and cyst growth, forming a good tumor control group.
‡ Poor tumor control included growth, initial shrinkage, and regrowth, forming a poor tumor control group.

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**Fig. 1.** Kaplan-Meier progression-free survival curve for patients with a residual or recurrent craniopharyngioma after GKS. The progression-free survival rates were 70.0% and 43.8% at the 5- and 10-year follow-ups, respectively. Obs = observed.

**Fig. 2.** Kaplan-Meier overall survival curve for patients with a residual or recurrent craniopharyngioma after GKS. The survival rates were 91.5% and 83.9% at the 5- and 10-year follow-ups, respectively.
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Fig. 3. A 55-year-old female patient had a cyst-type craniopharyngioma status post ventriculoperitoneal shunting and Ommaya reservoir implantation. She had bitemporal hemianopsia and hypopituitarism, and she underwent cyst aspirations several times before GKS. During the GKS, the cyst contents were aspirated, and then a 12-Gy radiation dose was delivered to the small enhanced nodule (0.6 ml in volume) at the 54% isodose line. At 52, 87, and 113 months (M) after GKS, the tumor appeared as a tiny ill-defined suprasellar spot with mild enhancement. Her neuroendocrinological and ophthalmological statuses were stable at the last follow-up.

Fig. 4. A 21-year-old female patient had a solid-type craniopharyngioma status post craniotomy. Double vision, hypopituitarism, and diabetes insipidus were noted before GKS. Axial and coronal images revealed a 7.3-ml tumor. A 12-Gy dose was delivered to the tumor margin via 17 isocenters. On a follow-up series of images, the tumor was seen to be significantly decreased in volume. It appeared as a small enhanced spot, and no cyst was visualized. The patient’s neuroendocrinological and ophthalmological statuses were stable at the last follow-up.

Fig. 5. Graph illustrating the influence of pre-GKS tumor volume (TV) on the tumor control rate of residual or recurrent craniopharyngiomas after GKS. The tumor control rate was better in the patients with a smaller tumor volume (< 5.5 ml); this difference was statistically significant (p = 0.011).

effects of neurological deficits and endocrinological dysfunction, the psychosocial consequences associated with radical resection are now recognized as the major limiting factors in quality of life as pediatric patients grow into adulthood. Thus, the minimization of surgical hypothalamic injury is crucial for optimizing the postoperative quality of life for patients with a craniopharyngioma,
especially for younger patients. To limit significant neurological, endocrinological, and psychosocial morbidities that may accompany radical resection, some physicians prefer less aggressive resection followed by RT. Some pediatric series have indicated that RT given immediately after surgery (up front) may be preferable to RT at the time of recurrence (salvage), with lower rates of morbidity and improved tumor control.12,31,36,43 However, for adult patients with a craniopharyngioma, there have been no significant differences in either tumor control or overall survival between up-front and salvage RT.10,29,35,42 Therefore, some clinicians advocate early postoperative RT or SRS for partially resected tumors.28

Because of the steep dose decrease with SRS compared with that with conventional RT, some physicians use SRS as a primary treatment for craniopharyngiomas. In a study of 5 pediatric patients with a craniopharyngioma in which SRS was the primary treatment for the solid portion of the mixed tumors after intracavitary phosphorus-32 was used to treat the cystic portion, 2 patients experienced tumor regression, and another 2 patients had tumor control.2 Other studies have shown higher tumor

| TABLE 6: Prognostic factors of patients with a craniopharyngioma undergoing GKS |
|----------------------------------|---------------|--------------|---------------|
| Factor                          | Univariate Logistic Regression | Multivariate Logistic Regression* |
|                                 | p Value | OR (95% CI) | p Value | OR (95% CI) |
| age (child vs adult)†          | 0.582    | 0.816 (0.395 to ~1.683) | —       | —           |
| sex (F vs M)                   | 0.555    | 0.805 (0.392 to ~1.654) | —       | —           |
| margin dose (>12 vs ≤12 Gy)    | 0.450    | 1.687 (0.435 to ~6.553)  | —       | —           |
| maximum dose (>21.8 vs ≤21.8 Gy) | 0.719    | 0.871 (0.411 to ~1.846)  | —       | —           |
| mean dose (>16 vs ≤16 Gy)      | 0.240    | 0.629 (0.290 to ~1.364)  | 0.779   | 1.010 (0.943 to ~1.081) |
| tumor vol (≤5.5 vs >5.5 ml)    | 0.050    | 2.042 (0.996 to ~4.187)  | 0.011   | 1.092 (1.021 to ~1.168) |
| tumor extension                 | —        | —               | —       | —           |
| suprasellar extension (yes vs no) | 0.453    | 0.622 (0.179 to ~2.154)  | —       | —           |
| 3rd ventricle extension (yes vs no) | 0.847    | 0.913 (0.359 to ~2.318)  | —       | —           |
| cavernous sinus (yes vs no)    | 0.531    | 1.891 (0.258 to ~13.867) | —       | —           |
| retrostellar extension (yes vs no) | 0.531    | 1.891 (0.258 to ~13.867) | —       | —           |
| visual field deficits at GKS (yes vs no) | 0.312    | 2.272 (0.463–11.153)    | —       | —           |
| pathology (adamantinomatous vs papillary) | 0.392    | 0.375 (0.04 to ~3.551)   | —       | —           |
| resection (GTR vs biopsy or drainage only) | 0.119    | 1.827 (0.857 to ~3.896)  | 0.251   | 1.585 (0.722 to ~3.479) |

* The factors with a p value of < 0.25 in the univariate analysis were put in multivariate analysis.
† The cutoff value between a child and an adult was 18 years.

Fig. 6. Tumor control rates for repeated GKS for craniopharyngiomas. The lower green line demonstrates the tumor control rate via single GKS. The blue line shows the tumor control rate via repeated GKS when tumors were recurrent. With repeated GKS, the tumor control rates achieved were 7%, 7%, 10%, and 17% higher at the 3-, 5-, 8-, and 10-year follow-ups, respectively.
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control rates in single-type tumors (solid or cystic) compared with that in mixed-type tumors. Chung et al.8 found that single-type tumors were more responsive to primary radiosurgical treatment in contrast to mixed-type tumors. It is also believed that solid-type tumors and the solid portions of mixed-type tumors are less responsive to intracavitary irradiation than are cystic tumors.19,20 As a result, Prasad et al.34 recommended that mixed-type tumors be treated with a combination of radioisotope instillation and SRS. The combination of SRS and intracavitary radiation has been advocated as a primary treatment for mixed cystic-solid tumors.2,47

Study Limitations

The current study was retrospective in nature. Inherent to this study design, there exist patient selection and treatment biases reflective of the treating clinicians and institutions. Selection bias may have been present in this study, because the majority of patients did not achieve GTR, which may indicate cases of higher complexity. In addition, the decisions of whether to use GKS or RT were not made by using a stringent guideline because these decisions were often made at the discretion of the treating physicians.

Conclusions

The messages we deliver from this report are the following: 1) the overall survival rates for patients after GKS performed to treat a residual or recurrent craniopharyngioma were 91.5% and 83.9% at the 5- and 10-year follow-ups, respectively; 2) the progression-free survival rates for patients after GKS for a residual or recurrent craniopharyngioma were 70.0% and 43.8% at the 5- and 10-year follow-ups, respectively; 3) a smaller tumor volume was associated with successful treatment with GKS; and 4) complications included hypopituitarism (8.0%), adverse radiation effects (1.5%), visual deterioration (1.5%), and new-onset cranial nerve palsy (0.7%)

The results of our study suggest that GKS is a relatively safe modality for the treatment of recurrent or residual craniopharyngiomas and is associated with improved tumor control and in-field progression-free survival rates. Acceptable rates of complications were observed.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Liu, Lee, Yang, Hung, Chung, Pan. Acquisition of data: Lee, Yang, Hung, Pan. Analysis and interpretation of data: Liu, Lee, Yang, Chen. Drafting the article: Lee, Chen, Hung. Critically revising the article: Liu, Lee, Yang, Chen, Chung. Reviewed submitted version of manuscript: Liu, Lee, Yang, Chen, Guo, Chung. Approved the final version of the manuscript on behalf of all authors: Liu. Statistical analysis: Lee,

### TABLE 7: Clinical outcomes of the patients who underwent regular follow-up after GKS for a craniopharyngioma

<table>
<thead>
<tr>
<th>Clinical Parameter (no.)†</th>
<th>Improvement (no.)</th>
<th>Stability (no.)</th>
<th>Deterioration (no.)</th>
<th>Not Available (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>visual field</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-GKS normal (10)</td>
<td>—</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>pre-GKS deficits (127)</td>
<td>13</td>
<td>77</td>
<td>28 (w/o tumor growth)</td>
<td>9</td>
</tr>
<tr>
<td>hypopituitarism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-GKS normal (19)</td>
<td>—</td>
<td>17</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>pre-GKS deficits (118)</td>
<td>0</td>
<td>99</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>cranial nerve function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-GKS normal (127)</td>
<td>—</td>
<td>111</td>
<td>7 (w/o tumor growth)</td>
<td>9</td>
</tr>
<tr>
<td>pre-GKS deficits (10)</td>
<td>1</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>diabetes insipidus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-GKS normal (52)</td>
<td>—</td>
<td>48</td>
<td>1 (w/o tumor growth)</td>
<td>3</td>
</tr>
<tr>
<td>pre-GKS deficits (85)</td>
<td>3</td>
<td>76</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

* Clinical neurological and endocrinological data were available for these 137 patients.
† Twelve of 137 followed patients died, for a mortality rate of 8.8%.

### TABLE 8: Complications of GKS in patients with a craniopharyngioma

<table>
<thead>
<tr>
<th>Complication</th>
<th>No. of Cases</th>
<th>Ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>adverse radiation effects</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>visual deterioration</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>new CN palsy</td>
<td>1†</td>
<td>0.7</td>
</tr>
<tr>
<td>cerebrovascular accident</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>secondary tumor</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>hypopituitarism</td>
<td>11</td>
<td>8.0</td>
</tr>
<tr>
<td>hypothyroidism</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>hypoadrenalism</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>hyposomatotropism</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>hypogonadism</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>panhypopituitarism</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>15</td>
<td>10.9</td>
</tr>
</tbody>
</table>

* The complications were found in 137 patients who underwent regular clinical follow-up.
† The patient with new-onset third cranial nerve palsy also had visual deterioration simultaneously.
### TABLE 9: GKS for craniopharyngioma in 14 studies*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No.</th>
<th>Mean Age in Yrs (no. of patients)</th>
<th>Prior Resection</th>
<th>Intracavitary Isotope Tx</th>
<th>Intracavitary Bleomycin Tx</th>
<th>Mean FU (yrs)</th>
<th>Mean Margin Dose (Gy)</th>
<th>Mean TV (ml)</th>
<th>Tumor Control Rate (%)</th>
<th>Further Treatment (%)</th>
<th>Morbidity Rate (%)</th>
<th>Mortality Rate (%)</th>
</tr>
</thead>
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<tr>
<td>present study</td>
<td>137</td>
<td>30</td>
<td>69</td>
<td>1.5</td>
<td>NA</td>
<td>2.1</td>
<td>0.8</td>
<td>4.4</td>
<td>12.0</td>
<td>5500</td>
<td>73</td>
<td>11.7</td>
</tr>
<tr>
<td>Jeon et al., 2011</td>
<td>13</td>
<td>34</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td>0.2</td>
<td>4.2</td>
<td>14.5</td>
<td>1600</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Xu et al., 2011</td>
<td>37</td>
<td>66</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>2.2</td>
<td>11.5</td>
<td>3500</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Yomo et al., 2009</td>
<td>18</td>
<td>36</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>5.2</td>
<td>13.0</td>
<td>1000</td>
<td>78</td>
<td>100</td>
</tr>
<tr>
<td>Niranjan et al., 2010</td>
<td>46</td>
<td>24</td>
<td>94</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td>2.2</td>
<td>13.0</td>
<td>1000</td>
<td>78</td>
<td>100</td>
<td>59</td>
</tr>
<tr>
<td>Kobayashi et al., 2012</td>
<td>98</td>
<td>&lt;15 (38), &gt;15 (60)</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>3</td>
<td>0</td>
<td>5.5</td>
<td>11.5</td>
<td>3500</td>
<td>93</td>
<td>100</td>
</tr>
<tr>
<td>Albright et al., 2005</td>
<td>5</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td>2.4</td>
<td>11.5</td>
<td>6500</td>
<td>2.2</td>
<td>11.5</td>
<td>80</td>
</tr>
<tr>
<td>Barua et al., 2003</td>
<td>7</td>
<td>NA</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>4.2</td>
<td>14.2</td>
<td>NA</td>
<td>NA</td>
<td>100</td>
<td>NA</td>
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<tr>
<td>Amendola et al., 2003</td>
<td>14</td>
<td>12</td>
<td>86</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3.3</td>
<td>14.0</td>
<td>3700</td>
<td>NA</td>
<td>100</td>
<td>NA</td>
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<tr>
<td>Ulfarsson et al., 2002</td>
<td>21</td>
<td>&lt;15 (11), &gt;15 (10)</td>
<td>56</td>
<td>19</td>
<td>23</td>
<td>NA</td>
<td>0</td>
<td>11.5</td>
<td>50</td>
<td>8000</td>
<td>57</td>
<td>100</td>
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<td>Chung et al., 2000</td>
<td>31</td>
<td>32</td>
<td>74</td>
<td>6.5</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3.0</td>
<td>12.2</td>
<td>8900</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Chiou et al., 2001</td>
<td>10</td>
<td>15</td>
<td>50</td>
<td>30</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>5.7</td>
<td>16.4</td>
<td>1700</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Yu et al., 2000</td>
<td>46</td>
<td>39</td>
<td>61</td>
<td>72</td>
<td>6.5</td>
<td>0</td>
<td>0</td>
<td>1.3</td>
<td>8–18†</td>
<td>13,500</td>
<td>90</td>
<td>86</td>
</tr>
<tr>
<td>Mokry, 1999</td>
<td>23</td>
<td>31</td>
<td>39</td>
<td>0</td>
<td>43</td>
<td>4</td>
<td>2.0</td>
<td>8–10†</td>
<td>7000</td>
<td>—</td>
<td>74</td>
<td>—</td>
</tr>
<tr>
<td>Prasad et al., 1995</td>
<td>9</td>
<td>38</td>
<td>67</td>
<td>44</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>12.9</td>
<td>10,000</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

* Not included in overall evaluation of morbidity due to ambiguity in the etiology of new symptoms and the effects of concurrent surgical manipulation. FU = follow-up; NA = information not available; TV = tumor volume.  
† Mean not given.
References

38. Shirane R, Ching-Chan S, Kusaka Y, Jokura H, Yoshimoto T: Surgical outcomes in 31 patients with craniopharyngiomas extending outside the suprasellar cistern: an evaluation...

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