Recurrent craniopharyngioma after conformal radiation in children and the burden of treatment

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OBJECT In this paper the authors present their experience treating children with recurrent craniopharyngioma who were initially managed with surgery followed by conformal radiation therapy (CRT).

METHODS A departmental oncology information system was queried to identify all children (< 18 years old) who received CRT for a craniopharyngioma between 1998 and 2010 (inclusive) and specifically those who experienced tumor progression. For each patient, the authors recorded the type of recurrence (solid, cystic, or both), the time interval to first progression and each subsequent progression, the associated treatment complications, and disease status at last follow-up evaluation.

RESULTS Among the 97 patients that met criteria for entry into this study, 18 (18.6%) experienced tumor progression (9 cystic, 3 solid, 6 cystic and solid). The median time to first recurrence was 4.62 years (range 1.81–9.11 years). The subgroup included 6 female and 12 male patients with a median age of 7.54 years (range 3.61–13.83 years). Ten patients experienced first progression within 5 years of CRT. The 5- and 10-year treatment-free survival rates for the entire cohort were 89.0% (95% confidence interval [CI] 80.5%–93.9%) and 76.2% (95% CI 64%–85%), respectively. Seven patients had a single episode of progression and 11 had more than 1. The time interval between each subsequent progression was progressively shorter. The 18 patients underwent 38 procedures. The median follow-up duration for this group was 9.32 years (range 4.04–19.0 years). Three patients died, including 1 from perioperative complications.

CONCLUSIONS Craniopharyngioma progression after prior irradiation is exceedingly difficult to treat and local control is challenging despite repeated surgical procedures. Given our results, gross-total resection may need to be the surgical goal at the time of first recurrence, if possible. Decompressing new cyst formation alone has a low rate of long-term success.

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KEY WORDS craniopharyngioma; conformal radiation therapy; tumor progression; oncology

CRANIOPHARYNGIOMA is a histologically benign tumor that most commonly arises from suprasellar nests of epithelium derived from Rathke's pouch, which is the embryonic precursor of the anterior pituitary gland. The adamantinomatous type predominates in children with solid and cystic components with calcifications, typically in an "egg-shell" pattern. The presenting signs and symptoms are due to involvement of local structures, namely the optic apparatus, hypothalamus, pituitary gland and stalk, and third ventricle. The management of this tumor continues to generate spirited debate among pediatric

neurosurgeons, which indicates that there is no preferred treatment paradigm.¹⁰ Historically, aggressive surgical extirpation has been advocated, with the goal being gross-total removal. Proponents argue that this approach affords the patient the best chance of a cure without having to endure further potentially harmful treatment, namely additional surgery or radiation. Alternatively, others have advocated conservative or maximal safe resection followed by radiotherapy as a means to provide adequate local tumor control while avoiding the significant morbidity associated with aggressive initial surgery. Two recent pe-

ABBREVIATIONS CI = confidence interval; CRT = conformal radiation therapy; GKS = Gamma Knife surgery; GTR = gross-total resection; IMRT = intensity-modulated radiation therapy; PBT = proton beam therapy; SJCRH = St. Jude Children's Research Hospital; STR = subtotal resection.

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diatric systematic reviews demonstrated that there was no difference in the 1- and 5-year progression free survival between the 2 treatment approaches; however, patients treated with gross-total resection (GTR) had a higher risk of developing diabetes insipidus and new neurological deficits.^{6,7} Similar findings were published by Schoenfeld et al. based on a 30-year experience treating both pediatric and adult patients.³² Iannalfi et al. performed a literature review covering the period from January 1990 to May 2012 and identified 43 studies including 1716 patients treated with radiation for craniopharyngioma.¹⁴ From these studies, the reported 10-year local control rates ranged between 77% and 100%, and the long-term toxicity of combined limited surgery and radiation was less than that associated with radical surgery.

For a number of years, our philosophy at St. Jude Children's Research Hospital (SJCRH) has been to limit the extent of surgical intervention and follow with conformal radiation therapy (CRT).²⁴ Initial surgery is tailored to the child's symptoms and the tumor's imaging features. For example, tumors that are causing obstructive hydrocephalus or visual loss as a result of compression of the optic apparatus are often debulked to re-establish CSF pathways or to decompress the visual apparatus, respectively. Tumors that are primarily cystic are often treated by placing a catheter—stereotactically or via craniotomy—into the cyst with immediate decompression, thus reducing the volume needed to be treated with radiation. Aggressive extirpation in an effort to accomplish a GTR is, in general, not pursued, especially if there is hypothalamic involvement noted on the preoperative imaging or at the time of surgery. Injury to the hypothalamus, which is usually due to surgical manipulation as opposed to tumor infiltration as suggested by some, can lead to well-described long-term debilitating complications, such as global loss of neuroendocrine function, uncontrollable appetite, changes in behavior, and cognitive decline.^{8,35} The principal objective for all patients is to minimize surgical morbidity and maximize quality of life by regaining and retaining as much neurological, endocrine, cognitive, and behavioral function for as long as possible.

Surgery is also indicated for tumors that progress after CRT with the focus typically being on the portion of the tumor that demonstrates regrowth. Recurrent craniopharyngioma in children is one of the most difficult challenges faced by pediatric neurosurgeons. Treatments following CRT are broadly divided into more surgery or stereotactic radiosurgery; further CRT is not an option. This report details our experience in treating children who have demonstrated either cystic or solid tumor progression following photon-based CRT.

Methods

Study Population

Using a prospectively maintained database, we identified all children (< 18 years old) who underwent CRT for a craniopharyngioma (with or without tissue confirmation) between 1998 and 2010 (inclusive) at SJCRH. Many of these patients were part of a previous SJCRH prospective observational trial.²³ Eligible patients were those who had

undergone preradiation surgery of any kind performed at Le Bonheur Children's Hospital or at an outside institution, but with radiation and follow-up visits at SJCRH. We stopped adding new patients beyond 2010 so that we could have at least 3.5 years of follow-up for each patient. From this group, we identified patients who developed solid and/or cystic recurrence or progression of residual tumor 1 year or more after CRT. Recurrence was defined as any new tumor in a patient who underwent a GTR or progression of previously radiologically stable residual tumor. For each recurrence, we recorded the type (solid, cystic, or both), the date and the method of subsequent surgical or radiosurgical treatment, and any treatment-related complications. The institutional review board at SJCRH approved this study.

Definitions

Time to first recurrence was defined as the number of days from the start of radiation to the date of surgical intervention for the recurrence (treatment-free survival). Time to subsequent recurrence was the number of days between treatments. Total follow-up duration was the number of days from the date of diagnosis to the last clinic follow-up evaluation, or death. At last follow-up, we classified patients as having either stable or progressive disease based on their last MRI examination. It should be noted that the presence of radiographic progressive disease does not mean that the patient has undergone treatment for its recurrence. Patients who had a GTR with no evidence of regrowth at last follow-up were still labeled as stable disease rather than as disease free.

Imaging and Radiation Treatment Planning

A CT scan and contrast-enhanced MR image was obtained approximately 1 week before the start of CRT. The gross tumor volume for the baseline plan was contoured on the T2-weighted MR image supplemented by the T1 contrast-enhanced sequence and the CT scan. The clinical and planning target volume margins used for treatment planning were 5 mm and 3 mm, respectively. The total radiation dose was 54 Gy, given in 1.8 Gy fractions, 5 days per week, over a total of 6 weeks. MRI was performed during treatment with a frequency determined by protocol or physician preference.²⁵

Results

Ninety-seven pediatric patients (52 boys and 45 girls) completed photon CRT during the time interval 1998–2010. The median age at the time of CRT was 8.94 years (range 3.2–17.64 years).

Treatment-Free Survival and Time to Subsequent Progression

Among the 97 patients, 18 (18.6%) experienced tumor progression. Table 1 details the characteristics of the 18 patients with tumor progression. There were 6 girls and 12 boys with a median age of 7.54 years (range 3.61–13.83 years) at the time that their recurrent tumor was treated. The median time to treatment for tumor progression was

TABLE 1. Characteristics of 18 patients with craniopharyngiomas and failed CRT

Case No.	Age at Dx (yrs), Sex	Initial Surgical Treatment	Time to 1st Recurrence (days)*	Recurrence Type	Treatment	Subsequent Recurrences (days)†/Type/Treatment	Status at Last Follow-Up
1	5.9, M	STR	1381	Cystic	Ommaya-s w/ bleomycin	738/cystic/Ommaya revision-s	Deceased/stable disease
2	6.8, M	STR	1052	Both	STR	1: 219/solid/STR & 28 days later GKS 2: 1815/cystic/GTR 3: 532/cystic/GTR	Progressive disease
3	13.6, M	STR	1476	Both	GTR	None	Deceased
4	9, M	Ommaya-s	1628	Solid	GTR	None	Stable disease
5	4, F	Biopsy	3324	Both	Endoscopic fenestration & Ommaya-s	672/solid/STR	Deceased/stable disease
6	5.5, F	Ommaya-s	2253	Solid	GTR	None	Stable disease
7	7.7, M	Biopsy	663	Both	STR	298/solid/GTR	Stable disease
8	8, M	Ommaya-s	1880	Cystic	Ommaya-o	None	Progressive disease
9	4.8, M	STR	2140	Cystic	GTR	1: 2959/cystic/GTR 2: 295/cystic/GTR	Stable disease
10	6.3, M	STR	1745	Cystic	STR	1056/cystic/STR	Stable disease
11	5.5, M	STR	969	Cystic	Ommaya-s	1: 802/both/GTR 2: 326/cystic/Ommaya-o 3: 79/cystic/STR	Stable disease
12	3.6, M	STR	1387	Cystic	Ommaya-s	None	Stable disease
13	12, F	Biopsy	1557	Cystic	Ommaya-s	1670/cystic/STR	Progressive disease
14	3.3, F	STR	2147	Both	STR	1: 670/cystic/STR 2: 344/cystic/Ommaya-s attempted but failed, then STR 5 days later	Progressive disease
15	3.9, M	STR	1835	Both	STR	214/cystic/STR & 28 days later GKS	Stable disease
16	9.4, F	Biopsy	2199	Cystic	Transsphenoidal cyst fenestration	177/cystic/STR	Progressive disease
17	3.5, M	None	3119	Solid	GTR	None	Stable disease
18	8.2, F	STR	1047	Cystic	Transsphenoidal STR	None	Stable disease

Dx = diagnosis; Ommaya-o = craniotomy ("open") to fenestrate tumor cyst and place Ommaya catheter; Ommaya-s = stereotactic placement of Ommaya catheter into tumor cyst with aspiration.

* Time to first recurrence = number of years between radiation start date and date of intervention.

† Time to subsequent recurrence = number of days in between interventions for recurrence.

4.62 years (range 1.81–9.11 years). The 5- and 10-year treatment-free survival rates were 89.0% (95% confidence interval [CI] 80.5%–93.9%) and 76.3% (95% CI 64%–85%), respectively. In 10 patients (56%), tumor progression requiring treatment occurred within 5 years of CRT.

The pattern of progression was cystic in 9 cases, solid in 3, and both cystic and solid in 6. There was no statistically significant difference in time to recurrence comparing patients based on progression pattern. Seven patients had a single recurrence, 7 had 2 recurrences, 2 had 3 recurrences, and 2 had 4 recurrences. The time interval between each treatment for a new recurrence was progressively shorter. The median and mean times to treatment of first recurrence, between first and second, second and third, and third and fourth, were respectively 1687 and 1767 days (range 663–3324 days), 672 and 861 days (range 177–2959 days), 335 and 695 days (range 295–1815 days), and 306 and 306 days (range 79–532 days), respectively.

Treatment for Progression

As shown in Fig. 1 and Table 1, these 18 patients un-

derwent a total of 38 procedures after CRT for recurrent disease: craniotomy (including GTR and subtotal resection [STR], $n = 27$), bur hole for stereotactic placement of an Ommaya reservoir ($n = 7$), transsphenoidal surgery ($n = 2$), and Gamma Knife surgery (GKS; $n = 2$). Of those with a cyst as the first recurrence ($n = 9$), 5 were initially treated with placement of an Ommaya catheter (either via craniotomy or stereotactic bur hole), 2 had STR of their entire tumor burden, 1 had a GTR, and 1 had a transsphenoidal cyst fenestration. Among those with cystic recurrence, 6 patients (67%) subsequently developed another recurrence, and at last follow-up 3 had progressive disease and 6 had stable disease, including 1 patient who died 7.6 years after diagnosis. The 6 patients who developed both solid and cystic first-time progression were treated initially with STR ($n = 4$), GTR ($n = 1$), and an Ommaya catheter ($n = 1$). All but 1 of these patients (83%) developed another recurrence requiring further treatment, and at last follow-up 2 had progressive disease, 2 had stable disease, and 2 had died at 4.1 and 13.1 years after diagnosis. One of these children died with stable disease and the other died

FIG. 1. Treatment summary for the 18 patients who developed recurrent tumor after CRT. F/U = follow-up; PD = progressive disease; SD = stable disease.

shortly after surgery (see *Morbidity and Mortality*). All 3 patients with a solid first-time recurrence went on to undergo GTR, have not required any further treatment, and have stable disease at the last follow-up evaluation.

In 8 patients, GTR was achieved 11 times, including 5 times for the first recurrence. In 1 patient (Case 3), the effectiveness of resection could not be assessed because he died shortly after surgery (see *Morbidity and Mortality*). Of the 4 patients alive at last follow-up who underwent GTR for their first recurrence, 3 of them have not had further recurrences and have radiologically stable disease at last follow-up.

Morbidity and Mortality

There were 13 notable treatment-related complications that occurred in 9 patients. Six patients developed diabetes insipidus after surgery, 2 of whom also experienced a seizure in the postoperative period as a result of serum sodium fluctuations, and 1 patient also developed hypocortisolemia. Two patients suffered a partial loss of vision after

resection. One patient suffered lower cranial neuropathies as a result of bleomycin leakage out of his tumor cyst (this patient was treated early in our series and is the only one treated with intracystic bleomycin). The final complication was radiation-induced vasculopathy requiring bypass surgery 2.5 years after completion of CRT. Three of 18 patients have died; 2 of these deaths were due to sepsis unrelated to any recent surgical procedure or shunt infection. The third death occurred in a 17-year-old boy who 4 years previously had undergone CRT and then developed a solid and cystic recurrence (Case 3). After undergoing a GTR, the patient's postoperative course was complicated by, in chronological order, severe hypertension requiring continuous antihypertensive infusion, hemiparesis with a CT scan that demonstrated diffuse bilateral cerebral edema, an anterior myocardial infarction, extreme fever (110°F), myoglobinuria, renal failure, and ultimately brain death 5 days after surgery. It is unclear what led to these events, but uncorrected preoperative endocrinopathy was believed to have been a significant factor; an autopsy was not performed.

Overall Survival

The median follow-up duration for the entire cohort ($n = 97$) was 9 years (range 0.7–19.0 years). The median follow-up duration for the cohort that experienced progression ($n = 18$) was 9.32 years (range 4.04–19.0 years). A total of 7 patients have died. Four died of complications related to the tumor and treatment without evidence of progression (i.e., opportunistic infection, vasculopathy, and secondary malignancy), including the first patient in the cohort. As discussed in the previous section, 3 of the patients in the progression cohort died. The overall 5- and 10-year survival rates for all 97 patients were 98.9% (95% CI 92.4%–99.8%) and 94.5% (95% CI 85.9%–98.0%), respectively. Among the patients who have not experienced progression, the 5- and 10-year survival rates were 100% and 96.3% (95% CI 85.4%–99.1%), respectively; for those who experienced tumor progression, the rates were 94.1% (95% CI 65%–99.2%) and 87.8% (95% CI 59.5%–96.8%), respectively.

Discussion

Conformal radiation therapy following maximal safe resection or decompression of a predominantly cystic tumor has been our general approach for children with craniopharyngiomas as a way to maximize local control and minimize surgical morbidity. In this study we report our experience with a cohort of 18 patients who failed CRT. Of the original group of 97 patients, almost 20% went on to develop tumor recurrence with a median and mean time to first recurrence of 4.6 and 4.8 years, respectively, and the 5- and 10-year treatment free-survival rates were 89% and 76%, respectively. Eleven of the 18 patients developed 1 or more subsequent recurrences, with the time interval between treatments for each recurrence becoming progressively shorter. Collectively, 38 procedures directed at the recurrence were performed or attempted. Do these statistics suggest that recurrent craniopharyngioma is a more biologically aggressive tumor than its original form? Unlike the work that is currently being performed to unlock the molecular mysteries of both the *de novo* and recurrent forms of other pediatric tumors, notably medulloblastoma,³⁰ such work has yet to be performed with craniopharyngioma. In a recent article, Prieto et al. reviewed the literature and found features of a craniopharyngioma that were related to a higher risk of recurrence included larger tumor size, tight adherence to the hypothalamus, the presence of whorl-like arrays, and high levels of Ki 67, p53, epithelial cell adhesion molecule, and pituitary tumor transforming gene.^{29,34} To this list, others have unequivocally demonstrated that patients with an STR without adjuvant CRT are at high risk of recurrence.^{7,20,32}

A number of groups have reported their experience with recurrent craniopharyngiomas, but direct comparison between our results and theirs is limited because of different treatment preferences, follow-up times, or the inclusion of adults. Jang et al. performed 32 operations in 7 pediatric patients, 4 of whom received CRT after their first surgery and 2 patients after their second.¹⁵ Like our study, they demonstrated that the interval between each surgery became shorter, and the median time to first re-

currence in their patients was almost identical to the one in our series (58 vs 55.4 months, respectively). Bishop et al. recently published results from 2 institutions.³ Fifty-two children were treated with either intensity-modulated radiation therapy (IMRT; $n = 31$) or proton beam therapy (PBT; $n = 21$) with a median follow-up of 59.6 months for the entire cohort, but 106 months for the patients treated with IMRT, similar to our patient population (9 years). Of their 31 patients who underwent IMRT, 3 (10%) developed a cystic recurrence requiring surgical intervention and 1 a nodular recurrence 24 months after IMRT, but they do not indicate whether this patient required surgery. Thus, their overall recurrence rate and treatment burden were both significantly less than our series.

In 2010, Elliott et al. published Dr. Wisoff's personal series of 86 children with craniopharyngiomas over a 22-year period.¹¹ Their treatment philosophy differs significantly from ours in that they have been staunch advocates of GTR in virtually all patients without adjuvant CRT. Their overall recurrence rate (22%) was similar to ours (18.6%), including a 20% rate for the 71 patients who underwent a GTR. The median time to recurrence in patients who had a GTR was much shorter (20 months, range 1–123 months) and all recurrences except 1 developed within 48 months of surgery. For those who had an STR, the median time to progression was even shorter at 3.5 months. Finally, as with our study, they also found that the time to subsequent recurrence was shorter in patients who had already developed a recurrence compared with those who did not. Minamida et al. reported their results in a series of 11 patients with recurrent tumors, 5 of whom were less than 18 years of age.²⁶ Their overall recurrence rate was 30% and the median time from first surgery to recurrence was 6.2 years. These 11 patients underwent 17 operations for recurrences, and none received radiation.

With only 18 patients with recurrent disease in our series, including 1 who died shortly after surgery for his first-time recurrence, it is difficult to make any robust treatment recommendations. Our patients who underwent GTR after their first recurrence appeared to have a lower risk of subsequent recurrence. Until now, we have been guided by two principles when faced with recurrent disease. We continue to believe that tumor that is adherent to critical neurovascular structures should not be excessively tampered with or manipulated for fear of causing irreversible neurological morbidity. The second principle was to resect only that portion of the tumor that has progressed after CRT. Given our results showing the high burden of treatments in those that recur after radiation, maximal safe resection of all disease may be the optimal surgical strategy at first recurrence, which will hopefully translate into a greater chance of long-term local tumor control, a position that is shared by others.⁹ Placing a catheter for cystic recurrence is unlikely to afford any long-term control, as only 1 patient in our series who underwent this procedure has not developed further tumor regrowth or radiological progressive disease at last follow-up. For those patients in whom complete resection cannot be safely accomplished, the use of stereotactic radiosurgery directed at the residual may be considered as it has been repeatedly demonstrated to be safe and effective.^{16–18,27,36,38}

Contrary to the view of other authors,^{26,35} surgery for recurrent disease is difficult and risky. In general, each ensuing surgery becomes progressively more demanding due to fibrosis and loss of the natural pial-arachnoid tissue planes that surround normal neurovascular structures and the tumor as a result of prior surgery, and to a lesser degree radiation, not to mention the intrinsic characteristics of the tumor itself (e.g., calcifications). Elliott et al. demonstrated that prior radiation and recurrent disease negatively impacted the surgeon's ability to achieve a complete resection.¹¹ Newer surgical techniques and technology, such as endoscopy/transsphenoidal surgery,^{4,19,37} supraorbital eyebrow craniotomy,²² and intraoperative MRI surgery^{1,5} may lead to better surgical results with less morbidity. Unfortunately, the reality is that a significant percentage of children with recurrent postradiation craniopharyngioma will not be cured and will suffer from treatment-related complications or toxicity.

Lastly, PBT as the initial form of CRT, as opposed to conventional photon IMRT, may provide better local control rates at reduced levels of whole-brain and body irradiation.^{2,21} Fitzek et al. treated 5 children with a median dose prescribed to the tumor of 56.9 cobalt Gray equivalents and a median follow-up of 13.1 years.¹³ None of these 5 patients experienced tumor recurrence. Bishop et al.³ demonstrated no superiority of PBT over IMRT with regards to survival and disease-control (cystic and nodular recurrence) outcomes. PBT is currently available in few centers and its use in children with craniopharyngioma is still in its early stages.

Our study has a number of limitations, some of which have already been mentioned. Our patient series is small and our findings are generalizable to those institutions that similarly prescribe adjuvant CRT in all of their pediatric patients. Because any one institution will have only a handful of these cases, multicenter efforts—and even international collaborative efforts—are necessary to properly develop treatment algorithms.³³ Our end points were limited and we did not have quality of life data, an important outcome to measure in this population that the disease and treatments directly impact.^{12,28,31}

Conclusions

The management of recurrent craniopharyngioma in children is extremely challenging. The overall rate of recurrence in children with craniopharyngioma treated at our institution using photon CRT was nearly 20%. Just over half of our patients required treatment for their first progression during the first 5 years after CRT. Eleven children developed more than 1 recurrence necessitating a high treatment burden. All available surgical tactics should be used to maximally resect the recurrent tumor without jeopardizing neurological, behavioral, and cognitive function. Stereotactic radiosurgery may be considered for any residual tumor after such resection. These patients require multidisciplinary long-term follow-up.

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Conception and design: Klimo. Acquisition of data: Klimo, Venable, Merchant. Analysis and interpretation of data: Klimo, Venable, Merchant. Drafting the article: Klimo. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Klimo. Statistical analysis: Klimo, Venable. Study supervision: Klimo.

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