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Scientific Article

Reirradiation for recurrent craniopharyngioma

Sarah J. Foran, BScH,[a,*] Normand Laperriere, MD,[b] Kim Edelstein, PhD,[b] Laura Janzen, PhD,[c] Tony Tadic, PhD,[b] Vijay Ramaswamy, MD, PhD,[c] David Shultz, MD, PhD,[b] Fred Gentili, MD,[d] Eric Bouffet, MD,[c] and Derek S. Tsang, MD[b,c]

[a]University of Toronto, Faculty of Medicine, Toronto, Canada; [b]Radiation Medicine Program, Princess Margaret Cancer Center, University Health Network, Toronto, Canada; [c]Division of Hematology/Oncology, Hospital for Sick Children, Toronto, Canada; [d]Toronto Western Hospital, University Health Network, Toronto, Canada

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Abstract

Purpose: Reirradiation is rarely administered to patients with recurrent craniopharyngioma owing to concerns regarding visual and endocrine side effects. The purpose of this case series was to evaluate our institutional experience of patients with craniopharyngioma treated with 2 courses of fractionated radiation therapy.

Methods and Materials: A retrospective study was performed of all patients with craniopharyngioma treated with 2 courses of fractionated radiation therapy at a single institution. Electronic medical records and radiation therapy records were reviewed.

Results: We identified 4 eligible patients with recurrent craniopharyngioma. With a median follow-up of 33 months after reirradiation, 3 patients attained disease control; 1 patient developed progressive disease, 27 months after reirradiation. In 3 evaluable patients, vision remained stable or improved after reirradiation; one patient had no light perception before reirradiation. None of the patients experienced additional endocrine toxicities after reirradiation, apart from one patient who had low serum thyroid stimulating hormone before reirradiation and later developed hypothyroidism after treatment.

Conclusions: Reirradiation may represent a safe and effective therapeutic option for selected patients with recurrent, refractory craniopharyngioma and without other salvage treatment options. Larger studies with longer-term follow up are warranted to better understand outcomes in these patients.

Introduction

Craniopharyngiomas are benign neuroepithelial brain tumors believed to arise from epithelial remnants of Rathke's pouch, that are cystic (or mixed cystic/solid) in nature and localized within the sellar or suprasellar region of the brain. They are rare, accounting for less than 5% of intracranial brain tumors, and tend to occur in children aged 5 to 14 and adults aged 65 to 74.[1] Because of the tumor's proximity to the pituitary gland, hypothalamus, and optic structures, patients may present with neurologic symptoms, endocrine disturbances, as well as visual field and acuity deficits.[2] The optimal treatment strategy for craniopharyngioma is challenging and depends on the tumor location and potential for adherence to surrounding structures. These factors often make gross total resection (GTR)

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* Corresponding author: Sarah J. Foran, BScH; E-mail: sarahforan6@gmail.com.

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hazardous owing to the associated high risk of hypothalamic damage.[3,4] Additionally, even after GTR, recurrence rates of these tumors have been reported to be as high as 50%.[5] Therefore, treatment often consists of subtotal resection (STR), followed by adjuvant treatment including radiation therapy (RT), or intracystic therapies.[6-8] Multiple studies have shown that recurrence-free survival rates are higher in patients who undergo subtotal resection followed by radiation therapy, compared with either conservative surgery or attempts at GTR alone.[9-12]

Despite this treatment, some patients develop recurrence after prior surgery and RT upon long-term follow-up.[13] Patients with recurrent craniopharyngioma after RT have few treatment options.[14] Repeat surgery is possible[15] but often challenging or not possible; many patients die of perioperative complications or the morbidity of multiple repeat operations.[9,16,17] Historically, reirradiation has been avoided owing to concerns for vision loss and endocrinopathy. At our institution, reirradiation has been offered to selected patients with recurrent craniopharyngioma who are unsuitable for further surgery. The purpose of this study was to review our experience of reirradiation for patients with craniopharyngioma, and to describe the incidence of any complications.

Methods and Materials

This was a retrospective case series of patients who received a diagnosis of craniopharyngioma and were treated with 2 courses of fractionated radiation therapy between 1998 and 2019 at a single institution. Data were collected from electronic medical records as well as RT records. The index time was the first day of reirradiation. This study was approved by the research ethics board of the institution.

The types of RT used included fractionated stereotactic RT, intensity modulated radiation therapy, or volumetric modulated arc radiation therapy, depending on the treatment era. For the first RT course (RT1), the gross tumor volume (GTV) included all solid and cystic tumor components. The clinical target volume (CTV) was created using a 5 to 10 mm expansion upon the GTV, modified for anatomic barriers and to include any region previously involved by craniopharyngioma cyst. A planning target volume (PTV) of 3 to 5 mm was used. For the second RT course (RT2), the CTV included a 5 mm expansion upon the GTV, modified for anatomic barriers. A 3 mm PTV was used for the course of reirradiation. In all courses of RT, the maximum dose to organs-at-risk (brain stem, optic nerves, chiasm) were maintained at or below the prescription dose. There was no cumulative dose limit to any structure.

To calculate cumulative physical doses to organs-at-risk, available archived plans from Pinnacle 7.6 to 9.8 for 3 patients were imported into RayStation version 6 (RaySearch, Stockholm, Sweden). Planning CTs for the first and second courses of RT were rigidly registered, followed by organ-specific deformable image registration (DIR) for the brain, optic nerves, and optic chiasm. Each DIR was evaluated qualitatively to ensure improved anatomic alignment compared with rigid registration. Subsequently, the DIRs were used to deform the RT1 plan dose onto the RT2 planning CT. The deformed RT1 dose was summed with RT2 to obtain cumulative organ-at-risk doses.

Results

A total of 4 patients who underwent reirradiation for craniopharyngioma were identified. Median follow-up time was 33 months (among living patients). Clinical and treatment details are reported in Table 1. Median RT1-to-RT2 interval was 5.8 years (range, 4.7-20.4). Three of 4 patients are alive without disease recurrence after reirradiation. Radiation doses to optic structures are reported in Table 2. Visual acuities before and after reirradiation are reported in Table 3, and endocrine toxicities and longitudinal neurocognitive testing results are reported in Table 4.

Patient 1

Patient 1 had remote vision loss in his left eye since the age of 3. At 13 years of age, the patient presented with headaches, vomiting, and personality changes. He received a diagnosis of craniopharyngioma, as well as a right (not left) monocular temporal hemianopia, central hypothyroidism, cortisol insufficiency, and diabetes insipidus. After his first surgery STR, he developed panhypopituitarism before undergoing RT at age 14. After RT, his vision was maintained at 20/200 in the nasal field of the right eye (which improved to 20/100 when examined at follow-up) and a subjective improvement in the vision of his left eye was noted.

At the age of 19 he presented with headaches, vomiting, visual changes, and left-sided hemi-hyperesthesia and hemiparesis, with normal fundoscopy bilaterally. After multiple surgeries, the patient became blind in both eyes, without light perception. The patient then underwent reirradiation at age 20, which resulted in a reduction in the size of the tumor by 50%. He did not experience any additional endocrine toxicities after completion of reirradiation; however, the tumor recurred 27 months after reirradiation. A trial of imatinib was attempted but the patient ultimately died owing to progression of the craniopharyngioma, 33 months after the start of reirradiation.

Patient 2

Patient 2 received a diagnosis of craniopharyngioma at the age of 2 after presenting with reduced vision,

Table 1 Patient characteristics, sequencing of imaging and treatments, details of radiation therapy, and status at follow-up

Patient	Sex	Histology	Age at first surgery	Extent of surgery before RT1	Chemotherapy before RT1	Age at RT1 start (y)	RT1 dose (Gy)/fractions	Age at RT2 start (y)	RT2 dose (Gy)/fractions	Disease progression	Duration of follow-up	Vital status
1	M	Craniopharyngioma, adamantinomatous	14	STR	N	14	54/30	20	54/30	Y	33 mo	Deceased (progressive disease)
2	M	Craniopharyngioma, NOS	4	STR	Intracystic bleomycin	10	54/30	15	54/30	N	42 mo	Alive
3	F	Craniopharyngioma, presumed*	14	Cyst fenestration	Intracystic interferon	16	54/30	22	54/30	N	23 mo	Alive
4	F	Craniopharyngioma, papillary	51	STR	N	51	50/25	72	54/30	N	9 mo	Alive

Abbreviations: F = female; FSRT = fractionated stereotactic radiation therapy; IMRT = intensity modulated radiation therapy; M = male; N = no; NOS = not otherwise specified; RT1 = first round radiation; RT2 = second round radiation (reirradiation); STR = subtotal resection; VMAT = volumetric-modulated arc therapy; Y = yes.

* This patient had an endoscopic fenestration performed at diagnosis, but no biopsy was taken.

nystagmus, and a wide-based gait. Before surgery he was found to be legally blind in both eyes. After undergoing a STR, he developed panhypopituitarism. At age 10, the patient was found to have a right temporal hemianopia with a visual acuity of 20/300, as well as a pendular nystagmus. The patient then underwent RT, which was well-tolerated and resulted in a stabilization of the residual tumor. A subsequent recurrence occurred 5 years later, at which point he underwent reirradiation, which resulted in a decrease in tumor size. At the patient's last follow-up, the tumor in the sellar and suprasellar region, as well as his vision, was stable and there were no new endocrine toxicities. Longitudinal neurocognitive testing pre- and post-RT revealed a clinically significant decline in working memory as well as depression after RT2.

Patient 3

Patient 3 initially presented with migraines with aura, decreased peripheral vision, and a history of hypoglycemic headaches, and received a diagnosis of craniopharyngioma. After an initial surgery at age 14, the patient experienced a mild compromise in vision associated with cyst enlargement, which was relieved with surgical drainage. At this time, the patient's vision was measured to be 20/50 in the right eye and 20/30 in the left eye. The patient then began RT at age 16, at which point her vision was measured to be 20/400 in the right eye and 20/40 in the left eye. Upon completion of RT, imaging revealed stabilization of the tumor.

During the next 6 years, the patient developed secondary hypogonadism and central ovarian failure. The tumor was later found to have increased in size and the patient underwent reirradiation at age 22 (Fig 1). Before the end of the course of reirradiation, the patient developed visual scotomas, although these improved 14 days later and she ultimately reported an overall improvement of vision during treatment. The patient subsequently developed secondary hypothyroidism. At 9 months after the second course of RT, the mass was found to have decreased in size, although the optic chiasm was still displaced anteriorly by the tumor. At the patient's last follow-up, she remained neurologically well with stable residual craniopharyngioma. Although the patient showed a marked decline in processing speed after RT1, short-term neurocognitive testing post-RT2 (10 months) was largely stable; the decrease in the verbal comprehension index is likely attributable to use of a different testing instrument at the 2 time points.

Patient 4

Patient 4 presented at age 52 with confusion, visual blurriness, and exophthalmos of the left eye and received a diagnosis of papillary craniopharyngioma. After surgery

Table 2 Maximum dose (cGy) radiation to the optic apparatus

Patient	RT1			RT2			Composite doses		
	Left optic nerve	Right optic nerve	Optic chiasm	Left optic nerve	right optic nerve	Optic chiasm	Left optic nerve	Right optic nerve	Optic chiasm
1	5296.8	5305.2	5356	5358.9	5441.3	~5400*	10,705	10,755	*
2	5174.1	5371.1	5397.9	5376.7	5347.7	5368.7	10,726	10,690	10,826
3	5368.1	5362.4	5404.6	5277	5352	5372	10,648	10,670	10,831
4	~5000†			4860	5099	5270	†	†	†

Abbreviations: RT1 = first course of radiation; RT2 = second course of radiation (reirradiation).

* Patient 1 had a bulky tumor recurrence in the suprasellar region, and the optic chiasm was indistinguishable from the tumor, which was prescribed 54 Gy (RT2).

† Volumetric RT1 plan was unavailable; the tumor in the sellar and suprasellar region was prescribed 50 Gy (RT1).

she underwent adjuvant RT, after which there was no residual tumor or endocrine deficit. The patient's vision was found to be 20/120 in the right eye and 20/20 in the left eye at this time.

The tumor recurred at age 68; however, the patient remained asymptomatic for the next 3 years, until she reported a subjective loss of peripheral vision and was found to have a left homonymous hemianopsia. The patient subsequently underwent 2 additional surgeries at age 71 and 72 with ommaya insertion. Testing of her recurrent tumor found a BRAF V600E mutation by immunohistochemistry; she received dabrafenib and trametinib but developed grade 3 fatigue and rash requiring hospitalization. Because of rapid cystic regrowth requiring frequent ommaya drainage, she received reirradiation at age 72. At the last follow-up, the cyst had shrunk and collapsed without radiologic recurrence, and the only positive visual finding on examination was a left-sided ptosis with intact visual fields, and no new endocrine toxicities.

Discussion

Our 4-patient case series is the largest published report on the efficacy and toxicities of repeat fractionated irradiation for patients with craniopharyngioma, which underscores the lack of evidence and importance for documenting treatment outcomes in these patients. There are 2 principal findings of this study: first, repeat RT appears to be well-tolerated and effective for tumor control in our sample. Second, no living patient had deterioration in vision after reirradiation.

Table 3 Visual acuity before and after reirradiation

Patient	Before RT2		After RT2		Time from RT2 (mo)
	OD	OS	OD	OS	
1	NLP	NLP	NLP	NLP	
2	20/400	NLP	20/400	NLP	33 mo
3	20/400	20/40	20/400	20/50	15 mo
4	20/200	20/50	20/150	20/50	4 mo

Abbreviations: NLP = no light perception; OD = right eye; OS = left eye; RT2 = second round of radiation (reirradiation).

Treatment involving reirradiation is often left as a last resort because of concerns of side effects, particularly visual consequences, with few studies reporting on this in the literature. One study that included reirradiation as a treatment modality consisted of a group of ten patients with craniopharyngioma that underwent a primary surgery followed by additional treatments (either multiple surgeries or reirradiation), all of whom required cortisol and thyroid axis replacement and 6 also experienced visual impairment.[18] However, a limitation of this study was that the patients who underwent reirradiation were not distinguished from those who only underwent multiple surgeries. In a study of 33 patients with primary brain tumors treated with reirradiation (via stereotactic radiation therapy, stereotactic radiosurgery, and intensity modulated radiation therapy) in South India, of whom one had craniopharyngioma, the 3-year survival posttreatment was found to be 74.1%.[19] In this study, the outcomes of the patient with craniopharyngioma were not separately reported, and thus a limitation includes the array of histologic tumor types captured in the aggregate results. Chiou et al evaluated the role of salvage stereotactic radiosurgery for treatment of craniopharyngioma in ten patients, one of whom had prior external beam RT.[20] Vision initially deteriorated 5 months post-stereotactic radiosurgery (SRS) but subsequently improved 10 months after SRS. In a separate study of 97 patients who underwent conformal radiation therapy for craniopharyngioma, 2 patients were subsequently treated with Gamma Knife surgery for recurrent disease: at last follow-up, one patient had progressive disease, and the other had stable disease.[14]

Our case series is one of the first studies to report on tumor control and vision outcomes after reirradiation for craniopharyngioma. This study demonstrates stability in visual outcomes in patients treated with reirradiation. There is limited prior evidence regarding vision after reirradiation. One study analyzed the tolerable dose of the optic chiasm in 100 patients with craniopharyngioma who

Table 4 Functional outcomes before and after reirradiation

Patient	Endocrine	After RT2	Neurocognition	After RT2
	Before RT2		Before RT2	
1	Panhypopituitarism	No additional endocrine toxicities	n/a	
2	Panhypopituitarism	No additional endocrine toxicities	WISC-IV VCI = 126 WISC-IV WMI = 121 37 mo pre-RT2	WAIS-IV VCI = 111 WAIS-IV WMI = 94 32 mo post-RT2
3	Central ovarian failure, low sTSH, secondary hypogonadism	Secondary hypothyroidism	WAIS-IV VCI = 119 WAIS-IV WMI = 91 WAIS-IV PRI = 114 WAIS-IV PSI = 91 6 y pre-RT2	VCI = 105 WMI = 91 PRI = 111 PSI = 88 10 mo post-RT2
4	None	No additional endocrine toxicities	n/a	

Abbreviations: n/a = not available; PRI = Perceptual Reasoning Index; PSI = Processing Speed Index; RT1 = first course of radiation; RT2 = second course of radiation (reirradiation); sTSH = serum thyroid stimulating hormone; VCI = Verbal Comprehension Index; WAIS-IV = Wechsler Adult Intelligence Scale, 4th edition; WASI-II = Wechsler Abbreviated Scale of Intelligence, 2nd edition; WISC-IV = Wechsler Intelligence Scale for Children, 4th edition; WMI = Working Memory Index.

underwent SRS, of whom 15 underwent repeat SRS for tumor recurrence. Among these 15 patients, with a cumulative maximum dose that varied from 14 to 20 Gy (exceeding the usual 12 Gy tolerance for SRS[21]), no patient developed an optic neuropathy at follow-up 42 months later.[22] Efficacy and nonvisual toxicities were not reported for those patients who underwent repeat SRS.

We observed a mild decline in neurocognitive outcomes in 2 of the patients who had prior testing (Table 4), although the literature is very limited regarding cognitive outcomes after reirradiation for craniopharyngioma. Among a group of 10 craniopharyngioma patients who underwent multiple surgeries or reirradiation, cognitive impairments occurred in 6 patients, although it is unclear how many of those 6 had reirradiation. The group also had significantly impaired functional status as measured by the Karnofsky Performance Scale, compared with the patients who had undergone surgery alone, or surgery and RT.[18] In another study of radiosurgery for craniopharyngioma, which included a patient who had previously also undergone external beam radiation, there were no reports of cognitive decline by either the patients or their families. However, in this study formal neuropsychological testing was not performed.[20] Systematic, serial neuropsychological assessments that include measures of memory and executive functions, acquired before and several years after reirradiation are warranted to understand potential detrimental effects of this treatment on cognitive functioning in craniopharyngioma.

Our study suggests both efficacy of reirradiation for tumor control, as well as safety in terms of vision and the

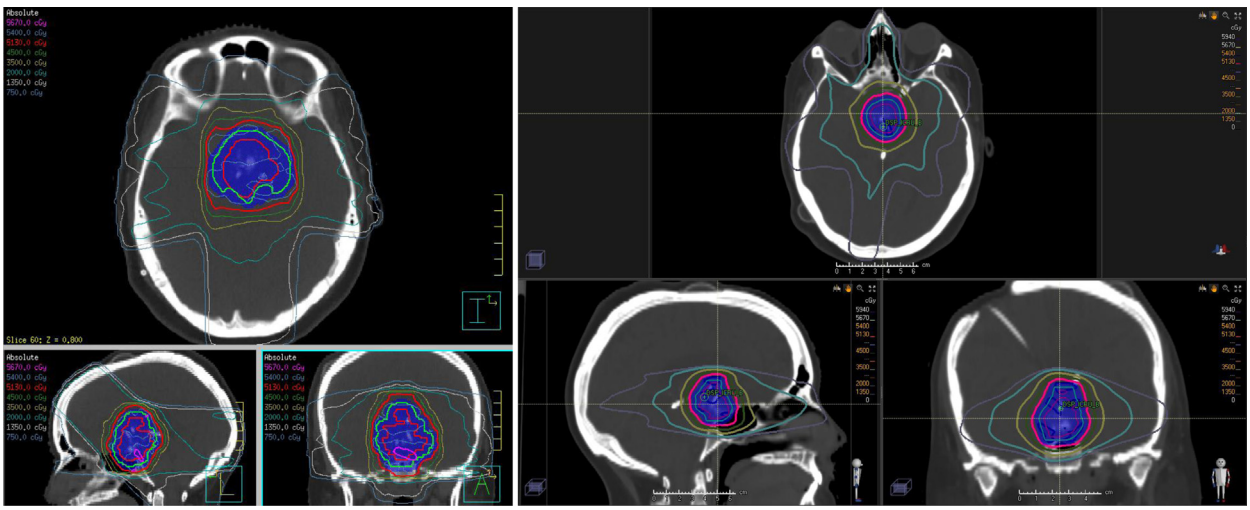

Figure 1 Radiation dose distributions for patient 3. (Left) First course of radiation therapy, commenced late 2011. (Right) Second course of radiation therapy, commenced early 2018. Note in-field treatment of the sella and suprasellar regions, including optic structures.

endocrine system. Limitations of this study include the small number of patients, which did not allow for meaningful analysis of survival and associations with tumor control or toxicity, and the fact that their baseline visual acuity was poor. The median follow-up is short; the occurrence of radiation-induced optic neuropathy peaks between 12- and 18-months after radiation, with the majority of patients experiencing symptoms within 3 years,[23] and endocrinopathies may develop anywhere from 7 months to 12 years after an initial course of RT.[24] Only 2 of our patients had follow-up beyond these timeframes. Additionally, there is limited cognitive data for 2 of the 4 patients (one of whom had a short follow-up time of 10 months from reirradiation to neurocognitive assessment). Finally, although reirradiation-induced optic neuropathies were avoided, whether this could be safely avoided for other patients is unclear; determination of the appropriateness of reirradiation necessitates consideration of many factors including pre-existing visual impairments, extent of the tumor, surgical salvage options, presence of targetable mutations (BRAF V600E),[25] and performance status of the patient.

Our current standard of care is to offer reirradiation as a treatment option for patients with recurrent craniopharyngioma who have no further surgical or targeted therapeutic options. Maximizing the latent time between RT1 and RT2 is desirable to allow for repair of subacute radiation damage; each patient in our series had a latent time of 4.7 years or longer. Our treatment approach is to prescribe 54 Gy in 30 fractions to the recurrent tumor, using a CTV expansion of 5 mm and a PTV expansion of 3 mm with daily cone beam computed tomography. The maximum reirradiation dose to optic chiasm, nerves, brain stem and for the plan overall are maintained at or below 54 Gy.

Conclusions

Reirradiation for patients with recurrent craniopharyngioma is a treatment option that appears safe and effective for tumor control. Despite exceeding usual tolerances for optic chiasm and nerves, visual outcomes were stable in all living patients. Reirradiation should be discussed as a treatment option for patients with recurrent craniopharyngioma, particularly in those with no other therapeutic options. Longer follow-up and prospective study are required to determine long-term tumor control probabilities and better ascertain risks of late toxicities, particularly optic neuropathy, endocrinopathy, and cognitive deficits.

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