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Case Report

Effective salvage of recurrent craniopharyngioma with fractionated stereotactic radiotherapy

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ABSTRACT

Craniopharyngiomas can invade surrounding structures, including the optic chiasm and hypothalamus. In such cases, subtotal resection is often preferred to limit perioperative morbidity and mortality; however, subtotal resection is associated with high rates of recurrence. Recurrent craniopharyngioma is typically treated with another subtotal resection and adjuvant radiotherapy. We present a case of a patient found to have a large craniopharyngioma compressing the optic chiasm, hypothalamus and left cavernous sinus. She underwent surgical debulking but developed recurrence shortly thereafter. Subsequently, she underwent a second debulking surgery, followed by fractionated stereotactic radiotherapy (SRT). Results show that she exhibited an impressive response to SRT with further tumor shrinkage, while remaining clinically well. This case demonstrates the efficacy of SRT in salvage of recurrent craniopharyngioma.

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Introduction

Craniopharyngiomas are rare embryonic tumors that arise from remnants of Rathke's pouch. Despite a low histological grade, craniopharyngiomas can cause significant morbidity as a result of growth into the surrounding region, with the most common location being the sellar/parasellar region [1]. Common clinical manifestations include symptoms of elevated intracranial pressure including headache, nausea and vomiting, visual impairment and endocrine deficits secondary

to hypothalamic-pituitary axis involvement. These endocrine deficits frequently lead to a reduced growth rate, significant weight gain and diabetes insipidus [2,3].

Given such morbidity, effective treatment is warranted. For craniopharyngiomas that do not involve the optic chiasm or hypothalamus, gross total resection is the preferred treatment [4,5]. Controversy remains about the optimal treatment when the optic apparatus and/or hypothalamus are involved [5,6]. Subtotal resection tends to be preferred, to minimize morbidity and mortality, but is associated with high recurrence rates; with rates of progression as high as 70%-90% [7,8].

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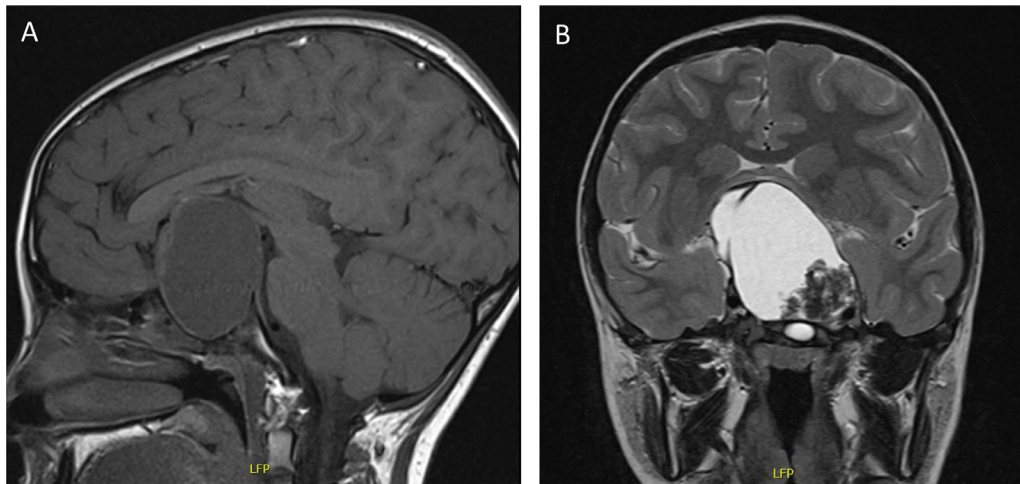


Fig. 1 – MR images at the time of diagnosis, prior to any surgical debulking; (A) sagittal spin echo T1, (B) coronal turbo spin echo T2.

Table 1 – The size of the craniopharyngioma at critical timepoints in the clinical course of this patient.

Timepoint	Size (AP, transverse, craniocaudal, in mm)
Preoperative/diagnosis	38 × 42 × 46
Postoperative, first debulking	20 × 32 × 30
Initial recurrence	44 × 51 × 38
Before second debulking	44 × 52 × 45
Postoperative, second debulking, preradiotherapy	27 × 28 × 21
Postradiotherapy	3 × 27 × 18

Consequently, subtotal resection is frequently followed by adjuvant radiotherapy, which reduces rates of progression by 75%-90% [7–9].

With this in mind, we present a case of recurrent craniopharyngioma that failed multiple surgical resections but demonstrates a significant response to fractionated stereotactic radiotherapy (SRT).

Case report

A 15-year-old girl was referred by her family physician to an endocrinologist for evaluation of primary amenorrhea. She was found to be prepubertal (Tanner stage 1) and had a significant growth delay. She had no signs or symptoms of increased intracranial pressure. She was growth hormone deficient and hypogonadal, and no evidence of central adrenal insufficiency, central hypothyroidism or diabetes insipidus was present. She complained of impaired vision in her right eye and ophthalmologic assessment revealed bitemporal hemianopsia as well as decreased visual acuity in the right eye. A central etiology was suspected given her symptom complex. MRI brain (Fig. 1) revealed a large (38 mm × 42 mm × 46 mm; sizes at various time points included in Table 1) solid and cystic

predominantly suprasellar mass lesion that was partially calcified. The optic chiasm, hypothalamus and left cavernous sinus were significantly compressed by the lesion. Additionally, there was no parenchymal invasion and no surrounding edema, and imaging findings were consistent with a craniopharyngioma.

She was sent for assessment by neurosurgery and underwent endoscopic transsphenoidal resection of the suprasellar mass lesion, with decompression of the optic chiasm, left cavernous sinus and hypothalamus. Pathology revealed World Health Organization grade 1 adamantinomatous craniopharyngioma. She developed panhypopituitarism postoperatively and was started on hydrocortisone, growth hormone, levothyroxine and estrogen. An early postoperative MRI brain (Fig. 2) revealed good debulking with maximal residual disease measuring 20 mm × 32 mm × 30 mm. In follow up, she felt well and noted improvement in her vision.

An MRI brain (Fig. 3) completed 4.5 months after debulking revealed significant recurrence of the cystic suprasellar lesion, now measuring 44 mm × 51 mm × 38 mm in size. There was mass effect from the tumor on the hypothalamus and right inferomedial temporal lobe. A repeat debulking surgery was recommended by neurosurgery. The patient was amid her academic year and wished to postpone her debulking until completion of the academic year. She remained clinically asymptomatic and so the decision was to proceed with her secondary surgery after completion of the school year.

A repeat MRI brain 2.5 months later demonstrated further interval tumor growth, now 44 mm × 52 mm × 45 mm. She remained asymptomatic, apart from significant weight gain. Eight months after her initial de-bulking surgery, she underwent a repeat endoscopic transsphenoidal resection of the suprasellar mass lesion. Pathology once again revealed World Health Organization grade 1 adamantinomatous craniopharyngioma, and an MRI brain 1 month postoperatively (Fig. 4) showed an interval decrease in size with the mass measuring 27 mm × 28 mm × 21 mm.

Given the rapid tumor regrowth following her first debulking surgery, she was referred to radiation oncology for

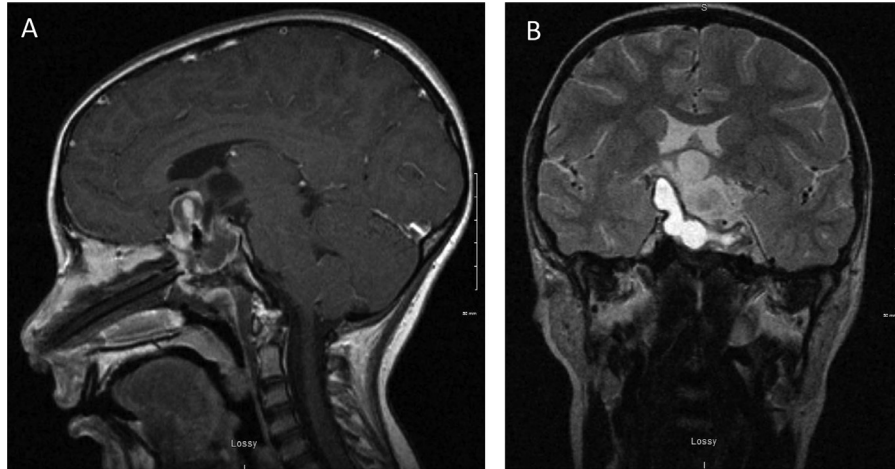


Fig. 2 – MR images on day 1 after first debulking surgery; (A) sagittal spin echo T1, (B) coronal turbo spin echo T2.

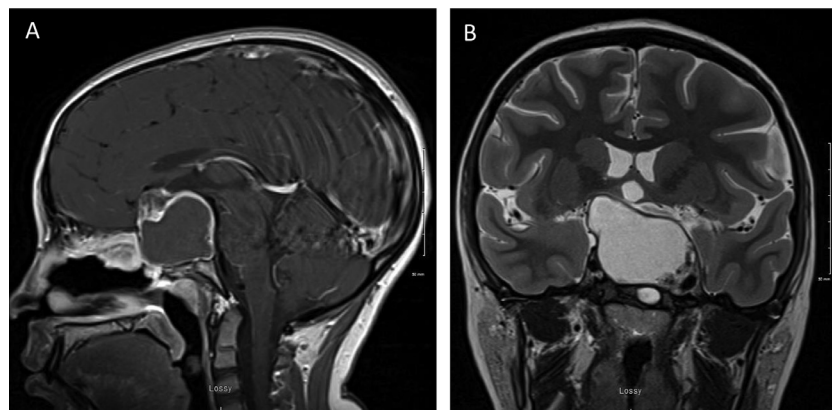


Fig. 3 – MR images 4.5 months after first debulking surgery, demonstrating rapid recurrence; (A) sagittal turbo spin echo T1, (B) coronal turbo spin echo T2.

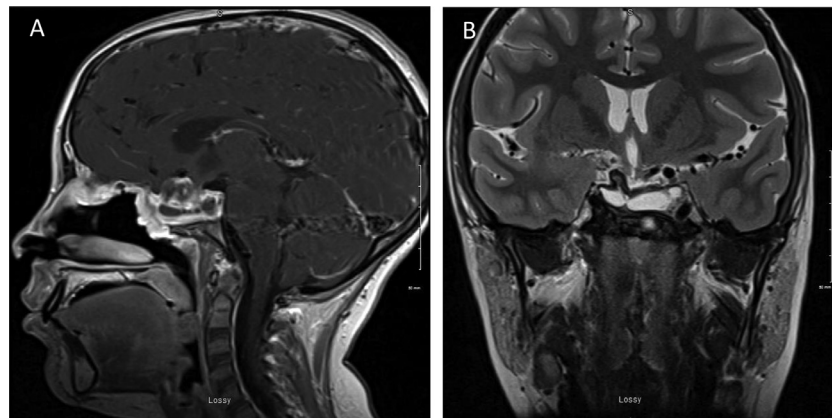


Fig. 4 – MR images 1 month postoperatively from second debulking surgery, demonstrating preradiotherapy disease burden; (A) Sagittal turbo spin echo T1, (B) coronal turbo spin echo T2 MR images.

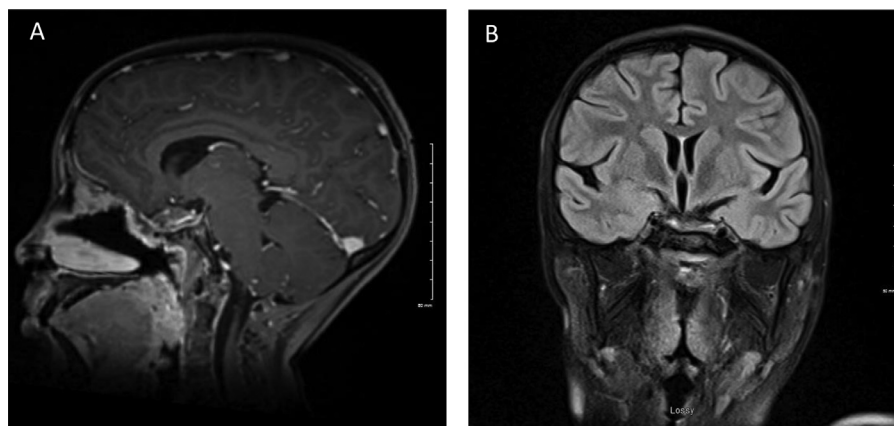


Fig. 5 – MR images 9 months after adjuvant radiotherapy, demonstrating excellent response (A) sagittal rapid gradient echo T1, (B) coronal fluid-attenuated inverse recovery T2.

consideration of radiotherapy. She was offered fractionated SRT, given the proximity to the optic chiasm, with the goal of improving local control. Fractionation was deemed important to spare the optic pathway while delivering an adequate radiotherapy dose to control the tumor. She underwent SRT with 5000 cGy delivered in 25 fractions over 5 weeks. SRT involved a 2 arc VMAT plan on an Elekta Linear Accelerator. Daily cone beam imaging was used for image guidance. SRT was completed approximately 1 year from her first debulking surgery. She tolerated SRT well with no nausea, fatigue or visual changes.

Follow up imaging 9 months after completion of SRT (Fig. 5) demonstrated significant interval regression of the suprasellar mass with the fluid component shrinking to 3 mm × 27 mm × 18 mm. No significant mass effect was demonstrated. She remains clinically well in follow-up with no new neurologic symptoms or cognitive deficits, as well as on full hormone replacement and she no longer has a bitemporal hemianopsia.

Discussion

Despite being low-grade tumors, craniopharyngiomas can cause significant sequelae due to their proximity and tendency to invade the optic chiasm and hypothalamic-pituitary axes [9,10]. Its relatively benign histology lends well to the possibility of cure with resection, and hence, the first line treatment is surgical resection [4–6]. There remains significant debate with regards to optimal surgical management, with any involvement of the optic apparatus or hypothalamic-pituitary axes, whether gross total resection or subtotal resection offer the best approach [11–14].

Typically with such involvement, subtotal resection is preferred to gross total resection, as gross total resections can lead to significant hypothalamic injury [13,15,16]. However, this choice is associated with high rates of recurrence. The results of a multicenter prospective trial by Muller et al., demonstrated a 3-year overall survival of 97%, but an event-free survival of 46%; highlighting the high rates of recurrence in this population [8]. In patients who were able to have a complete resection, the 3-year event-free survival was 64%, but this de-

creased significantly to only 31% in those who had a subtotal resection. While subtotal resection remains the safer option with any involvement of the optic chiasm or hypothalamic-pituitary axes, this approach comes at the cost of significantly increased recurrence rates; with relative recurrence rates 80% higher following subtotal relative to gross total resection. This same prospective trial also found that the risk of progression or recurrence was 88% lower in patients who received adjuvant radiotherapy. This effectively highlights the potential benefit of adjuvant radiotherapy, but the recurrence rates still remain high in patients following subtotal resection combined with adjuvant radiotherapy.

At the time of her initial presentation, given the compression of the optic chiasm, hypothalamus and left cavernous sinus, the neurosurgeon in this case opted to proceed with the more conservative approach of subtotal resection. Unfortunately, the patient in this case was among most patients who undergo incomplete resection and developed progression of her disease, requiring further treatment. This may have been avoided with the use of adjuvant radiotherapy, but the use of radiotherapy is not without consequences and so the decision was to defer any such treatment.

It is important to note, though, that the management of recurrent craniopharyngioma remains a challenge. This is primarily due to scarring from previous surgery and potential radiotherapy as well as the eloquent location of the tumor near the optic chiasm. This results in a significantly reduced ability to achieve complete resection with a second surgery [1,4] and perioperative morbidity and mortality is also significantly higher. Therefore, radiotherapeutic options tend to be preferred, often preceded by a debulking surgery [4,17]. This is how the patient in our report was managed when she recurred following initial subtotal resection; with repeat debulking surgery followed by fractionated SRT.

Adjuvant radiotherapy is an effective means of treatment in patients with craniopharyngioma [18]. Several retrospective series have demonstrated excellent long-term control with adjuvant radiotherapy, reporting 5-year, 10-year and 20-year progression-free survival of 78%-95%, 56%-95% and 54%-66%, respectively [13,14,19–24]. Studies have also investigated the timing of adjuvant radiotherapy, whether it can wait until relapse, as was done in this case. No significant difference in

tumor control has been demonstrated between early radiotherapy and radiotherapy following relapse [17,25]. Accordingly, with the hopes of delaying side effects of radiotherapy, it is frequently delayed until relapse. The patient in our case report completed adjuvant radiotherapy 1 year after her initial surgery, having started radiotherapy 3 months postoperatively from her second debulking surgery. While common, this strategy may not be ideal. Retrospective data exists to suggest that neurocognitive outcomes may be improved with a single subtotal resection followed by adjuvant radiotherapy, rather than attempting complete resection or to wait for relapse and subsequent interventions [26]. This data remains quite limited though, and further study is required.

Lastly, with advances in radiotherapeutic techniques, there are more radiotherapy options in the treatment of craniopharyngioma. These include stereotactic radiosurgery, fractionated SRT and proton beam radiotherapy. Proton therapy, where dose deposition increases with penetration up until a maximum (Bragg peak), after which no dose is deposited, offers conformal dose distributions, with reduced integral dose and critical tissue sparing [27]. Stereotactic radiosurgery involves delivery of single (or few) fractions of radiotherapy with limited margins. Often, patients with craniopharyngioma treated with this modality have small (<3 cm) tumors >3 mm away from critical structures and strict dose constraints to the optic nerve, chiasm and brain stem [28,29]. Fractionated SRT also offers sparing of normal tissues while having advantages of fractionation [30], particularly helpful in larger tumors and tumors near critical structures, minimizing toxicities from radiotherapy [31,32]. Data in patients treated with proton therapy, stereotactic radiosurgery and SRT are still somewhat limited, but there have been promising results with good local control [28,31–34]. The patient in this case was treated with fractionated SRT, due to the proximity of the tumor to the optic chiasm. This allows for the benefits of conformality that stereotactic techniques offer, while taking advantage of radiobiological effects of fractionation to spare the optic chiasm.

Herein, we reviewed a case of a patient with craniopharyngioma treated with an initial debulking surgery who had rapid regrowth of her craniopharyngioma. Recurrence is common and is often treated with a second debulking surgery followed by adjuvant radiotherapy. She was treated in this manner and demonstrated an impressive response following completion of fractionated SRT.

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Competing interest

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