Craniopharyngiomas develop in a region of the brain surrounded by numerous critical structures, including the optic pathway, pituitary, hypothalamus, temporal lobes, brainstem, and major intracerebral blood vessels. This complex intracranial environment creates a challenge for radiation dose delivery and carries a risk of significant radiation-induced toxicity. Compared to photon-based radiation therapy, proton therapy allows for a decrease in the radiation dose to uninvolved tissues surrounding the target. Reports on efficacy of proton therapy for craniopharyngioma are comparable to those achieved with photons, with minimal acute effects and a reduction in late effects. The inconstant nature of the cystic component of craniopharyngiomas poses yet another challenge for the radiation oncologist. The optimal technical approach for treating craniopharyngiomas with proton therapy is currently controversial because treatment requires a robust plan that offers high conformality with flexibility to modify the treatment course in the event of cyst growth.

Keywords: craniopharyngioma; pediatric radiation therapy; brain tumor; late toxicity; neurocognitive dysfunction; neuroendocrine dysfunction

Introduction

Radiation therapy plays an important role in achieving local control in subtotally resected or unresectable craniopharyngiomas. Current chemotherapy options are not curative. Patients with craniopharyngioma who are treated with modern radiation doses have a good prognosis and often achieve long-term survival. These tumors most commonly arise in the pediatric population, with a peak incidence between ages 5 and 14 years. Therefore, late effects of radiation therapy, which can permanently affect function and quality of life, are a highly relevant survivorship issue.

Craniopharyngiomas are located in the central aspect of the brain, close to critical structures like the optic pathway, carotid arteries, Circle of Willis, pituitary, hypothalamus, and temporal lobes. The tumor itself can cause functional disruption of these intracranial structures, as can biopsy or surgical resection. Radiation therapy also contributes to dysfunction of these regions. Partial or complete loss of vision or vasculopathy precipitating stroke can result in lifelong impairments. Partial or complete loss of pituitary and hypothalamic function can result in lifelong medicine supplementation. Memory, processing speed, and intelligence quotient (IQ) can decrease permanently after incidental irradiation of the temporal lobes and hippocampi, with the greatest detriments seen in the youngest patients.

Radiation therapy plays a pivotal role in tumor control, but can be associated with these significant and enduring side effects. Proton therapy may increase the therapeutic ratio of radiation therapy for craniopharyngioma by maintaining efficacy while reducing toxicity.
Clinical Experience: Efficacy and Toxicity

Proton therapy for craniopharyngioma has been shown to be well-tolerated with high efficacy. Early outcomes of efficacy and toxicity are important to understand, but long-term control and toxicity are of vital importance in this slow-growing tumor surrounded by critical structures. One study reported that children treated with photons for craniopharyngioma remained at risk for death related to treatment toxicity up to 10 and even 20 years after the completion of therapy [1]. Deaths were attributed to multiple factors, including uncontrolled diabetes insipidus, panhypopituitarism, and cerebrovascular disease. Only 1 death occurred due to disease progression. This study highlights that treatment toxicity continues to develop decades after the completion of therapy, placing patients at risk of premature death years after their tumor has been controlled.

Early Outcomes and Acute Toxicity of Proton Therapy

Available clinical data suggest that acute toxicity for central nervous system malignancies is low in pediatric patients treated with proton therapy. Chang et al presented retrospective data on 14 patients with craniopharyngioma treated between 2004 and 2008. Local control was 100% with a median follow-up of 16.5 months and stabilization or improvement of vision was observed in all patients [2]. In a retrospective review of 48 pediatric patients treated with proton radiation (including 4 with craniopharyngioma), fatigue was the most common acute symptom [3]. Approximately two-thirds of the cohort developed grade 1 fatigue, 10% developed grade 2 fatigue, and 0% developed grade 3 fatigue or higher. Alopecia and dermatitis were the other most common acute toxicities, with 73% experiencing grade 1 or 2 alopecia and 63% grade 1 or 2 dermatitis. Another retrospective review of 13 patients treated with proton therapy for craniopharyngioma reported no grade 3 acute toxicities and 1 grade 2 headache [4]. Acute toxicity data collected prospectively on 40 patients supports the retrospective data, with no grade 3 toxicities [5]. Grade 2 toxicities in this cohort included emesis (n=10), headache (n=1), and presyncope (n=2). Nine patients required antiemetics; none required steroids.

Late Outcomes and Toxicity

Proton Therapy

With the primary aim to assess safety and efficacy, Fitzek et al reported on 15 patients treated between 1981 and 1988, including 5 children and 10 adults [6]. One-third of the patients were treated with proton therapy alone and two-thirds with a combined proton-photon technique. As one of the initial studies on the clinical use of proton therapy for craniopharyngioma, these data provide information on late toxicity, with over 20 years of follow-up. The median doses for the pediatric and adult patients were 55.6 Gy (relative biological effectiveness [RBE]) and 62.7 Gy (RBE), respectively. The delivered doses were higher than the prescribed doses due to a change in calibration technique for the proton dosimetry in 1997. For the patients treated with a combined technique, the median proton component was 47% of the total dose.

In this study, actuarial local control rates were 93% and 85% at 5 and 10 years, respectively. No pediatric patients experienced tumor progression. Four patients died, 2 from tumor recurrence and 2 from treatment toxicity. All deaths occurred 5 years or more after completing radiation therapy. Of note, both patients with tumor progression had an interruption in their radiation course of more than 20 consecutive days. Both patients who ultimately died from treatment toxicity experienced late visual deficits prior to their death.
One patient spent 3 years in a nursing home before his death, with memory loss, hypothalamic syndrome, and hemianopsia that developed 10 months after radiation therapy (optic chiasm dose, 64 Gy [RBE]) in addition to a non-malignant necrotic mass resected without symptom improvement. The other patient developed unilateral blindness 5 months after radiation therapy (optic chiasm dose, 55.3 Gy [RBE]) and died from vascular causes.

The remaining patients without tumor progression experienced stable or improved vision. The optic chiasm dose was constrained to 56 Gy (RBE) or less in 73% of patients. The majority of patients required endocrine supplementation prior to radiation therapy (100% of the children and 80% of the adults), but following radiation all patients required endocrine supplementation. For the pediatric patients in this study, all 5 completed high school and 3 attended college. All were able to live independently and support themselves. One of the 5 had some learning difficulties (in verbal, math, and writing) but was able to pass college courses despite these impediments. The patients treated in adulthood all resumed their previous professional duties.

Three years later, Winkfield et al published the next series of this cohort from the same institution, with 24 children treated between 2001 and 2007 [7]. No tumor progression had occurred with a median follow-up of 40.5 months. In a retrospective review of 16 patients with craniopharyngioma treated with proton therapy, local control with proton therapy was achieved in 14 of the 15 patients [8]. Mean follow-up was 60.2 months (range, 12–121 months). Twelve of these patients were undergoing treatment for progressive disease after surgery alone. Actuarial rates of tumor control were not reported in this study. The sole relapse occurred 80 months after radiation therapy, and the patient ultimately succumbed to disease. Two treatment-related deaths occurred—sepsis and right middle cerebral artery infarct. New toxicity developed in 3 of the 12 living patients after radiation therapy. Panhypopituitarism developed 26 months after radiation therapy, a cerebrovascular accident occurred 34 months after radiation therapy with complete neurologic recovery, and posterior fossa meningioma was found 59 months after radiation therapy in a patient who had previously received external-beam radiation therapy before salvage proton therapy.

Bishop et al reported on 19 pediatric patients with craniopharyngioma treated with proton therapy between 2007 and 2012. The median follow-up was 31.8 months. The 5-year actuarial overall survival rate was 93% and the 5-year progression-free survival rate was 91% [9]. The actuarial rate of tumor control was not reported. Two of 19 patients developed vasculopathy after radiation therapy. Neuroendocrine dysfunction was common: 89% of patients required hormone replacement therapy and 42% had panhypopituitarism (N–8; 6 diagnosed before and 2 after radiation therapy). One patient died due to complications of diabetes insipidus, the diagnosis of which preceded the radiation therapy. For a summary of proton therapy studies, refer to Table 1 and Table 2. No radionecrosis was reported in these studies. Neurovascular and neuroendocrine toxicity attributable to proton therapy was rare and did not exceed contemporary photon-based outcomes. For critical organs within the planning target volume (PTV) and immediately adjacent to the PTV, such as the Circle of Willis, optic chiasm, and hypothalamus-pituitary axis, there is no indication that proton therapy is associated with increased acute or late toxicity compared to conventional radiation.

**Photon Therapy**

The local control rates compare favorably between these proton series and results reported with conventional therapy. Specifically, 79 pediatric patients with craniopharyngioma...
Craniopharyngioma were treated from 1976 to 2003 [10]. The therapies were variable, with 43 patients undergoing treatment with limited surgical intervention and adjuvant radiation therapy. The radiation therapy was delivered using a variety of photon techniques, including fractionated stereotactic radiation therapy, conformal arc therapy, 3-dimensional (3D)-conformal radiation therapy and intensity-modulated radiation therapy (IMRT). For the entire cohort, local control was 74% at 5 years and 69% at 10 years; for the 43 patients treated with surgery and radiation therapy, the 10 year local control was 84%. In the surgery and RT group, 67% had an endocrinopathy post-treatment, 53% visual deficits, 5% blindness, 56% obesity, 9% with seizures, 9% developed moyamoya, and 7% developed a second malignancy. In another large series of patients treated with photon therapy, Schoenfeld et al reported 2 year PFS of 73% for the patients in their cohort who were treated with subtotal resection and photon radiation (n = 48) [11]. Three patients in this group experienced one or multiple strokes. These events occurred between 2 and 16.5 years after completion of radiation. Another series reports vasculopathy in 6 of 20 children treated with conventional radiation [12]. Based on these data, routine post-radiation magnetic resonance angiograms are recommended.

Neurocognitive Dysfunction

Neurocognitive dysfunction is a common late effect of radiation therapy in pediatric brain tumors, including craniopharyngioma. While clinical outcomes for neurocognitive function and change in IQ after proton therapy for craniopharyngioma are actively being collected, a model to estimate IQ based on patient age, mean dose to the supratentorium, and time since irradiation has been developed [13]. Differences in IQ were detected based on type of radiation therapy (double-scattered protons versus photons) and patient age in this longitudinal model (Figure 1). In a prospective study of 70 craniopharyngioma patients treated with photons, longitudinal IQ was associated with mean whole-brain radiation dose and time at a rate of 0.00227 points/cGy/year, as estimated for an average patient based on linear mixed-effects models [14]. These cognitive dose models allow predictive comparisons of expected outcomes following proton therapy. Through reduction of the

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Median follow-up (y)</th>
<th>Treatment modality</th>
<th>5-year actuarial LC</th>
<th>10-year actuarial LC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitzek et al, 2006^6</td>
<td>15</td>
<td>13.1</td>
<td>Surgery/biopsy + proton-photon</td>
<td>93%</td>
<td>85%</td>
</tr>
<tr>
<td>Luu et al, 2006^6</td>
<td>16</td>
<td>5</td>
<td>Surgery + proton or proton alone (n=12 being treated for progression after surgery)</td>
<td>94%^b</td>
<td>NR</td>
</tr>
<tr>
<td>Chang et al, 2009^2a</td>
<td>14</td>
<td>1.4</td>
<td>Surgery/biopsy + proton</td>
<td>100%^b</td>
<td>NR</td>
</tr>
<tr>
<td>Alapetite et al, 2012^16a</td>
<td>49</td>
<td>4.4</td>
<td>Surgery + proton-photon (n=10); Surgery + proton (n=39)</td>
<td>90%^b</td>
<td>NR</td>
</tr>
<tr>
<td>Confer et al, 2012^4a</td>
<td>13</td>
<td>0.7</td>
<td>Surgery/biopsy + proton</td>
<td>85%^b</td>
<td>NR</td>
</tr>
<tr>
<td>Indelicato et al, 2012^5a</td>
<td>40</td>
<td>0.7</td>
<td>Surgery/biopsy + proton</td>
<td>100%^b</td>
<td>NR</td>
</tr>
<tr>
<td>Bishop et al, 2013^2a</td>
<td>19</td>
<td>2.7</td>
<td>Surgery/biopsy + proton (n=15); Proton alone (n=4)</td>
<td>91%</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: LC, local control; NR, not reported

^aabstract only
^bCrude rate at time reported
low-dose regions with proton therapy, the mean whole-brain dose will be decreased, mitigating the decline in IQ over time based on these models.

These changes in cognition occur through various mechanisms, including radiation dose to the temporal lobes and hippocampi, through mechanisms such as demyelination and axonal degradation [15]. Fractional anisotropy (FA) and radial diffusivity (RD) can estimate white matter demyelination using diffusion tensor imaging. After photon therapy, FA decreased and RD increased linearly over time (Figure 2) [16]. These parameters returned to baseline at 6 months following proton therapy after an initial decrease in FA and increase in RD at 3 months after radiation compared to baseline (Figure 3) [17]. This data suggest that white matter demyelination after proton therapy is mild and transient. The temporary nature of this demyelination after proton therapy may contribute to an improvement in neurocognitive function. Data to support this hypothesis include a study by Chapman et al in which changes in diffusivity in the parahippocampal cingulum correlated linearly with a decline in verbal recall [18].

Alapetite et al presented their data in 2012 on the treatment of 49 children with craniopharyngioma, 10 having received mixed photon-proton beams and 39 protons alone, from 1994 to 2009 [19].

Table 2. Literature review of selected outcomes following proton therapy for patients with craniopharyngioma

<table>
<thead>
<tr>
<th>Study</th>
<th>Acute toxicity, no. of patients</th>
<th>Late toxicity, no. of patients</th>
<th>Absolute no. of deaths due to tumor progression</th>
<th>Absolute no. of deaths due to treatment toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitzek et al, 2006&lt;sup&gt;a&lt;/sup&gt;</td>
<td>none, 7; nausea, 1; fatigue, 3; headaches, 4</td>
<td>Visual deficits, 2; endocrinopathy, 15; neurocognitive, 1</td>
<td>2 (5 and 9.1 years after RT)</td>
<td>2 (5.6 and 6.9 years after RT)</td>
</tr>
<tr>
<td>Luu et al, 2006&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NR</td>
<td>Vasculopathy, 2; second tumor, 1; endocrinopathy, 14; sepsis, 1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Chang et al, 2009&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NR</td>
<td>Endocrinopathy, 11 (of 11 with endocrine results)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alapetite et al, 2012&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NR</td>
<td>Neuropsychologic dysfunction (altered short-term memory, social and emotional functioning, school difficulties, behavioral disorders), no. pts. NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Confer et al, 2012&lt;sup&gt;a&lt;/sup&gt;</td>
<td>headache, 1</td>
<td>NR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Indelicato et al, 2012&lt;sup&gt;a&lt;/sup&gt;</td>
<td>emesis, 1; headache, 1; presyncope, 2; nausea, 9</td>
<td>None to date</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bishop et al, 2013&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NR</td>
<td>Vasculopathy, 2; endocrinopathy, 17</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: NR, not reported; RT, radiation therapy
<sup>a</sup>abstract only
median follow-up of 53 months. Survival rates were not addressed in this abstract. Radiation-induced optic neuropathy did not affect any patients in this cohort. Despite V20 for the temporal lobes at less than 10%, neurocognitive dysfunction was still reported. Symptoms included altered short-term memory, social and emotional functioning, school difficulties, and behavioral disorders. These data suggest that neurocognitive decline in craniopharyngioma patients is multifactorial.

**Second Malignancy**

Due to its physical properties, proton therapy decreases the integral dose to a patient. In a retrospective cohort study with a median follow-up of 6.7 years, the rate of second malignancies was 5.2% in patients treated with proton therapy compared to 7.5% in those treated with photon therapy (hazard ratio, 0.52; 95% CI, 0.32-0.85; p=0.009) [20]. More than 90% of the participants in both the proton and photon cohorts were adults.
Interestingly, second malignancy did not occur in any pediatric patients during this follow-up period. However, it is well-known that pediatric craniopharyngioma patients treated with photons can be affected by second malignancies [21]. It is likely that a cohort richer in pediatric patients with longer follow-up would reveal a more pronounced difference in cumulative incidence rates for second malignancies among children than adults. Modeling for other primary tumors treated with proton therapy demonstrates a 2- to 15-fold decrease in the rate of second malignancies with proton therapy compared to photon radiation therapy due to a reduction in integral dose [22].

**Quality of Life in Survivorship**

Survivor quality of life is altered by toxicities that can develop years after treatment and then persist indefinitely. These side effects can include lifelong medication and enduring feelings of isolation and depression. Laffond et al report on 29 families with a child treated with proton therapy for craniopharyngioma [23]. The mean age at diagnosis was 7 years and 10 months. With a mean follow-up period of approximately 6 years (minimum, 1 year), the overall quality-of-life self-report was in the normal range. The children most commonly experienced depression and altered executive function, and the presence of these symptoms corresponded with lower quality-of-life scores. Furthermore, 78% reported daily fatigue. Other common areas of difficulty for these children included initiation, working memory, organization, shift, and emotional control. Forty-one percent received psychological or psychiatric care, with 2 patients on medication for anxiety or depression. Isolation, frustration, and helplessness were common descriptors used by the families. While 26 children in this cohort attended mainstream school, 34% repeated a year of school. Of the 5 patients 18 years or older, 2 graduated from high school. This study highlights that quality of life and survivorship care is critical in all patients treated for craniopharyngioma regardless of the radiation treatment modality. In a different cohort of 29 patients treated with conventional radiation, 79% reported impairment in one or more quality of life categories, most frequently emotion and pain (with 41% reporting impairment in each) [24]. “Normal” functionality was seen in 6 of the 29 patients. Self-care was compromised in 14%, cognition in 35%, sensation in 38%, and mobility in 38%. While
differences in quality of life with proton therapy versus photon therapy cannot be directly compared between these two studies, they provide essential information to help physicians address survivorship issues and serve as a benchmark to compare future investigations.

Dosimetry and Techniques of Proton Therapy

Dosimetric studies suggest proton therapy affords a reduction in dose to critical structures compared to conventional photon radiation, including IMRT, for patients with craniopharyngioma. In a dosimetric comparison of 10 pediatric patients with craniopharyngioma, both proton techniques (3-dimensional conformal and intensity-modulated proton therapy [IMPT]) decreased the dose to normal tissues and structures, including the hippocampi, dentate gyri, subventricular zones, major vascular structures, infratentorial and supratentorial brain, and brainstem, compared to IMRT [25]. The primary dosimetric goal for all plans consisted of hippocampal avoidance. All plans utilized the same beam orientation: vertex beam and two symmetric lateral beams. Adequate PTV coverage was achieved with all radiation techniques. In this study, IMPT was superior to 3D conformal proton therapy in the dose delivered to the vascular structures and subventricular zone, but 3D conformal proton therapy was superior in the dose delivered to the infratentorial brain and brainstem. IMPT offered the highest conformality index in a dosimetric study from St. Jude Children's Research Hospital (Memphis, TN, USA) evaluating 14 patients with craniopharyngioma [26]. This study compared double-scatter proton therapy, IMPT, and IMRT. IMRT had a higher conformality index and lower optic nerve dose compared to double-scatter proton therapy. However, double-scatter proton therapy was superior to IMRT in minimizing the dose to the cochlea, optic chiasm, and brain as well as a reduction in scanned body dose. In addition, double-scatter proton therapy was less sensitive to changes in target volume due to cyst growth. The reduced integral dose and reduced dose to many surrounding critical structures with proton therapy suggests that superiority of this treatment modality will manifest clinically primarily through reduction in late side effects. Within proton therapy, the optimal technique continues to be investigated. Figure 4 depicts the dose distribution for treatment of a craniopharyngioma with double-scatter proton therapy, IMRT, and IMPT.

Spot-scanning proton therapy is a newer technique that employs active scanning to increase dose conformality compared to the passive techniques. The conformality is related to the spot size of the proton beam: a smaller spot size allows tighter conformality at the cost of increased treatment time and thus susceptibility to target motion. With increasing depth, spot-scanning proton therapy has a larger penumbra compared to the double-scatter technique; therefore, in some cases, the compromise may be a more conformal high-dose distribution but increased regions of low dose. Spot-scanning plans can be optimized based on a single field or multiple fields. With single-field optimization, the entire target is covered by the prescribed dose for each field. In multiple-field optimization, partial target coverage is achieved with each beam, and the sum of the beams results in full target coverage by the prescription dose. While this technique improves conformality and normal-tissue sparing, it is the most sensitive of all the techniques to variations in daily set-up and change in tumor volume [27, 28].

These technique considerations are important, as change in tumor volume is a known concern during treatment of craniopharyngioma, and weekly magnetic resonance imaging is standard during radiation therapy due to concern for cyst expansion [29]. In one study of

Bradley and Indelicato (2014), *Int J Particle Ther*
17 patients treated with proton therapy who underwent imaging during radiation therapy, significant cyst growth occurred in 6 patients [7]. In 4 of these 6 patients, the radiation therapy plan was modified to account for the cyst enlargement and prevent underdosing the tumor. A different threshold for adaptive planning is recommended based on radiation modality. For IMPT, a change in target volume $\geq 5\%$ requires replanning, compared to a change in target volume $\geq 10\%$ for IMRT and $\geq 25\%$ for double-scatter proton therapy [26]. Replanning for proton therapy is more complex than for conventional radiation. In double-scattered treatments, extending the clinical target volume (CTV) and PTV requires a change in the aperture and compensator, first on the planning computer and then with the actual hardware manufacture. In addition, the distal margin of one or more beams may require adjustment.

In a clinical case study, Yeung et al created IMPT plans for 8 patients who had been treated with double-scatter proton therapy [30]. IMPT increased the therapeutic ratio through improved target coverage conformity and normal-tissue avoidance compared to double-scatter proton therapy. For IMPT techniques, multiple-field optimization better...
avoided normal tissue compared to the single-field uniform dose (Figure 5). In a pediatric craniopharyngioma case report by Amsbaugh et al, the authors advocate for spot scanning with single-field optimization for it “creates highly conformal plans yet is less sensitive to proton range uncertainties” than MFO [31]. At present, spot-scanning techniques lack clinical maturity and, therefore, the optimal technique remains debatable.

Summary

Early and mature data from multiple institutions consistently demonstrate that proton therapy is an effective and well-tolerated radiation therapy modality for patients with craniopharyngioma. The dosimetric advantage of proton therapy allows radiation oncologists to spare critical areas of the developing brain without compromising local control. However, proton therapy data still lack the extensive follow-up available for photon therapy in this rare disease. Therefore, continued long-term surveillance of patients treated with proton therapy is critical to quantifying the reduction in late toxicities. This will be most valuable when collected in a prospective, controlled setting. Current clinical trials such as RT2CR (“A Phase II Trial of Limited Surgery and Proton Therapy for Craniopharyngioma and Observation for Craniopharyngioma after Radical Resection”) allow rigorous evaluation of proton therapy for craniopharyngioma and are expected to contribute critical data to the current body of literature on this topic. Even with the decrease in toxicity associated with proton therapy, quality-of-life issues can linger after primary therapy. Therefore efforts must continue in identifying which tumors are amenable to safe therapy with resection alone. In those patients who require proton therapy, the dynamic cystic elements presents a unique challenge. Meticulous planning and frequent tumor monitoring are necessary to ensure successful treatment, along with thoughtful selection of proton therapy technique and optimization methods.

ADDITIONAL INFORMATION AND DECLARATIONS

Acknowledgments: We would like to thank Meng Wei Ho (University of Florida Proton Therapy Institute, Jacksonville, FL, USA) for his assistance with Figure 5.

Conflicts of Interest Disclosure: The authors have no conflicts of interest to disclose.
References


