# Advances in the management of craniopharyngioma [version 1; referees: 3 approved]

Lillie O’steen\(^1\), Daniel J. Indelicato\(^2\)

\(^1\)Department of Radiation Oncology, University of Florida, 2000 SW Archer Road, Gainesville, FL 32610, USA
\(^2\)Department of Radiation Oncology, University of Florida, 2015 North Jefferson Street, Jacksonville, FL 32206, USA

## Abstract

Craniopharyngioma is a curable benign tumor, but owing to its intimate relationship to critical structures in the central brain—such as the optic apparatus, pituitary, hypothalamus, intracranial vasculature, brain stem, and temporal lobes—its management introduces the risk of long-term treatment morbidity. Today, the most common treatment approach is conservative subtotal resection followed by radiotherapy, and the goal is to limit long-term toxicity. Many recent advances in the treatment of craniopharyngioma are attributable to improved surgical techniques and radiotherapy technologies.

## Keywords

Benign, pediatric, radiation therapy, surgery, outcomes, treatment side effects
Introduction
Cranioopharyngioma is a benign tumor typically treated with both surgery and radiation, an approach that offers 5-year progression-free survival (PFS) rates exceeding 90%.\(^1\) Historically, these high tumor control rates have come at the cost of long-term side effects, such as endocrinopathy, hypothalamic dysfunction, visual field deficits, cerebrovascular sequelae, secondary malignancies, and neurocognitive decline, which significantly impact quality of life among this mostly pediatric population.

Whereas most benign tumors can be treated surgically, craniopharyngiomas present a surgical challenge because of their central location and close proximity to sensitive structures, such as the optic apparatus, pituitary, hypothalamus, circle of Willis, brainstem, and temporal lobes. Schoenfeld \textit{et al.} retrospectively reviewed 122 patients whose craniopharyngioma was treated between 1980 and 2009 with gross total resection (GTR) or subtotal resection (STR) and radiotherapy.\(^2\) GTR was associated with a significantly higher incidence of histologic evidence of insipidus (56.3% versus 13.3%, \(p<0.001\)) and panhypopituitarism (54.8% versus 26.7%, \(p=0.014\)) and showed no improvement in PFS or overall survival.\(^2\) In an analysis of 644 patients from the Surveillance, Epidemiology, and End Results Program whose craniopharyngioma was treated between 2004 and 2008, Zacharia \textit{et al.} examined factors such as younger age, smaller tumor size, and combined-modality therapy.\(^3\) They found that STR and radiotherapy significantly improved survival. In addition, the 10-year local control rate was higher with STR plus radiation than with surgery alone (84% versus 52%; \(p=0.006\)).\(^4\) STR alone has been associated with significantly inferior PFS compared with surgery and radiation.\(^5\) Because aggressive surgery carries a higher risk of morbidity and the rates of progression with STR alone are unsatisfactory, the standard of care for most craniopharyngiomas involves conservative surgery with the goal of preserving vision and controlling hydrocephalus, followed by radiotherapy to optimize local control. Conservative surgical resection is of particular importance in cases with radiographic evidence of hypothalamic involvement, which is associated with decreased 10-year overall survival and an enduring impact on psychosocial quality of life.\(^6\) Only a select subset of tumors, usually small and separate from the hypothalamus and optic pathway, may be cured with surgery alone.

The most recent advances in the treatment of craniopharyngioma have focused on minimizing treatment-related toxicity. These advances include endoscopic surgery and precision radiotherapy. Radiation therapy technology has improved dose conformality and provided decreased doses to adjacent critical structures with the goal of reducing long-term sequelae in this highly curable pediatric population.

Endoscopic endonasal surgery
Prior to the advent of endoscopy, only intrasellar, infradiaphragmatic lesions could be resected through an endonasal approach. With the advent of endoscopic endonasal surgery (EES), suprasellar and select intraventricular tumors, which were accessible only using craniotomy, can now be resected using EES, often with improved clinical outcomes compared with transcranial resection. Karavitaki \textit{et al.} reviewed 64 craniopharyngioma patients who underwent EES.\(^7\) The GTR and near total resection rates were 37.5% and 34.4%, respectively, similar to historical rates with transcranial resection.\(^8\) There was no difference in extent of resection between intrasellar and suprasellar tumors. The rates of visual deterioration (0%) and new endocrinopathies (58.3%) were lower with EES compared with published results with transcranial resection.\(^9\)

Intensity-modulated photon radiation therapy
The fundamental objective of radiotherapy is to deliver a therapeutic dose to the tumor target while limiting the dose to nearby normal structures. Intensity-modulated proton radiotherapy (IMRT) is a precise radiotherapy modality that delivers small beamlets of varying intensities to a complex target structure. Compared with three-dimensional conformal radiotherapy (3DCRT), IMRT offers improved dose conformality and reduced dose to adjacent normal structures. In a dosimetric study of 15 pediatric craniopharyngioma patients who underwent treatment planning for both 3DCRT and IMRT, IMRT reduced the mean dose to the cochlea from 18.2 to 13.3 Gy (\(p<0.001\)), temporal lobes from 14.3 to 7.9 Gy (\(p<0.001\)), and hippocampus from 26.8 to 17.6 Gy (\(p<0.001\)).\(^10\)

Proton therapy
Protons from a cyclotron or synchrotron travel through tissue delivering small dose until reaching their maximum depth, where, depending on their energy, they deposit a narrow distribution of dose before stopping, producing the characteristic Bragg peak. Unlike in photon-based radiation, no “exit” dose is delivered beyond the target with proton therapy. A “spread-out” Bragg peak can be created by delivering protons across a range of energies. In a dosimetric study of 10 pediatric craniopharyngioma patients who underwent treatment planning using IMRT, three-dimensional conformal proton radiotherapy (3DCPT), and intensity-modulated proton therapy (IMPT), both 3DCPT and IMPT demonstrated a relative reduction in the integral dose to the brain stem, hippocampus, dentate gyrus, vascular structures, subventricular zone, infratentorial region, supratentorial region, and whole brain.\(^11\) Such a dose reduction to these intimately located critical structures can help lessen the acute and late toxicities of radiotherapy. Investigators of a Childhood Cancer Survivor Study analyzing pediatric patients with a variety of tumors calculated a 2- to 15-fold reduction in the incidence of second malignancies when proton therapy replaces conventional photon radiotherapy.\(^12\) Compared with proton therapy, proton therapy offers a better opportunity to preserve IQ scores in patients with craniopharyngioma.\(^13\) In a review of 40 pediatric craniopharyngioma patients who received proton radiotherapy, the 5-year local control and overall survival rates were 100%.\(^14\) Table 1 reviews the published outcomes on patients with craniopharyngioma treated with proton therapy.\(^15\) A comparison of photon stereotactic radiotherapy and 3DCPT plans is shown in Figure 1.
| Study; number of patients | Median follow-up, years | Treatment modality | Actuarial 5-year local control rate | Acute toxicity, number of patients | Late toxicity, number of patients | Mortality (absolute number), number of patients |
|---------------------------|------------------------|-------------------|-----------------------------------|----------------------------------|----------------------------------|---------------------------------------------|
| Fitzek et al. (2006); N = 15 | 13.1 | Surgery/biopsy + proton-photon | 93% 5-year | None; 7; nausea, 1; fatigue, 3; headaches, 4 | Visual deficits, 2; endocrinopathy, 15; learning difficulty, 1 | PD, 2; vascular complications, 1; treatment related hypothalamic syndrome, 1 |
| Luu et al. (2006); N = 16 | 5 | Surgery + proton or proton alone (surgery + RT; recurrent after surgery; re-resection + RT; RT; RT, 4) | 94% (recurrence at 80 months, 1) | NR | Panhypopituitarism, 1; CVA, 1 with full recovery; meningioma, 1 following re-irradiation | 3 at 12, 52, and 120 months after re-resection and RT (PD, 1; sepsis, 1; MCA infarct, 1) |
| Winkfield et al. (2008); N = 24 | 3.7 | Surgery/biopsy + proton therapy | 100% | NR | NR | Intracranial hemorrhage at 1 year, 1 (in a child with 3 previous surgeries followed by RT) |
| Chang et al. (2009); N = 14 | 1.3 | Surgery/biopsy + proton therapy | 100% | NR | Vision, stable or improved; endocrinopathy, 11 (of 11 with results) | 0 |
| Alapetite et al. (2012); N = 49 | 4.4 | Surgery + proton-photon; surgery + proton, 10; surgery + proton, 39 | 90% | NR | Altered short-term memory, social and emotional functioning and significant school difficulties in children who had RT after several surgeries. Behavioral disorder rates lower after STR + RT. | NR |
| Confer et al. (2012); N = 13 | 0.7 | Surgery/biopsy + proton | 85% | Grade 2 headache, 1 | NR | 0 |
| Indelicato et al. (2012); N = 40 | 0.7 | Surgery/biopsy + proton therapy | 100% | Emesis, 1; headache, 1; presyncope, 2; nausea, 9 | None to date | 0 |
| Bishop et al. (2014); N = 21 | 2.75 | Surgery/biopsy + proton, 15; proton alone, 4 | 92% | NR | Vasculopathy, 2; endocrinopathy, 16 | Secondary to surgically induced DI, 1 |
| Merchant et al. (2017); N = 94 | 2.65 | Surgery/biopsy + proton therapy | 97.8% (3-year) | NR | Preservation of academic achievement | NR |

*CVA, cerebrovascular accident; DI, diabetes insipidus; MCA, middle cerebral artery; NR, not reported; PD, progression of disease; RT, radiation therapy; STR, subtotal resection.

Spot scanning and intensity-modulated proton therapy
Spot scanning provides better proximal and distal target conformity compared with passive-scatter proton therapy by covering the target with small mono-energetic pencil beams steered by magnets. Dosimetric studies have shown that IMPT decreases the dose to normal surrounding tissue compared with double-scatter proton therapy, as shown in Figure 2. However, spot scanning is more sensitive to changes in the volume of cystic craniopharyngiomas during treatment, which could lead to underdosing at the margins. Furthermore, most spot-scanning systems do not allow aperture-based delivery, which means that the beam penumbra may be less conformal at the lateral target.

Reducing radiation target margins
In radiation planning for all modalities, target volumes are delineated by using computed tomography simulation images fused to T1- and T2-weighted post-contrast thin-sliced (1 to 1.5 mm slice thickness) magnetic resonance imaging (MRI). The gross tumor volume (GTV) has historically been expanded by a margin of 10 mm to create the clinical target volume (CTV). However, in a prospective analysis of 88 children who received
radiotherapy between 1998 and 2009, a 5 mm and a 10 mm expansion for the CTV provided comparable PFS. A recent phase II protocol (RT2CR, NCT01419067) at the University of Florida in conjunction with St Jude Children’s Research Hospital prospectively evaluated a 5 mm CTV margin using proton therapy. Early results are promising in terms of both disease control and reduced toxicity.22,24.

Adaptive planning
Improved conformity with the most recent technological advances in radiation therapy delivery increases the susceptibility of the proton dose distribution to the effects of dynamic cyst changes that occur throughout the 6 weeks of treatment. The GTV, by virtue of cyst reduction or enlargement, has been observed to change on average by 28.5% (range of ~20.7% to 82%) during treatment when weekly MRIs are obtained.10 Weekly MRIs during radiotherapy are used to identify these changes, and adaptive planning is necessary when changes in tumor volume may impact target coverage, as shown in Figure 3.

Summary
Cranioopharyngioma is a curable benign tumor treated primarily by conservative resection and radiotherapy. Reducing the late toxicities of radiotherapy remains of pivotal importance in treating cranioopharyngioma. Recent technological advances in radiotherapy offer the promise of reducing side effects while maintaining high cure rates.
**Figure 2.** Dosimetric comparison of passive-scatter proton therapy and pencil-beam scanning. An example of the dose distribution for passive-scatter proton therapy (top) and pencil-beam scanning (bottom) in a patient with craniopharyngioma demonstrates comparable and acceptable target coverage in both plans. In this example, however, the pencil-beam modulation is used to create a more homogenous dose plan. The maximum doses to the optic chiasm are 55.6 Gy for the passive-scatter plan and 54.6 Gy for the pencil-beam scanning plan. The figures are original images taken in our clinic for this publication.

**Figure 3.** Dynamic cyst changes. Pictured are the T2-weighted magnetic resonance images (MRIs) in an axial, sagittal, and coronal presentation (left to right) taken weekly during radiotherapy for craniopharyngioma. The most superior MRI was obtained for radiation planning purposes, and the red line represents the contoured gross tumor volume. The images in the second row were obtained during the first week of radiation treatment and demonstrate cyst growth. The most inferior images were obtained during the second week of radiation treatment after the cyst had been drained via the Ommaya reservoir. The figures are original images taken in our clinic for this publication.
Abbreviations

3DCPT, three-dimensional conformal proton therapy; 3DCRT, three-dimensional conformation radiation therapy; CTV, clinical tumor volume; EES, endonasal surgery; GTV, gross tumor volume; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiation therapy; MRI, magnetic resonance imaging; PFS, progression-free survival; STR, subtotal resection

References

1. Merchant TE, Kun LE, Hua CH, et al.: Disease control after reduced volume conformal and intensity-modulated radiation therapy for childhood craniopharyngioma. Int J Radiat Oncol Biol Phys. 2013; 86(4): e167–82. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

2. Schoenen A, Pelmmezzi M, Barnes MJ, et al.: The superiority of conservative resection and adjuvant radiation for craniopharyngiomas. J Neurooncol. 2012; 108(1): 133–9. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

3. Zachariais BE, Bruce SS, Goldstein H, et al.: Incidence, treatment and survival of patients with craniopharyngioma in the surveillance, epidemiology and end results program. Neuro Oncol. 2012; 14(8): 1070–8. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

4. Gerken AS, Hoffmann A, Gebhardt U, et al.: Survival, hypothalamic obesity, and neuropsychological/psychosocial status after childhood-onset craniopharyngioma: newly reported long-term outcomes. Neuro Oncol. 2015; 17(7): 1029–38. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

5. Müller HL: Craniopharyngioma: long-term consequences of a chronic disease. Expert Rev Neurother. 2015; 15(11): 2045–47. PubMed Abstract | Publisher Full Text | F1000 Recommendation

6. Karavitaki N, Cudlip S, Adams CB, et al.: Craniopharyngiomas. Endocr Rev. 2006; 27(4): 371–97. PubMed Abstract | Publisher Full Text

7. Koutourou D, Gardiner PA, Fernandez-Miranda JC, et al.: Endoscopic endonasal surgery for craniopharyngiomas: surgical outcome in 64 patients. J Neurosurg. 2013; 119(5): 1194–207. PubMed Abstract | F1000 Recommendation

8. Chokrubari I, Amar AP, Coulthard W, et al.: Long-term neurological, visual, and endocrine outcomes following transnasal resection of craniopharyngioma. J Neurosurg. 2005; 102(4): 650–7. PubMed Abstract | Publisher Full Text

9. Fernandez-Miranda JC, Gardner PA, Snyderman CH, et al.: Craniopharyngiomas: a pathologic, clinical, and surgical review. Head Neck. 2012; 34(7): 1036–44. PubMed Abstract | Publisher Full Text

10. Beltran C, Naik M, Merchant TE: Dosimetric effect of target expansion and setup uncertainty during radiation therapy in pediatric craniopharyngioma. Radiother Oncol. 2016; 120(3): 399–403. PubMed Abstract | Publisher Full Text | F1000 Recommendation

11. Boehling NS, Grosshans DR, Bluett JB, et al.: Dosimetric comparison of three-dimensional conformal proton radiotherapy, intensity-modulated proton therapy, and intensity-modulated radiotherapy for treatment of pediatric craniopharyngiomas. Int J Radiat Oncol Biol Phys. 2012; 82(2): 643–52. PubMed Abstract | Publisher Full Text | F1000 Recommendation

12. Friedman DL, Whilton J, Leisnann W, et al.: Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2010; 102(14): 1083–95. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

13. Merchant TE, Hua CH, Shukla H, et al.: Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. Pediatr Blood Cancer. 2008; 51(1): 119–27. PubMed Abstract | Publisher Full Text

14. Indelicato DJ, Rotondo R, Flam F, et al.: Proton Therapy for Craniopharyngioma: Early Clinical Outcomes. Int J Radiat Oncol Biol Phys. 2012; 84(3): S634. PubMed Full Text

15. Fitzek MM, Lingwood RM, Adams J, et al.: Combined proton and photon irradiation for craniopharyngioma: Long-term results of the early cohort of patients treated at Harvard Cyclotron Laboratory and Massachusetts General Hospital. Int J Radiat Oncol Biol Phys. 2006; 64(5): 1348–54. PubMed Abstract | Publisher Full Text

16. Luo QT, Loredo LN, Archambeau JO, et al.: Fractionated proton radiation treatment for pediatric craniopharyngioma: preliminary report. Cancer J. 2006; 12(2): 155–9. PubMed Abstract

17. Winkfield KM, Linsermoere C, Yao BY, et al.: Proton Radiotherapy for Childhood Craniopharyngioma: Initial Clinical Outcomes. Int J Radiat Oncol Biol Phys. 2008; 72(1): S496. Publisher Full Text

18. Chang AL, Fitzek MM, Kruter LE, et al.: Outcomes of Pediatric Craniopharyngioma Treated with Proton Radiation Therapy. Int J Radiat Oncol Biol Phys. 2009; 75(3): S513. PubMed Full Text

19. Alapetite C, Puget S, Ruffer A, et al.: Proton therapy for craniopharyngioma in children: Update of the Orsay Proton Center experience. Neuro Oncol. 2012; 14(12): i22–i5: CR-09. PubMed Abstract

20. Confer ME, McNall-Knapp R, Krishnan S, et al.: Proton Radiation Therapy for Pediatric Craniopharyngioma: Initial Results. Int J Radiat Oncol Biol Phys. 2012; 84(3): S635. Publisher Full Text

21. Bishop A, Greenfield B, Mahajan A, et al.: Proton beam therapy versus conformal photon radiation therapy for childhood craniopharyngioma: multi-institutional analysis of outcomes, cyst dynamics, and toxicity. Int J Radiat Oncol Biol Phys. 2014; 90(2): 354–61. PubMed Abstract | Publisher Full Text | Free Full Text

22. Merchant TE, Hua CH, Sabin ND, et al.: Progression-Free Survival after Proton Therapy for Childhood Craniopharyngioma: Early Results From a Prospective Trial. Int J Radiat Oncol Biol Phys. 2017; 99(2): S59. Publisher Full Text

23. Yeung D, McKenzie C, Indelicato DJ: A dosimetric comparison of intensity-modulated proton therapy optimization techniques for pediatric craniopharyngiomas: a clinical case study. Pediatr Blood Cancer. 2014; 61(1): 89–94. PubMed Abstract | Publisher Full Text

24. Merchant T, Indelicato D, Hua CH, et al.: Comparison of academic achievement scores after proton and photon therapy in children and young adults with craniopharyngioma [abstract]. Ped Blood Cancer. 2017; 64: S3.

Grant information

The author(s) declared that no grants were involved in supporting this work.

Acknowledgments

The authors thank Jessica Kirwan for editing and preparing the manuscript for submission.
Open Peer Review

Current Referee Status: ✔ ✔ ✔

Editorial Note on the Review Process

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty and are edited as a service to readers. In order to make these reviews as comprehensive and accessible as possible, the referees provide input before publication and only the final, revised version is published. The referees who approved the final version are listed with their names and affiliations but without their reports on earlier versions (any comments will already have been addressed in the published version).

The referees who approved this article are:

Version 1

1 Hermann L Müller Department of Pediatrics and Pediatric Hematology and Oncology, Klinikum Oldenburg AoR, Medical Campus University Oldenburg, Oldenburg, Germany
   Competing Interests: No competing interests were disclosed.

2 Kristian Aquilina Department of Neurosurgery, Great Ormond Street Hospital for Children NHS Trust, London, UK
   Competing Interests: No competing interests were disclosed.

3 Yen-Ching Chang Cancer Services, University College London Hospitals NHS Foundation Trust, 1st Floor Central, 250 Euston Road, London, NW1 2PG, UK
   Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com