Preservation of endocrine function after Ommaya reservoir insertion in children with cystic craniopharyngioma

Laura-Nanna Lohkamp
Division of Neurosurgery, The Hospital for Sick Children, University of Toronto, Toronto
Abhaya V. Kulkarni
Division of Neurosurgery, The Hospital for Sick Children, University of Toronto, Toronto
James M. Drake
Division of Neurosurgery, The Hospital for Sick Children, University of Toronto, Toronto
James T. Rutka
Division of Neurosurgery, The Hospital for Sick Children, University of Toronto, Toronto
Peter B. Dirks
Division of Neurosurgery, The Hospital for Sick Children, University of Toronto, Toronto
Michael Taylor
Division of Neurosurgery, The Hospital for Sick Children, University of Toronto, Toronto
George M. Ibrahim
Division of Neurosurgery, The Hospital for Sick Children, University of Toronto, Toronto
Jill Hamilton
Division of Endocrinology, The Hospital for Sick Children, University of Toronto, Toronto
Ute K. Bartels (ute.bartels@sickkids.ca)
Division of Haematology/Oncology, The Hospital for Sick Children, University of Toronto, Toronto

Research Article

Keywords: Ommaya reservoir, craniopharyngioma, cystic, resection, endocrine function

Posted Date: June 1st, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1693727/v1

Abstract

Introduction: Children with craniopharyngiomas (CP) can experience significant morbidities caused by extensive surgery and/or radiation. Ommaya reservoir insertion (ORI) into cystic CP represents a minimally invasive approach allowing immediate decompression and aims to avoid additional injuries. The purpose of this study was to determine the surgical outcome and relevance of upfront ORI (+/- intracystic treatment) for preservation of endocrine function.

Methods: We performed a retrospective chart review of children with CP treated at the Hospital for Sick Children between 01/01/2000 and 15/01/2020. Endocrine function was reviewed at the time of initial surgery and throughout follow-up. New endocrinological deficits related to the index procedure were defined as immediate failure (IF), whereas postoperative duration of endocrinological stability was defined as event-free survival. The rate of IF and EFS were compared between the treatment groups.

Results: Seventy-nine patients were included and had a median age of 8.3 years (range 2.1–18.0 years); 31 were males. Fifty-three patients with upfront surgical treatment, including 29 ORI and 24 gross total or partial resections had sufficient endocrinological follow up data. Endocrine dysfunction occurring immediately after the index procedure was observed in 15 patients (62.5%) in the resection group compared to 2 patients (6.8%) in the ORI group, odds ratio: 0.05 (CI: 0.01–0.26, $p < 0.0001$). Along those with immediate deficits, mean EFS after ORI was 19.4 months (CI: 11.6–34.2), compared to 13.4 months (CI:10.6-NA) after surgical resection.

Conclusions: Endocrine function was preserved in patients with upfront ORI (+/- intracystic treatment), which was confirmed as a minimally invasive procedure with an overall low morbidity profile.

Introduction

Craniopharyngiomas (CP) are the most common non-glial CNS tumors in children representing 1.2-4% of all intracranial tumors[1]. Being classified as WHO grade I tumor, its predominant histological variant in childhood and adolescence is adamantinomatous with cyst formation, recognized as separate tumor entity[2 3]. Theoretically, the benign nature of CP implies that complete tumor resection would provide a sustainable cure[4]. However, complete resection comes with a price due to the lesional intimacy with critical structures, imposing a significant risk to neurological, visual, and endocrinological function[5–8]. Given the morbidity related to surgery and radiation, which often results in severe long-term consequences with injury and impaired function of the hypothalamus, the management of CP in children remains controversial[4 7 9–11]. Other therapies, such a systemic chemotherapy haven't proven a substantial value in the treatment of CP[12 13]. With this in mind and acknowledging the need for a paradigm change away from radical surgery, efforts have been made over the last 2 decades to develop alternative treatment strategies, which allow for less extensive resection whilst protecting structures at risk and still provide efficacy[14 15]. In this context, intralesional therapies via Ommaya reservoir insertion (ORI) into the cystic component of the CP have been established. ORI represents a minimally invasive

intervention, which allows cystic decompression via aspiration and/or intracystic installation of agents, both designed to obtain durable cyst shrinkage with minimal overall toxicity[16–18]. Previous studies have addressed the efficacy of different agents, including bleomycin and interferon-alpha (IFN-α)[19–22]. IFN-α, especially, was found to delay disease progression and potentially offer a protracted time to definitive surgery or radiotherapy with a favorable toxicity profile compared with other therapeutic modalities[23–26]. The purpose of this study was to assess the overall morbidity of ORI in pediatric CP patients and its potential influence on endocrine function.

Material And Methods

We performed a single center, retrospective observational study including pediatric patients with diagnosed CP between January 1, 2001, and January 15, 2020, at the Hospital for Sick Children (Sickkids) Toronto, Canada. The study subjects were identified using an electronic database of all craniopharyngioma patients and demographic, clinical, surgical and radiographic data were obtained through a retrospective chart review. The study was approved by the Research Ethics Board at Sickkids and conducted in accordance with their ethics guidelines and those of the University of Toronto. Due to the retrospective design of the study, the requirement for informed consent was waived by the REB.

Patients

Patients younger than 18 years at the time point of diagnosis with clinically and radiographically confirmed diagnosis of CP, who completed their entire treatment course at HSC were included in this retrospective study. Patients not treated at HSC and with incomplete clinical, surgical, radiographic, endocrine and follow-up data were excluded.

Surgical treatment and outcome analysis

A dedicated review of ORI procedures was performed. The patient's chart, OR reports and postoperative MRIs were assessed for the anatomical approach, the technical approach, including the use of technical devices, intra- and postoperative complications, the indication and number of revision surgeries, as well as the indications for secondary ORI. Intraoperative and postoperative complications related to ORI as well as delayed events requiring revision, or additional resection surgery were defined as secondary outcome.

Endocrinological data and outcome analysis

Endocrine data were retrieved via chart review from documentations of our endocrine clinic, including diagnosis, follow up data as well as the need for substitution. Endocrine function was assessed preoperatively and at different time points postoperatively via laboratory tests. To assess the pituitary-adrenal axis an 8 am cortisol level was obtained, followed by an adrenocorticotropic hormone (ACTH) stimulation test in cases with borderline results. IGF-1 was assessed as a measure of GH secretion followed by a GH stimulation test if the index results were low, or the clinical symptoms were present.

Further test included the basal serum levels of follicle-stimulating hormone (FSH), growth hormone (GH), luteinizing hormone (LH)+/- testosterone (boys) and estrogen (girls), thyroid-stimulating hormone (TSH)+/free T4. Neurohypophyseal function was determined by serum sodium and osmolarity levels in both serum and urine in the context of increased urine output that might suggest diabetes insipidus. Charts were equally reviewed for documented presence of diabetes insipidus (DI) and for the need of hormone substitution or medical treatment of DI. Endocrinological deficits were classified as incomplete or complete depending on the number of dysfunctional axes and/or the type of required substitution or hormonal replacement medication. Endocrine deterioration was defined as dysfunction of any additional hormone axis and/or the need for substitution or hormonal replacement medication of any new or pre-existing dysfunction. The time point of endocrinological deterioration after the index procedure was recorded, used for calculation of EFS and correlated to any potential event, including radiographical tumor progression and secondary interventions. Any secondary intervention was considered as indicator for tumor progression with potential worsening of endocrine function. Accordingly, the primary outcome was endocrinological stability, defined as EFS, and describing the time period between the primary treatment event and first post-operatively detected endocrinological deterioration. Follow up data of our patients, which were available after the age of 18 were also included in the outcome analysis.

Statistical analysis

A two-staged survival model was applied to determine the rate of IF (an EFS of zero) in both treatment groups using Fishers exact test. P-value and estimated odds ratio are presented. For those patients with a positive EFS time, Kaplan–Meier curves of EFS were fitted and median EFS times for each treatment group are presented along with 95% confidence intervals. A cox-proportional hazard model was used to estimate the hazard ratio between ORI and resection in those with a positive survival time. Statistical significance was reached at a *p*-value equal or less than 0.05. All tests were performed using IBM SPSS Statistics Version 26.0 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp, USA).

Results

Demographic data

Seventy-nine patients were diagnosed and treated with CP at the Hospital for Sick Children between 01/01/2000 and 15/01/2020. The median age at diagnosis was 7.8 years (range 0.8-18.0 years), the median follow-up duration 6.1 years (range 0.02-17.2 years) and the gender ratio was 1.3 (males/females). The diagnosis was obtained clinically, including endocrinological and ophthalmological examination, and radiographically via MR imaging (+/- contrast). Additional histopathological results, confirming the adamantinomatous CP diagnosis, were available from 45 patients. The choice of the primary treatment was determined within an interdisciplinary tumor board, which included neurooncologists, neurosurgeons, neuroradiologists, neuropathologists and radiation oncologists and

based on the patient's clinical and neurological presentation, the tumor size and configuration (with/without cystic component).

Treatment overview

A total of 66 out of 79 patients underwent initial surgical treatment. The remaining 13 patients received either non-surgical treatments (irradiation, observation) or were followed elsewhere. ORI was performed in total in 41 patients and was the primary treatment in 32 patients, alone (n=20) or in combination with cyst fenestration (n=6), tumor resection (n=2), biopsy (n=2) or biopsy and cyst fenestration (n=2). The remaining 34 patients underwent surgery, including 2 ventriculoperitoneal shunt insertions, 6 subtotal resections (STR), 1 subtotal resection combined with cyst fenestration, 19 gross total resections (GTR), 2 biopsies (BX), 3 biopsies with cyst fenestration and 2 cyst fenestrations alone. Secondary ORI was performed in 9 of those patients at a later time point (table 1). The surgical and endocrinological outcome after ORI will be reported separately in the following sections and according to the available FU data. A comprehensive overview of all treatments is illustrated in Fig. 1.

Surgical outcome after ORI

ORI was performed in 41 patients, including 22 females and 19 males. These patients underwent a total of 75 Ommaya reservoir (OR) related surgeries, comprised of 62 new catheter insertions (83%) and 13 revisions (17%). For 32 patients ORI was the initial treatment and 21 patients required multiple catheter insertions: 15 patients underwent 2 catheter insertions, 5 patients 3 and 1 patient 4, respectively (Fig 2A).

The surgical approaches for new catheter insertions were mainly performed as a burr hole technique (n = 45) in the frontal (n = 40) or temporal region (n = 5). Seventeen surgeries used an open craniotomy for catheter insertion, equally with a preference for the frontal (n = 15) versus temporal (n = 2) region. Technically, ORI was supported using ultrasound (n = 49), navigation (n = 32) and the endoscope (n = 24), often in a combined fashion. In 6 of 17 open craniotomies the microscope was introduced during ORI (Fig 2B). Catheter function was tested post-operatively by manual aspiration from the Ommaya reservoir. In case of considered intracystic treatment a permeability study was performed to assess the contrast distribution within the cystic portion of the CP after direct contrast injection into the Ommaya reservoir and to rule out leakage (Fig. 3).

The reasons for additional ORI were diagnosis of a new cystic CP component (n=15), or the need for revision surgery in the presence of catheter dysfunction (n=6). Complications related to ORI occurred in 11 patients (27%): five patients (12%) required one or more immediate revisions due to mispositioning of the catheter (n=3) or infection (n=2). Intraoperative bleeding occurred in 2 patients and 4 patients showed transient visual deficits after the surgery (table 2). There were no permanent neurological deficits observed following ORI.

Postoperative treatments via the OR were variable and included intracystic administration of chemotherapy. Bleomycin was administered in 9 patients (22%) and IFN-α in 18 patients (44%).

Intermittent cyst fluid aspiration was performed in 2 patients (5%). Twelve patients did not receive any OR-related treatments (29%) (Fig. 2C).

Endocrinological outcome after ORI

Fifty-five surgical patients had sufficient endocrine FU information (follow-up provided at Sickkids and minimum of 3 months post-OP), including 29 patients with upfront ORI and 24 patients with GTR or STR, and 2 patients with VP-shunt insertion. The median duration of follow up in the surgical cohort was 6.5 years (range 0.3 -17.6 years). Sixteen patients were diagnosed with endocrine deficits pre-operatively, 7 patients undergoing resection, 9 patients ORI, respectively. One patient in the ORI group presented with panhypopituitarism at the time point of diagnosis. The remaining 39 patients had normal endocrine function at the time point of their index surgery and were monitored for endocrine changes throughout the follow up period.

A survival model using a 2-stage process was applied to compare the rate of IF (defined as an EFS of zero) and the EFS between the treatment groups (Fig. 4A). Endocrine dysfunction (partial or complete) occurring immediately after the index procedure was observed in 15 patients (62.5%) in the resection group compared to 2 patients (6.8%) in the ORI group, odds ratio: 0.047 (CI: 0.004-0.263, $p<0.0001$). In the remaining patients with no IF, endocrine stability after the index procedure (EFS, median) was 13.4 months (CI:10.6-NA, we are unable to accurately estimate a 95% CI in this group due to the low sample size of 9) in the resection group compared to a median EFS of 19.4 months (CI:11.6-34.2) in the ORI group, all coinciding with new treatment necessity. The hazard ratio was 0.460 (CI: 0.203-1.044, $p=0.063$) (Fig. 4B).

In patients with pre-existing endocrine deficits, comparative analysis of their perioperative endocrine function showed an increase in the number of dysfunctional axes and/or the need for substitution in the resection group whereas it remained stable after ORI (Fig. 4C). We could not detect any difference in endocrine function in patients with intracystic treatment after ORI compared to those without or intermittent aspiration only.

Discussion

In this study we analyzed the surgical impact of ORI and its effect on endocrine function in children with CP. Surgical tumor resection lead in 62.5% of the patients to immediate post-operative endocrinological dysfunction, compared to 6.8% after ORI. Furthermore, we saw that upfront ORI (+/- intracystic treatment) maintained endocrine stability with a median duration of 19.4 months (CI: 11.6–34.2) until the next intervention/ tumor progression, compared to a shorter, albeit not significantly shorter ($p = 0.063$) duration in most of the patients after GTR or STR. Also, in patients with pre-existing deficits, we could observe that the number of dysfunctional endocrine axis remained stable after ORI, however, increased in patients, who underwent upfront resection. The ORI-related treatments were variable and included intracystic administration of bleomycin or IFN-α, but also consisted of intermittent cyst fluid aspiration or no ORI-related treatment at all.

Previous studies have addressed variable effects of ORI-related therapies in CP disease. The stereotactic or open surgical implantation of an intracystic catheter with a subcutaneous reservoir was found to be a useful means of reducing the volume of the cyst and to prolong the interval until radiotherapy or surgical resection, in particular, in patients with large cysts exerting mass effect[27]. Accordingly, Moussa et al observed a significant improvement of the clinical status and visual acuity in symptomatic patients after cyst drainage via ORI[28]. Similar effects were seen in patients after cyst drainage with subsequent radiosurgery of the solid tumor component and/or cyst remnants[29–31]. Another report by Schubert et al. indicates the superiority of stereotactic ORI placement, cyst drainage and radiotherapy over tumor resection with respect to progression-free survival (PFS)[32]. Beyond the drainage-related, mechanical decompression of critical anatomical structures, intracystic treatments, such as bleomycin and IFN-α have shown effectiveness with respect to cyst size reduction[3 20 23 24 33–36]. Only one study focused on the endocrinological outcome after open microsurgical resection versus minimally invasive drainage procedures and systematically analyzed the tumor control rates and functional scores in a cohort of 79, mainly adult CP patients[37]. The minimally invasive procedure included a stereotactic catheter implantation in cystic CP, providing continuous bidirectional cyst drainage into the supratentorial ventricular system and the basal cisterns. They could show that the endocrinological deterioration rate was significantly lower for cystic tumors undergoing stereotactic treatment (23.1%) than after microsurgery (85.7%), ($P < .001$)[37]. Despite the technical differences in drainage and catheter implantation, we could demonstrate, that, in line with their results, ORI leads to preservation of endocrine function compared to other types of microsurgical intervention. Given that more than 30% of our patients did not receive any intracystic agent after ORI, and that we did not observe any difference in endocrine outcome in relation to the type of ORI-associated treatment, we presume that already cyst drainage alone via ORI contributes significantly to the preservation of endocrine function, analogous to the observation of Rachinger et al[37].

Despite the sparsity of studies comparing the effect of ORI and open microsurgery on endocrine function, we have learned from previous studies, that open tumor resection in CP carries a significant risk of secondary morbidity and mortality related to endocrinological deterioration[7 9 38 39]. Clark et al found in their analysis, that postoperative endocrine function is the main morbidity outcome that varies with respect to extent of resection and adjuvant therapy in pediatric craniopharyngioma[40]. Irreversible DI was reported by Mueller et al in 80–93% of all complete resections and growth hormone deficiency in 75% of cases[41]. Elsewhere it was shown that radical surgical strategies are associated with poor hypothalamic and endocrine outcome and furthermore substantially reduced the quality of life (QoL) of approximately 50% of long-term survivors[8]. Another study by Merchant et al confirmed the strong relationship between endocrine deficiency and its impact on the quality of life. They stratified a cohort of 30 CP patients into 2 groups: those who had aggressive resection compared with those who had a limited resection combined with radiotherapy. Both groups demonstrated a similar rate of tumor recurrence, but a higher rate of diabetes insipidus and lower QoL in the aggressive resection group[42]. Therefore, we consider a delay of endocrine deterioration after ORI, as experienced in our cohort, a substantial benefit for patients with cystic CP.

Although ORI is a minimally invasive approach and preserved endocrine function, we experienced surgical complications in 11 out of 41 patients, including 3 mispositioned catheters, 2 infections, 2 minor hemorrhages as well as 4 transient visual deficits. Catheter revisions or multiple ORI were required in patients with catheter blockage or complex, multi-cystic lesions. Zuccarelli et al reported a very rare case of delayed bilateral, right greater than left hemiballismus in a CP patient 2 years following ORI due to position change of the catheter after cyst decompression[43]. Searching for optimization of the ORI procedure, Zanon et al. performed different techniques of catheter insertion. They experienced complications, namely misplacement or leakage in 16,3% of their patients, independent of the technical approach. These observations of misplacement of the catheter or contrast leakage in 7 to 16% of ORI procedures have been summarized by Pettorini and colleagues[44]. Different outcomes have been reported by Peyrl et al. Their overall complication rate was 1% in 98 patients with ORI undergoing repetitive administration of chemotherapeutic agents into the cerebrospinal fluid, concluding that Ommaya reservoirs are safe and complications infrequent when provided by a well-trained team and under strict aseptic conditions[45]. In comparison to this study, our perioperative complication rate is slightly elevated. However, there is a difference between their surgical approach, namely the catheter insertion into the ventricular system, and our approach, which intends to place the catheter directly into the CP cyst. The latter one is more challenging and therefore may be related to a higher complication rate. Furthermore, complications, such as catheter blockage are more frequent in cystic ORI given the higher protein content of the CP cyst fluid compared to the CSF. However, only 5 out of 41 patients required further complication-directed treatments, indicating an acceptable morbidity profile, but room for improvement according to the protocol of Peyrl A et al[45].

Despite its comprehensive results, this retrospective study suffers several limitations. One is the high variability within the performed surgical approaches, predominantly concerning the technical aspects, the combination of procedures and the use of guidance tools, such as the endoscope, navigation or ultrasound. We acknowledge that the neurosurgical decision making in our cohort was dependent on the expertise and preference of the surgeon and related to the clinical urgency, but not necessarily following any internal standards, which are usually in place for outcome optimization and minimalization of complications, respectively. Given the relatively small patient number, we could not systematically analyze the impact of these different technical approaches. Similarly, the fact that we did not observe any difference in the endocrine function after either IFN-α, bleomycin, cyst aspiration or no treatment at all must be interpretated in the context of a small patient cohort and emphasizes the need for evaluation in prospective studies. Another limitation with respect to the patient numbers can be observed in the statistical analysis of the EFS in the resection group. Only 9 patients have a positive (event free) survival time after elimination of the patients with IF, which did not allow the determination of the confidence interval. Lastly our study lacks analysis of radiographic measurements on the initial cyst volumes and their change over time. This could represent a complementary outcome correlate for the explanation of the endocrine changes and may be worthwhile investigating in a separate study.

Although the surgical outcome in our study confirms a low to moderate morbidity profile of ORI, the benefits of endocrine function preservation are multifold. Endocrine stability was maintained after ORI in

93.2% of the patients with a mean EFS of 19.4 months (CI: 11.6–34.2). compared to 37.5% (odds ratio: 0.047 (CI: 0.004–0.263, p < 0.0001) with a mean EFS of 13.4 months (CI:10.6-NA) after resection, hazard ratio: 0.460 (CI: 0.203–1.044, p = 0.063). Considering the importance of endocrine function in a developing child, ORI represents a valuable procedure and was shown to have a comparably good safety profile as VP-shunts[46]. Further studies are required to elucidate the implications of ORI with respect to hypothalamic, ophthalmological, vascular and neurocognitive long-term outcome.

Conclusions

ORI is a minimal invasive procedure in pediatric CP patients with a low overall morbidity. Catheter revisions are common due to blockage and multiple catheters may be necessary to address recurrent cystic lesions at new locations. Endocrine function was preserved in patients with upfront ORI (+/- intracystic treatment). Further studies are required to elucidate the implications of ORI with respect to ophthalmological, vascular and neurocognitive long-term outcome.

Abbreviations

ACTH	Adrenocorticotropic hormone
BX	Biopsy
CT	Computerized tomography
CCT	Cranial computerized tomography
cMRI	Cranial magnet resonance imaging
DI	Diabetes insipidus
EFS	Event-free survival
FSH	Follicle-stimulating hormone
GH	Growth hormone
GTR	Gross total resection
HSC	Hospital for Sick Children
IF	Immediate failure
IFN-α	Interferon-alpha
LH	Luteinizing hormone

MRI	Magnet Resonance Imaging
PFS	Progression-free survival
QoL	Quality of Life
STR	Subtotal resection
TSH	Thyroid-stimulating hormone

Declarations

Acknowledgements

We thank the entire interdisciplinary team, including our nurses, nurse practitioners and social workers, who were involved in the care of these patients.

Funding

The authors declare that no funds, grants, or other support were received for this study nor during the preparation of this manuscript.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Laura-Nanna Lohkamp. The first draft of the manuscript was written by Laura-Nanna Lohkamp and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by the Research Ethics Board at Sickkids and conducted in accordance with their ethics guidelines and those of the University of Toronto.

Consent to participate

Due to the retrospective design of the study, the requirement for informed consent was waived by the REB.

References

1. Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, Bruner JM (1998) The descriptive epidemiology of craniopharyngioma. J Neurosurg 89(4):547–551. doi: 10.3171/jns.1998.89.4.0547[published Online First: Epub Date]|
2. Louis DN, Perry A, Wesseling P et al (2021) The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neurooncology 23(8):1231–1251. doi: 10.1093/neuonc/noab106[published Online First: Epub Date]|
3. Bartels U, Laperriere N, Bouffet E, Drake J (2012) Intracystic therapies for cystic craniopharyngioma in childhood. Front Endocrinol 3:39. doi: 10.3389/fendo.2012.00039[published Online First: Epub Date]|
4. Puget S (2012) Treatment strategies in childhood craniopharyngioma. Front Endocrinol 3:64. doi: 10.3389/fendo2012.00064[published Online First: Epub Date]|
5. Srinivasan S, Ogle GD, Garnett SP, Briody JN, Lee JW, Cowell CT (2004) Features of the metabolic syndrome after childhood craniopharyngioma. J Clin Endocrinol Metab 89(1):81–86 : 10.1210/jc.2003-030442[published Online First: Epub Date]|
6. Villani RM, Tomei G, Bello L et al (1997) Long-term results of treatment for craniopharyngioma in children. Child's Nerv system: ChNS : official J Int Soc Pediatr Neurosurg 13(7):397–405 : 10.1007/s003810050108[published Online First: Epub Date]|
7. Kalapurakal JA, Goldman S, Hsieh YC, Tomita T, Marymont MH (2003) Clinical outcome in children with craniopharyngioma treated with primary surgery and radiotherapy deferred until relapse. Med Pediatr Oncol 40(4):214–218. doi: 10.1002/mpo.10247[published Online First: Epub Date]|
8. Müller HL (2011) Consequences of craniopharyngioma surgery in children. J Clin Endocrinol Metab 96(7):1981–1991 : 10.1210/jc.2011-0174[published Online First: Epub Date]|
9. Müller HL (2010) Childhood craniopharyngioma: current controversies on management in diagnostics, treatment and follow-up. Expert Rev Neurother 10(4):515–524. doi: 10.1586/ern.10.15[published Online First: Epub Date]|
10. Puget S, Garnett M, Wray A et al (2007) Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. J Neurosurg 106(1 Suppl):3–12 [published Online First: Epub Date]|
11. Pierre-Kahn A, Recassens C, Pinto G et al (2005) Social and psycho-intellectual outcome following radical removal of craniopharyngiomas in childhood. A prospective series. Child's nervous system: ChNS. : official journal of the International Society for Pediatric Neurosurgery 21(8–9):817–824. doi: 10.1007/s00381-005-1205-6[published Online First: Epub Date]|

12. Hargrave DR (2006) Does chemotherapy have a role in the management of craniopharyngioma? J Pediatr Endocrinol metabolism: JPEM 19(Suppl 1):407–412
13. Jakacki RI, Cohen BH, Jamison C et al (2000) Phase II evaluation of interferon-alpha-2a for progressive or recurrent craniopharyngiomas. J Neurosurg 92(2):255–260. doi: 10.3171/jns.2000.92.2.0255[published Online First: Epub Date]|
14. Puget S, Grill J, Habrand JL, Sainte-Rose C (2006) Multimodal treatment of craniopharyngioma: defining a risk-adapted strategy. J Pediatr Endocrinol metabolism: JPEM 19(Suppl 1):367–370
15. Flitsch J, Aberle J, Burkhardt T (2015) Surgery for pediatric craniopharyngiomas: is less more? J Pediatr Endocrinol metabolism: JPEM 28(1–2):27–33 : 10.1515/jpem-2014-0417[published Online First: Epub Date]|
16. Frio F, Solari D, Cavallo LM, Cappabianca P, Raverot G, Jouanneau E Ommaya Reservoir System for the Treatment of Cystic Craniopharyngiomas: Surgical Results in a Series of 11 Adult Patients and Review of the Literature. World neurosurgery 2019 doi: 10.1016/j.wneu.2019.07.217[published Online First: Epub Date]|.
17. Gutin PH, Klemme WM, Lagger RL, MacKay AR, Pitts LH, Hosobuchi Y (1980) Management of the unresectable cystic craniopharyngioma by aspiration through an Ommaya reservoir drainage system. J Neurosurg 52(1):36–40 [published Online First: Epub Date]|
18. Rogers LR, Barnett G (1991) ;**41**(2 (Pt 1)):279 – 82 doi: 10.1212/wnl.41.2_part_1.279[published Online First: Epub Date]|
19. Hukin J, Steinbok P, Lafay-Cousin L et al (2007) Intracystic bleomycin therapy for craniopharyngioma in children: the Canadian experience. Cancer 109(10):2124–2131. doi: 10.1002/cncr.22633[published Online First: Epub Date]|
20. Mottolese C, Stan H, Hermier M et al (2001) Intracystic chemotherapy with bleomycin in the treatment of craniopharyngiomas. Child's nervous system: ChNS. : official journal of the International Society for Pediatric Neurosurgery 17(12):724–730. doi: 10.1007/s00381-001-0524-5[published Online First: Epub Date]|
21. Zhang S, Fang Y, Cai BW, Xu JG, You C Intracystic bleomycin for cystic craniopharyngiomas in children. The Cochrane database of systematic reviews 2016;**7**:Cd008890 doi: 10.1002/14651858.CD008890.pub4[published Online First: Epub Date]|.
22. Steinbok P, Hukin J (2010) Intracystic treatments for craniopharyngioma. NeuroSurg Focus 28(4):E13. doi: 10.3171/2010.1.focus09315[published Online First: Epub Date]|
23. Kilday JP, Caldarelli M, Massimi L et al (2017) Intracystic interferon-alpha in pediatric craniopharyngioma patients: an international multicenter assessment on behalf of SIOPE and ISPN. Neurooncology 19(10):1398–1407. doi: 10.1093/neuonc/nox056[published Online First: Epub Date]|
24. Ierardi DF, Fernandes MJ, Silva IR et al (2007) Apoptosis in alpha interferon (IFN-alpha) intratumoral chemotherapy for cystic craniopharyngiomas. Child's Nerv system: ChNS : official J Int Soc Pediatr Neurosurg 23(9):1041–1046. doi: 10.1007/s00381-007-0409-3[published Online First: Epub Date]|

25. Cavalheiro S (2017) Intracystic interferon-alpha in pediatric craniopharyngioma patients. Neurooncology 19(10):1419. doi: 10.1093/neuonc/nox123[published Online First: Epub Date]|
26. Dastoli PA, Nicacio JM, Silva NS et al (2011) Cystic craniopharyngioma: intratumoral chemotherapy with alpha interferon. Arq Neuropsiquiatr 69(1):50–55
27. Choux MLG, Genitori L (1991) children. Ci, Neurochirurgie 37(Suppl. 1),
28. Moussa AH, Kerasha AA, Mahmoud ME (2013) Surprising outcome of ommaya reservoir in treating cystic craniopharyngioma: a retrospective study. Br J Neurosurg 27(3):370–373. doi: 10.3109/02688697.2012.741732[published Online First: Epub Date]|
29. Rahmathulla G, Barnett GH (2013) Minimally invasive management of adult craniopharyngiomas: An analysis of our series and review of literature. Surg Neurol Int 4(Suppl 6):S411–S421. doi: 10.4103/2152-7806.121612[published Online First: Epub Date]|
30. Reda WA, Hay AA, Ganz JC (2002) A planned combined stereotactic approach for cystic intracranial tumors. Report of two cases. J Neurosurg 97(5 Suppl):610–612. doi: 10.3171/jns.2002.97.supplement[published Online First: Epub Date]|
31. Jarebi M, Coutte A, Bartier F, Khormi Y, Peltier J, Lefranc MA, Novel Hybrid, Stereotactic Approach (Radiosurgery and Dual Ommaya Reservoirs) for the Treatment of Mixed (Polycystic and Solid) Craniopharyngioma. Stereotactic and functional neurosurgery 2019; **97**(4):266–71doi: 10.1159/000503690[published Online First: Epub Date]|.
32. Schubert T, Trippel M, Tacke U et al (2009) Neurosurgical treatment strategies in childhood craniopharyngiomas: is less more? Child's nervous system: ChNS. : official journal of the International Society for Pediatric Neurosurgery 25(11):1419–1427. doi: 10.1007/s00381-009-0978-4[published Online First: Epub Date]|
33. Cavalheiro S, Di Rocco C, Valenzuela S et al (2010) Craniopharyngiomas: intratumoral chemotherapy with interferon-alpha: a multicenter preliminary study with 60 cases. NeuroSurg Focus 28(4):E12. doi: 10.3171/2010.1.focus09310[published Online First: Epub Date]|
34. Mrowczynski OD, Langan ST, Rizk EB, Craniopharyngiomas (2018) A systematic review and evaluation of the current intratumoral treatment landscape. Clin Neurol Neurosurg 166:124–130. doi: 10.1016/j.clineuro.2018.01.039[published Online First: Epub Date]|
35. Takahashi H, Yamaguchi F, Teramoto A (2005) Long-term outcome and reconsideration of intracystic chemotherapy with bleomycin for craniopharyngioma in children. Child's nervous system: ChNS. : official journal of the International Society for Pediatric Neurosurgery 21(8–9):701–704. doi: 10.1007/s00381-005-1208-3[published Online First: Epub Date]|
36. Hukin J, Visser J, Sargent M, Goddard K, Fryer C, Steinbok P (2005) Childhood craniopharyngioma: Vancouver experience. Child's nervous system: ChNS. : official journal of the International Society for Pediatric Neurosurgery 21(8–9):758–765. doi: 10.1007/s00381-005-1220-7[published Online First: Epub Date]|
37. Rachinger W, Oehlschlaegel F, Kunz M et al (2017) Cystic Craniopharyngiomas: Microsurgical or Stereotactic. Treatment? Neurosurg 80(5):733–743 : 10.1227/neu.0000000000001408[published

Online First: Epub Date]|

38. Olsson DS, Andersson E, Bryngelsson IL, Nilsson AG, Johannsson G (2015) Excess mortality and morbidity in patients with craniopharyngioma, especially in patients with childhood onset: a population-based study in Sweden. J Clin Endocrinol Metab 100(2):467–474 : 10.1210/jc.2014-3525[published Online First: Epub Date]|
39. Lucas C, Benderitter T, Choux M (1982) [Pre- and postoperative endocrine function in children with craniopharyngioma]. Archives francaises de pediatrie 39(5):303–307
40. Clark AJ, Cage TA, Aranda D, Parsa AT, Auguste KI, Gupta N (2012) Treatment-related morbidity and the management of pediatric craniopharyngioma: a systematic review. J Neurosurg Pediatr 10(4):293–301 7.Peds11436[published Online First: Epub Date]|
41. Müller HLSN, – K, Multizentrische PB, vKuJ (eds) (2001)Verlag KMlHE, Isensee O, Germany
42. Merchant TE, Kiehna EN, Sanford RA et al (2002) Craniopharyngioma: the St. Jude Children's Research Hospital experience 1984–2001. Int J Radiat Oncol Biol Phys 53(3):533–542 : 10.1016/s0360-3016(02)02799-2[published Online First: Epub Date]|
43. Zuccarelli B, Aalbers B, Grabb P (2016) Hemiballismus as a complication of an intratumoral chemotherapy catheter. J Clin neuroscience: official J Neurosurgical Soc Australasia 30:129–131. doi: 10.1016/j.jocn.2016.01.031[published Online First: Epub Date]|
44. Pettorini BL, Tamburrini G, Massimi L, Caldarelli M, Di Rocco C (2009) Endoscopic transventricular positioning of intracystic catheter for treatment of craniopharyngioma. Technical note. J Neurosurg Pediatr 4(3):245–248. doi: 10.3171/2009.4.peds0978[published Online First: Epub Date]|
45. Peyrl A, Chocholous M, Azizi AA et al (2014) Safety of Ommaya reservoirs in children with brain tumors: a 20-year experience with 5472 intraventricular drug administrations in 98 patients. J Neurooncol 120(1):139–145. doi: 10.1007/s11060-014-1531-1[published Online First: Epub Date]|
46. Kramer K, Smith M, Souweidane MM (2014) Safety profile of long-term intraventricular access devices in pediatric patients receiving radioimmunotherapy for central nervous system malignancies. Pediatr Blood Cancer 61(9):1590–1592. doi: 10.1002/pbc.25080[published Online First: Epub Date]|

Tables

Table 1

Index surgery	Patient number (n) Total n=66	Secondary ORI Total n=9
BX	2	-
BX and cyst fenestration	3	-
Cyst fenestration	2	2
GTR	19	3
ORI	20	-
ORI and BX	2	-
ORI and cyst fenestration	6	-
ORI and tumor resection	2	-
ORI, BX and cyst fenestration	2	-
STR	5	2
STR and cyst fenestration	1	-
VP shunt	2	2

Table 2

Complications (C) and Indications for Revision (R) or Second Surgery (S)	Patient number n (%)
Bleeding (C)	2 (4.9)
Infection (C)	2 (4.9)
Permanent neurological deficits (C)	0 (0)
Transient visual deficits (C)	4 (9.8)
Mispositioning of catheter (R)	3 (7.3)
Blocked catheter (S)	6 (14.6)
New cyst requiring new insertion (S)	15 (36.6)

Figures

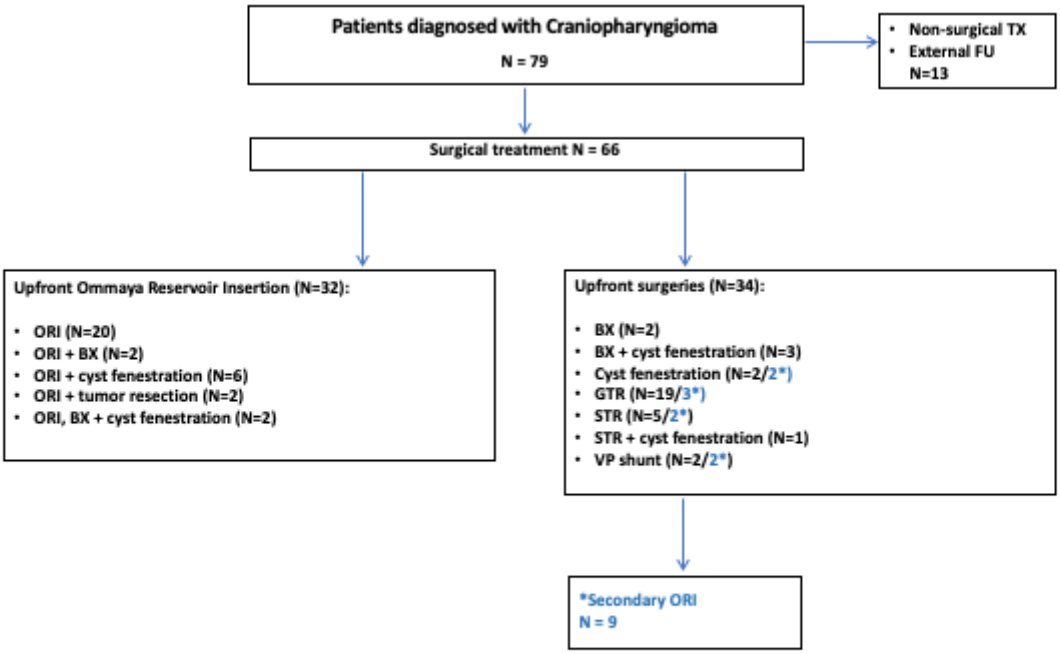

Figure 1

Legend not included with this version

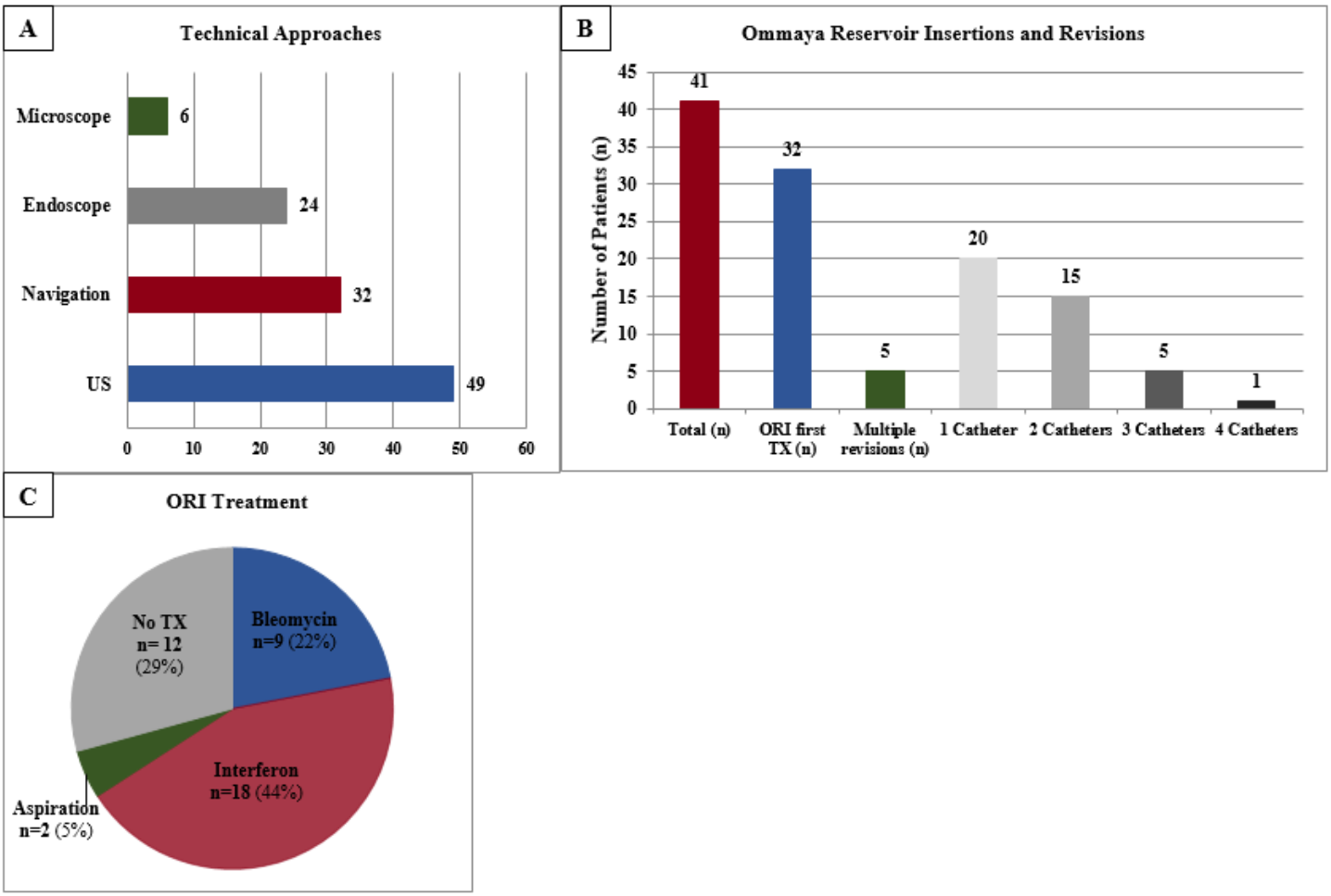

Figure 2

Legend not included with this version

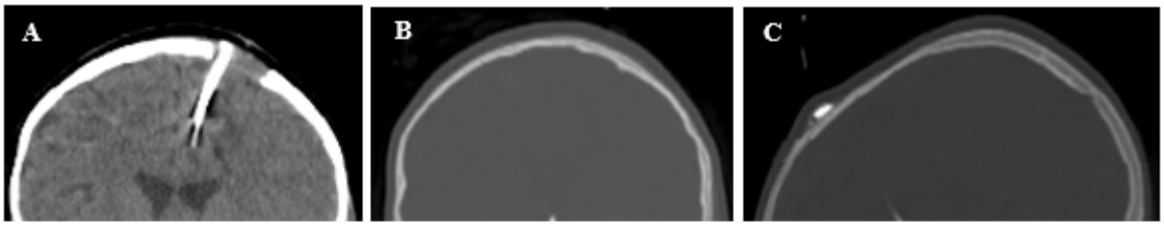

Figure 3

Legend not included with this version

Figure 4

Legend not included with this version