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ORIGINAL ARTICLE

Sixty years single institutional experience with pediatric craniopharyngioma: between the past and the future

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Abstract

Purpose To demonstrate the paradigm shift in management strategies of pediatric craniopharyngioma at our institution over the past six decades.

Methods Retrospective analysis of all pediatric patients with craniopharyngioma treated at Boston Children's Hospital between 1960 and 2017.

Results One hundred seventy-eight patients with craniopharyngioma were treated between 1960 and 2017; 135 (70 males and 65 females) fulfilled the inclusion criteria. Forty-five patients were treated in the old era (1960–1984) and 90 patients were treated in the new era (1985–2017). Gross total resection (GTR) was achieved in 4% and 43% of patients in old and new eras respectively. Sub-total resection (STR) and radiotherapy (XRT) were performed in 27% and 28% of patients in old and new eras respectively. STR without XRT was performed in 20% and 29% of patients in old and new era respectively. Cyst drainage and adjuvant radiotherapy were performed in 49% of patients in the old era while no patients in the new era underwent such conservative management. Aggressive surgical resection was associated with a higher risk of worsening visual outcomes (20% vs 16%), panhypopituitarism and diabetes insipidus (86% vs 53%), psycho-social impairment (42% vs 26%), and new-onset obesity (33% vs 22%). The mortality rate was higher in the old era in comparison with that of the new one (9% vs 2%).

Conclusion There was a paradigm shift in management strategies of pediatric craniopharyngioma over the past six decades which in turn affected the long-term outcomes and quality of life of patients.

Keywords Obesity · Radiotherapy · Moyamoya · Panhypopituitarism

Introduction

Craniopharyngioma is a rare tumor arising from Rathke's pouch, a remnant of the primitive pharynx [4]. Craniopharyngioma accounts for 1–3% of all pediatric intracranial tumors [2, 4]. Craniopharyngioma is a histologically benign tumor (WHO grade I). However, the clinical behavior is aggressive with many pediatric patients experiencing frequent recurrence and significant morbidities, and therefore, recent studies recommend that the adamantinomatous sub-type should be classified as grade II tumors due to the higher rates of tumor recurrence and significant morbidities [4, 17]. Craniopharyngioma is typically located in the sellar and suprasellar regions [1, 4].

The proximity of this tumor to the pituitary stalk, hypothalamus, third ventricle, optic chiasm, and optic nerves, as well as the major intracranial vessels bridging this area makes safe surgical resection challenging [1, 4, 5]. The optimal management of pediatric craniopharyngioma has been controversial for years [5]. The benign histological nature and high survival rate were the bases supporting complete resection as the treatment of choice [3, 5, 7, 10, 18, 22]. Perioperative mortality is low, ranging from 0 to 3% even in the setting of planned

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aggressive resection [4, 8, 15]. Elliot et al. in a large series of pediatric patients with craniopharyngioma noted significantly longer progression-free survival (PFS) with gross total resection (GTR) [4, 8]. In contrast, Merchant et al. reported that there is almost no difference in the rate of tumor recurrence in patients undergoing planned GTR or planned sub-total resection (STR) with adjuvant radiotherapy [4, 15]. Although there are many reports of trans-sphenoidal surgeries performed in adults, there are few reports published for pediatric craniopharyngioma [1, 6, 9, 11, 14, 20].

Radiotherapy has been reported to have favorable results in terms of tumor control. However, it may carry additional risk for significant long-term vasculopathy, secondary malignancies, and neurocognitive dysfunction [3, 5, 12, 16]. In a study of pediatric patients with primary brain tumors treated at Boston Children's Hospital/Dana-Farber Cancer Institute between 1990 and 2000, the crude incidence of post-radiation moyamoya syndrome was found to be 29% for optic glioma, 4.3% for craniopharyngioma, and 1.5% for medulloblastoma [21, 24].

None of the patients in Boston Children's Hospital/Dana-Farber's study were of Asian descent. In a Korean study, the crude incidence of post-radiation moyamoya syndrome in pediatric patients with craniopharyngioma was found to be 13.5% [13, 24].

In this study, we analyzed the data of all pediatric patients with craniopharyngioma treated at our institution over the past six decades. Given the wide time range of this study, we classified patients into old (1960–1984) and new (1985–2017) eras to demonstrate the paradigm shift in management strategies based on the advancement in the perioperative imaging techniques and intraoperative technologies.

Methods

Study design Retrospective analysis of clinical database of all pediatric craniopharyngioma patients treated at Boston Children's Hospital (BCH) between 1960 and 2017. This study was approved by the Institutional Review Board (IRB-P00027869) at BCH.

We reviewed the clinical characteristics (headaches, nausea, vomiting, papilledema, visual impairment, and endocrinologic dysfunction), preoperative radiographic findings (size and site of the tumor, position of the chiasm, calcifications, and presence of hydrocephalus), postoperative radiographic findings (residual, and presence of hydrocephalus), management strategies (GTR, STR with adjuvant radiotherapy, and STR only), and long-term outcomes (visual impairment, diabetes insipidus, panhypopituitarism, psycho-social impairment, and post-radiation complications such as moyamoya and secondary malignancies) of all patients included in this study.

Inclusion criteria Pediatric patients (range 0–21 years at time of diagnosis), postoperative follow-up for at least one year, and definitive pathological diagnosis of craniopharyngioma.

Exclusion criteria Patients were excluded if they were missing any of the inclusion criteria or had undergone surgical excision elsewhere.

Time frame Given the wide time range of this study, we classified patients into two cohorts: the old era before the MRI technology (1960–1984) and the new era or the MRI era (1985–2017).

Treatment options A multidisciplinary team including members of the departments of neurosurgery, pediatric oncology, radiation therapy, radiology, and neurology determined the overall treatment plan for each patient. For the purpose of analysis, GTR was defined as removal of all tumor as determined from the operative report and postoperative imaging studies. Any surgical excision that is less than GTR was deemed STR [23].

Results

One hundred seventy-eight patients with craniopharyngioma were treated at BCH between 1960 and 2017; 135 (70 males and 65 females) fulfilled the inclusion criteria. Forty-five patients were treated in the old era (1960–1984) and 90 were treated in the new era (1985–2017). The median age of patients at the time of diagnosis was 8.5 years (range 1 to 21 years).

The median follow-up period was 10 years (range 1 to 34 years).

Clinical features Symptoms and signs suggesting high intracranial pressure (ICP) were evident in 104 (77%) patients. Visual impairment was documented in 56 (41%) patients. Endocrinological dysfunction was present in 85 (63%) patients. Obesity was evident in 35 (26%) patients at the time of diagnosis. Seizures and motor dysfunction were evident in 5 and 7 patients respectively (Table 1).

Preoperative radiographic findings Brain CT, brain MRI, and skull X-rays were done in 129 (96%), 90 (67%), and 12 (9%) patients, respectively. All lesions were located in the suprasellar region, of which 53 (39%) had a sellar extension and 56 (41%) had a third ventricular extension. The vast majority of the lesions had cystic and solid components, while only 21 (16%) presented as purely cystic lesions. Coarse calcifications were evident in 37 (27%) lesions. Pre- and post-fixed chiasm were seen in 21 (16%) and eight (6%) patients, respectively. Puget classification was only applied for patients

Table 1 Clinical characteristics of patients at time of diagnosis

Characteristics	No. of patients (%)	
	1960–1984	1985–2017
Male:female	23:22	47:43
Headaches	35 (78)	62 (69)
Nausea	19 (42)	21 (23)
Vomiting	21 (47)	28 (31)
Papilledema	15 (33)	36 (40)
Impaired visual field	14 (31)	25 (28)
Impaired visual acuity	7 (16)	19 (21)
Lethargy	12 (27)	16 (18)
Growth delay	13 (29)	26 (29)
Polyuria	5 (11)	13 (14)
Abnormal sexual development	4 (9)	13 (14)
Hormonal deficiency	20 (44)	31 (34)
Obesity	10 (22)	25 (28)
Seizures	3 (7)	2 (2)
Motor dysfunction	1 (2)	6 (7)

who underwent brain MRI, of whom 76 (84%) were grade 0, five (6%) grade I, and nine (10%) grade II [19]. Hydrocephalus was evident in 53 (39%) patients at the time of diagnosis, of whom 24 (45%) underwent CSF diversion prior to any surgical intervention.

Management strategies In the old era, the initial intent of management was STR with adjuvant radiotherapy, whereas in the modern era when MRI became the initial diagnostic tool, GTR was the initial intent of management for all patients. However, based on the intraoperative findings, the surgeon may not perform GTR if the tumor is invading the hypothalamus, optic chiasm, optic nerves, and any of the cerebrovascular structures in order to avoid any further damage to the patients.

For the entire cohort, GTR was achieved in 41 (30%) patients and STR in 72 (53%) patients, whereas cyst drainage

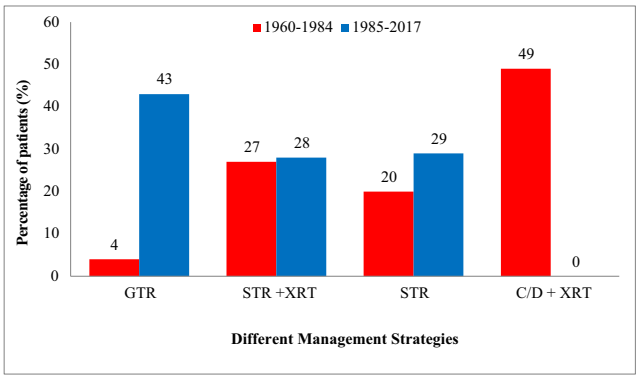

Fig. 1 Management strategies

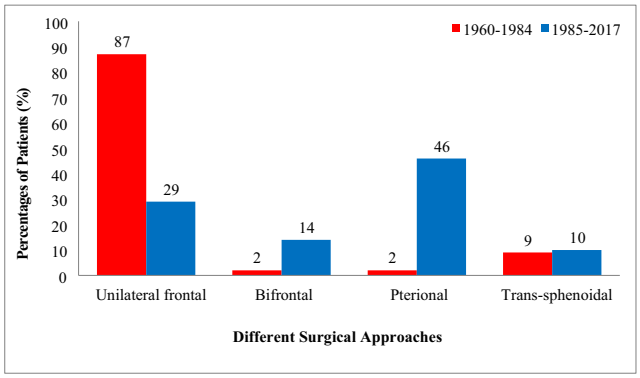

Fig. 2 Surgical approach

without further resection was achieved in 22 (16%). Management strategies in both eras are illustrated in Fig. 1. Surgical excision was undertaken via unilateral frontal, bifrontal, pterional, and trans-sphenoidal approaches in 65, 14, 43, and 13 patients, respectively, and surgical approaches in both eras are illustrated in Fig. 2. Lamina terminalis approach was utilized in 33 (37%) patients.

Radiotherapy For the entire cohort, 80 (59%) patients received radiotherapy through the entire clinical course. At time of initial management, 59 (74%) patients received radiotherapy as an adjuvant treatment in addition to surgical intervention. At time of recurrence, 16 patients received radiotherapy at time of first recurrence (of whom 10 received it alone without surgical intervention), and five patients received it at time of second recurrence (of whom four received it alone without surgical intervention). The median age of patients at the time of radiation therapy was 11 years (range one–21 years). The youngest age at time of radiation was one year in the old era and four years in the new one. The median dose of radiation was 5400 cGy (range 5000–5670 cGy).

Postoperative radiographic findings The pituitary stalk was preserved in 70 patients (42% in the new era vs 71% in the

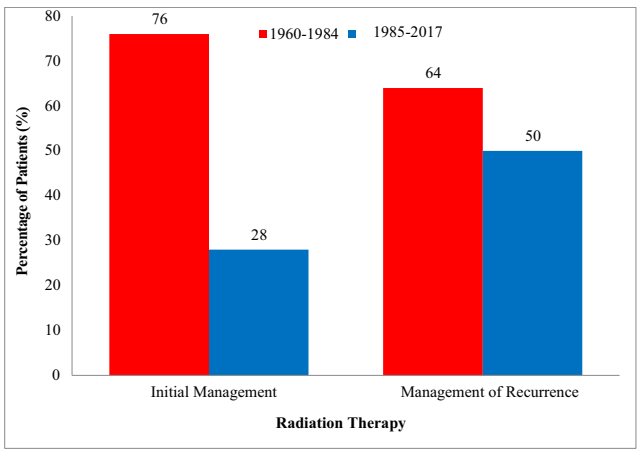

Fig. 3 Radiation therapy

Table 2 Overall long-term outcomes

Outcomes	No. of patients (%)	
	1960–1984	1985–2017
Deteriorated visual function	7 (16)	18 (20)
Improved visual function	6 (13)	12 (13)
Growth delay	14 (31)	11 (12)
Panhypopituitarism	24 (53)	77 (86)
Diabetes insipidus	18 (40)	64 (71)
Psycho-social impairment	12 (26)	38 (42)
New-onset obesity	13 (29)	33 (37)
Recurrence	14 (31)	26 (29)
Death	4 (9)	2 (2)

old era). Arterial vasospasm was seen in 12 (9%) patients (two patients developed aneurysmal dilatation and needed no intervention, whereas one patient developed moyamoya and underwent surgical intervention and other patients had stable clinical and radiographic course). Puget classification was only applied to patients who underwent brain MRI, of whom 73 (81%) were grade 0, 12 (13%) grade I, and five (6%) grade II [19]. Hydrocephalus was evident in 11 (8%) patients of whom four (36%) underwent CSF diversion.

Long-term outcomes Six (4%) patients died, two of tumor progression at two and 10 years after diagnosis, respectively, one of severe electrolyte disturbance at one year after diagnosis, one of secondary malignant pontine astrocytoma at eight years after diagnosis, one of post-radiation vasculopathy at five years after diagnosis, and one of sleep apnea due to morbid obesity at 22 years after diagnosis. Visual function improved in 18 (13%) patients while it deteriorated in 25 (18%) patients. Panhypopituitarism was evident in 101 (75%) patients (of whom 39 patients had evident hormonal deficiency at time of diagnosis). New-onset diabetes insipidus was evident in 82 (61%) patients. New-onset growth delay was present in 25 (19%) patients. New-onset amenorrhea, precocious puberty, and delayed sexual development were

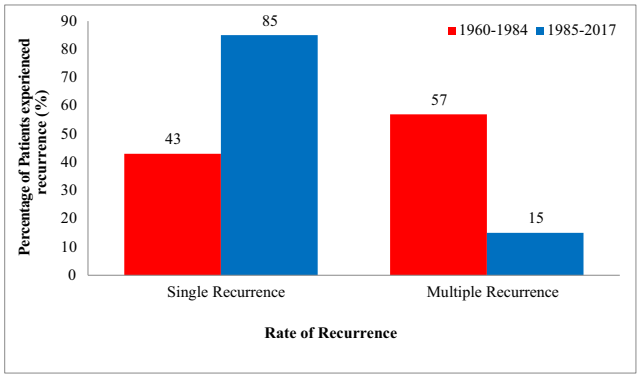

Fig. 5 Rate of recurrence

evident in 18, 4, and 8 patients, respectively. Radiation-induced moyamoya was evident in nine (11%) patients, and all underwent surgical intervention. Intracranial aneurysm was evident in seven (5%) patients, of whom two underwent surgical intervention (one coiling and one clipping), while the other five had stable clinical and radiographic course (all patients have been followed by MR angiography). Psychological impairment was documented in 30 (22%) patients (11 depression and 19 anxiety). Learning disabilities were evident in 38 (28%) patients. New-onset hypothalamic obesity was evident in 46 (34%) patients. Radiation-induced secondary malignancies were seen in three (4%) patients (two meningiomas WHO grade II and one malignant pontine astrocytoma). Seizures were evident in 15 patients (three had seizures preoperatively). Motor dysfunction was evident in seven patients (only one patient was hemiplegic preoperatively). Forty (23%) patients developed recurrence, of whom nine developed a second recurrence and three suffered from repeated cyst re-accumulation. With respect to the timing of recurrence, 60% occurred in the first two postoperative years.

Discussion

In this study, we analyzed our institutional experience with pediatric craniopharyngioma over the past six decades, with

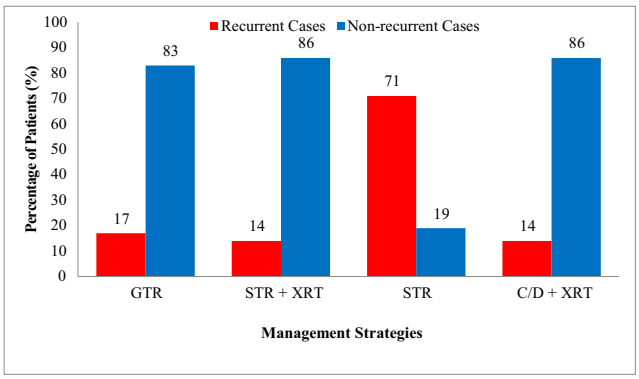

Fig. 4 Rate of recurrence based on management strategies

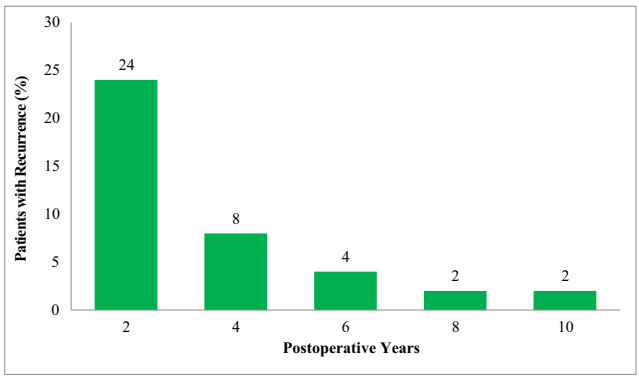

Fig. 6 Time of recurrence in relation to postoperative years

respect to the clinical presentation, the perioperative radiographic assessment, and the paradigm shift in management strategies over the past six decades.

There is a significant difference between both eras based on imaging techniques and advances in the operative and perioperative management, as well as the postoperative care and radiation therapy. In the new era, brain MRI and brain CT were obtained for all patients pre- and postoperatively while in the old era, MRI was not available. Advances in imaging technologies offered more information and better assessment of tumor location, size, nature, the extent of calcification, and proximity to vital neurovascular structures which helped surgeons perform better assessment and surgical planning.

Given the significant advancement in the imaging and intraoperative technologies, there was a paradigm shift in the management strategies between both eras. In the new era, the main strategy was aggressive resection as the initial intent to treat was for GTR whereas conservative management was the main strategy in the old era. GTR was achieved in 4% in the old era and in 43% of patients in the new era (Fig. 1).

With respect to the surgical approach, unilateral frontal was the most common in the old era versus pterional in the new era (Fig. 2). At time of presentation, 49% of patients in the old era underwent cyst drainage and subsequent adjuvant radiotherapy while no patients in the new era underwent such a conservative management. At the time of presentation, 76% of patients in the old era received radiotherapy as an adjuvant treatment due to presence of tumor residual following surgical intervention versus 28% in the new era (Fig. 3). In the new era, 10% of patients underwent EES, and we noticed that it was associated with similar rates of GTR (44% vs 46%) in comparison with craniotomies. However, it was associated with 0% risk of worsening visual function and hypothalamic obesity. Aggressive surgical resection was associated with a higher risk of worsening visual outcomes (20% vs 16%), panhypopituitarism (86% vs 53%), diabetes insipidus (71% vs 40%), psycho-social impairment (42% vs 26%), and new-onset obesity (36% vs 29%) (Table 2). Conservative surgical resection with adjuvant radiotherapy has almost the same rates of tumor control in comparison with GTR. However, radiotherapy is associated with a higher rate of secondary malignancies and radiation-induced vasculopathy. In our study, 11% of patients who received radiotherapy at any time through their entire clinical course developed moyamoya and 4% developed secondary malignancies. The mortality rate was higher in the old era in comparison with the new era (9% vs 2%).

Tumor progression and radiation-induced morbidities are the main causes of mortality. The risk of recurrence is slightly lower in the new era in comparison with that of the old era (29% vs 31%). STR/cyst drainage followed by adjuvant radiotherapy has similar rate of recurrence in comparison with GTR. STR without adjuvant radiation therapy was associated with a 71% risk of recurrence (Fig. 4). The number of multiple recurrences was much higher in the old era (57% vs 15%) (Fig. 5). The risk of recurrence is the highest in the first two postoperative years and declines over time (Fig. 6).

Conclusions

The optimal management of pediatric craniopharyngioma remains controversial. Over the past six decades, we witnessed two different eras in our institution with respect to perioperative imaging modalities, intraoperative technologies, and management strategies. Over this time period, our management strategies changed from conservative to aggressive surgical resection. Although the conservative management is associated with lower risk of long-term morbidities, it carries a higher risk of multiple recurrences and radiation-induced vasculopathy. Trans-sphenoidal surgery offers almost similar rates of GTR in comparison with craniotomies with a lower risk of long-term morbidities. Based on our institutional experience over the past six decades, we demonstrate that aggressive resection-related morbidities are balanced by the avoidance of radiation-induced morbidities. In conservative management, radiation-induced morbidities are balanced by similar rates of tumor control in comparison with GTR and lower risk of aggressive surgery-related morbidities.

Compliance with ethical standards

This study was approved by the Institutional Review Board (IRB-P00027869) at BCH.

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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