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ORIGINAL ARTICLE

Outcome of Chinese children with craniopharyngioma: a 20-year population-based study by the Hong Kong Pediatric Hematology/Oncology Study Group

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Abstract

Purpose Craniopharyngioma is a rare low-grade neoplasm in children. Tumor progression occurs frequently, and survivors are at risk of long-term disease and treatment-related morbidities. We reviewed the population-based experience of managing pediatric craniopharyngioma in Hong Kong.

Methods The Hong Kong Pediatric Hematology/Oncology Study Group database was interrogated for patients with craniopharyngioma younger than 18 years between 1999 and 2018. Patient demographics, clinical characteristics, outcomes, and long-term morbidities were summarized.

Results Twenty-eight patients with craniopharyngioma were included (approximate incidence of 1.1 per 1,000,000 individuals). The treatment approaches were heterogeneous and included surgery only, surgery with adjuvant radiation, and surgery with intracystic interferon. With a median follow-up of 6.1 years, 12 (43%) patients experienced disease progression, and 3 patients died of progression, postoperative complication, and gastrointestinal bleeding. The 5-year progression-free survival (PFS) and overall survival (OS) rates were 56.8% (± 10.0%) and 92.0% (± 5.4%), respectively. The 10-year PFS and OS rates were 37.3% (± 11.4) and 92.0% (± 5.4%), respectively. Patients receiving treatment in a high-volume center had significantly better outcomes than did those treated at other centers (PFS, $p = 0.007$; OS, $p = 0.029$). Period of diagnosis, sex, age at diagnosis, greatest tumor dimension, extent of resection, and radiotherapy use did not significantly affect patient survival. Long-term visual impairment (60%) and endocrinopathies (92%) were common.

Conclusion Prognosis of pediatric craniopharyngioma in Hong Kong compares unfavorably with published reports. Centralization and standardization of treatment may prove valuable in mitigating patient outcomes.

Keywords Craniopharyngioma · Pediatric · Chinese · Radiotherapy · Endocrinopathy · Centralization

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Introduction

Accounting for 3% of pediatric brain tumors, craniopharyngioma is a histologically low-grade neoplasm arising from the embryological remnants of the craniopharyngeal ductal epithelium [1]. Despite recent studies deciphering the genomic alterations underlying the pathogenesis of craniopharyngioma, surgical resection with or without adjuvant radiotherapy, coupled with the option of intracystic therapies for select patients, remains the mainstay of treatment for the adamantinomatous subtype occurring in children [2–7]. The role of aggressive resection is, however, controversial in regard to efficacy for disease control and potential long-term morbidities. The optimal strategy for managing this rare disease may also depend on the experience and expertise of the clinicians and hospitals available [8–13]. In this study, we reviewed the population-wide experience of managing craniopharyngioma in Hong Kong Chinese pediatric patients over the past 20 years. We also investigated patient survival, predictors of outcome, and long-term morbidities.

Methods

Patient cohort

Children with brain tumors in Hong Kong were primarily treated in one of the five pediatric oncology centers, which are institutional members of the Hong Kong Pediatric Hematology/Oncology Study Group (HKPHOSG). The HKPHOSG prospectively manages a database for all pediatric patients with cancer diagnoses at these centers. In this retrospective analysis, we analyzed data for all pediatric patients (< 18 years) with craniopharyngioma who were treated between January 1999 and December 2018. Patient medical records were reviewed for additional demographic, clinical, radiographic, and treatment details. We also analyzed patient outcomes according to disease status, as determined by April 30, 2019. Central radiographic and histologic review was not performed. Disease incidence was estimated according to population data collected from the 5-yearly census conducted by the Hong Kong Special Administrative Region Government [14]. The study was approved by the University of Hong Kong/Hong Kong West Cluster Institutional Review Board, and the requirement for informed consent was waived.

Treatment approach

All patients were initially treated by surgical resection, with surgical drainage considered for large cystic lesions. Analysis of the extent of resection was based on operative records and early postoperative imaging, when available. Adjuvant treatment was administered at the discretion of the treating pediatric oncologist, with radiotherapy recommended for patients with marked residual disease. Intracystic interferon, when offered, was delivered according to the Toronto schedule (3 mIU for three doses per week, 4 weeks per cycle) [6].

Visual and endocrine outcomes

Most patients received multidisciplinary follow-up, with input from ophthalmologists and endocrinologists. Chronic visual impairments and endocrinopathies for surviving patients were summarized. Patient growth parameters at the latest evaluation were analyzed with age- and sex-specific growth charts, with overweight and obesity defined as a body mass index greater than or equal to the 90th and 97th percentiles, respectively, for age and sex.

Statistical analysis

All analyses were performed with R, v3.5.2 (www.r-project.org). The date of diagnosis was defined as the date of first tumor resection. Progression-free survival (PFS) was defined as the duration between the date of diagnosis and date of neuroimaging showing tumor progression, date of patient death from any cause, or date of last follow-up, whichever occurred earlier. Overall survival (OS) was defined as the duration between the date of diagnosis and date of death from any cause or date of last follow-up. Potential prognostic factors, including period of diagnosis (1999–2008 vs 2009–2018), treatment center, sex, age at diagnosis (< 7 years vs ≥ 7 years), greatest tumor dimension (< 4 cm vs ≥ 4 cm), extent of resection (gross total resection [GTR]/near total resection [NTR] vs subtotal resection [STR]/biopsy [Bx]), and radiotherapy use, were evaluated for their effect on PFS and OS. Survival analyses were performed with the Kaplan–Meier estimate, and comparisons were made by log-rank tests. *P* values less than 0.05 were considered significant.

Results

Demographic and incidence

Craniopharyngioma was diagnosed in 28 patients during the study period, resulting in an approximate incidence rate of 1.10 per 1,000,000 individuals per year. Eighteen (64%) patients were treated in one of the five pediatric oncology units (Hospital A). Fifteen (54%) patients were male, and the median age of diagnosis was 6.7 years (range: 0.1–16.5 years). One patient had an extracranial nasopharyngeal primary tumor (Patient 24, Table 1). The common presenting symptoms included vomiting ($n = 14$, 50%), headache ($n = 13$, 46%), visual impairment ($n = 10$, 36%), growth disturbance ($n = 5$, 18%), and polyuria ($n = 4$, 14%). Most tumors were diagnosed with magnetic resonance imaging, demonstrating suprasellar

Table 1 Clinical characteristics, treatment, and outcome of children with craniopharyngioma from our cohort

Patient number	Sex	Age at diagnosis (y)	Primary site	Treatment approach	Extent of resection	PD	Latest status	Dx to FU (y)
1	M	2.12	Suprasellar	Surgery only	GTR/NTR	N	Died of postoperative complication	0.01
2	F	0.12	Suprasellar	Surgery only	Bx/STR	Y	DOD	13.62
3	M	15.08	Suprasellar	Surgery only	GTR/NTR	N	Died of GI bleeding	2.71
4	M	6.09	Suprasellar	Surgery only	GTR/NTR	Y	Alive with SD	8.17
5	F	3.84	Suprasellar	Surgery only	GTR/NTR	Y	Alive with SD	5.96
6	F	5.68	Suprasellar	Surgery + RT	Bx/STR	N	Alive with SD	3.54
7	M	13.20	Suprasellar	Surgery only	Bx/STR	Y	Alive with NED	16.82
8	F	9.66	Suprasellar	Surgery only	Bx/STR	Y	Alive with SD	5.69
9	F	10.84	Suprasellar	Surgery + RT	Bx/STR	N	Alive with SD	19.57
10	F	8.41	Suprasellar	Surgery + RT	GTR/NTR	N	Alive with NED	19.12
11	M	6.55	Suprasellar	Surgery + RT	Bx/STR	N	Alive with NED	14.39
12	F	15.40	Suprasellar	Surgery only	GTR/NTR	N	Alive with NED	13.18
13	M	6.84	Suprasellar	Surgery + RT	Bx/STR	Y	Alive with NED	12.02
14	M	11.63	Suprasellar	Surgery + RT	GTR/NTR	N	Alive with NED	11.75
15	F	2.74	Suprasellar	Surgery only	Bx/STR	Y	Alive with SD	11.49
16	M	16.52	Suprasellar	Surgery + RT	Bx/STR	N	Alive with SD	8.66
17	M	10.60	Suprasellar	Surgery + RT	Bx/STR	Y	Alive with NED	6.24
18	M	1.75	Suprasellar	Surgery only	GTR/NTR	N	Alive with NED	5.60
19	M	7.35	Suprasellar	Surgery + intracystic IFN	Bx/STR	Y	Alive with SD	3.40
20	F	7.64	Suprasellar	Surgery + RT	Bx/STR	Y	Alive with NED	3.34
21	F	2.58	Suprasellar	Surgery only	Bx/STR	Y	Alive with NED	11.14
22	F	16.07	Suprasellar	Surgery only	Bx/STR	N	Alive with SD	6.35
23	F	3.81	Suprasellar	Surgery + intracystic IFN	Bx/STR	Y	Alive with NED	2.03
24	M	5.35	Nasopharyngeal	Surgery only	Bx/STR	N	Alive with SD	2.05
25	M	3.29	Suprasellar	Surgery + intracystic IFN	Bx/STR	N	Alive with SD	1.30
26	M	1.05	Suprasellar	Surgery only	GTR/NTR	N	Alive with NED	1.30
27	M	15.01	Suprasellar	Surgery only	GTR/NTR	N	Alive with NED	1.10
28	F	3.96	Suprasellar	Surgery only	GTR/NTR	N	Alive with NED	4.54

Patient number	GH deficiency	Hypothyroidism	Hypogonadism	Precocious puberty	Diabetes insipidus	ACTH deficiency	Growth (BMI)	Impaired VA
1	N	N	NA	N	Y	N	Underweight	N
2	Y	Y	Y	N	Y	Y	Overweight	Y
3	Y	Y	Y	N	Y	Y	Obese	N
4	N	Y	Y	N	Y	Y	Obese	Y
5	Y	Y	Y	N	Y	Y	Obese	Y
6	Y	Y	Y	N	Y	Y	Obese	N
7	Y	Y	Y	N	Y	Y	Overweight	Y
8	Y	Y	Y	N	Y	Y	Normal	Y
9	Y	Y	Y	N	Y	Y	Overweight	N
10	Y	Y	Y	N	Y	Y	Overweight	N
11	Y	Y	Y	N	Y	Y	Normal	N

Table 1 (continued)

12	N	Y	Y	N	Y	Y	Obese	N
13	Y	Y	Y	N	Y	Y	Overweight	N
14	Y	Y	Y	N	Y	Y	Normal	N
15	Y	Y	Y	N	Y	Y	Obese	N
16	N	Y	Y	N	N	Y	Obese	Y
17	Y	Y	Y	N	Y	Y	Obese	Y
18	Y	Y	NA	N	N	Y	Overweight	N
19	N	N	NA	Y	N	N	Underweight	Y
20	y	y	NA	N	y	y	Obese	N
21	Y	Y	Y	N	Y	Y	Obese	Y
22	N	Y	N	N	N	Y	NA	N
23	N	Y	NA	N	Y	Y	NA	Y
24	n	N	NA	N	N	N	Normal	N
25	N	N	NA	N	N	N	Normal	N
26	Y	Y	NA	N	Y	Y	Obese	Y
27	N	N	N	N	N	Y	Overweight	Y
28	Y	Y	NA	N	Y	Y	Normal	Y

ACTH adrenocorticotropic hormone; *BMI* body mass index; *Bx* biopsy; *DOD* died of disease; *Dx* diagnosis; *F* female; *FU* follow-up; *GH* growth hormone; *GI* gastrointestinal; *GTR* gross total resection; *M* male; *N* no; *NA* data not available; *NED* no evidence of disease; *NTR* near total resection; *PD* progressive disease; *RT* radiation therapy; *SD* stable disease; *STR* subtotal resection; *VA* visual acuity; *Y* yes; *y* year(s)

mixed cystic and solid lesions, with signal changes suggestive of calcifications (Fig. 1). The median largest tumor dimension was 4.3 cm (range: 1.8–9 cm, $n = 22$). None of the patients had evidence of metastases.

Surgical and adjuvant treatment

At diagnosis, the extent of tumor resection included GTR/NTR in 11 (39%) patients, STR in 14 (50%) patients, and Bx in 3 (11%) patients. An intracystic Ommaya/Rickham reservoir was implanted in four (14%) patients. Ten (36%) patients required ventriculoperitoneal shunt insertion. As part of their upfront treatment, adjuvant focal radiotherapy was administered to nine (32%) patients (median dose = 45 Gy, range: 32.4–50.4 Gy) after GTR/NTR in two patients and after STR in seven patients. The three patients who received Bx only were later treated with intracystic interferon.

Disease progression, patient survival, and predictors of outcome

With median follow-up of 6.1 years (range: 0.01–19.6 years), 12 (43%) patients experienced disease progression (median time to progression = 1.4 years), all of which represented local failures (Figs. 2 and 3). Three patients died of disease progression, acute postoperative complication from tumor resection, and gastrointestinal bleeding due to anticoagulant use. Treatment for progression included resection in six patients, surgery with radiotherapy in four patients, radiotherapy in one patient, and intracystic interferon in one patient.

At the latest evaluation, 14 of the survivors had no evidence of disease, and 11 had stable disease. The 5-year PFS and OS rates were 56.8% (± 10.0%) and 92.0% (± 5.4%), respectively. The 10-year PFS and OS rates were 37.3 (± 11.4) and 92.0% (± 5.4%), respectively (Fig. 4A–B). Patients treated in a high-volume center (Hospital A) had significantly better outcomes than did those treated at other centers (PFS, $p = 0.007$; OS, $p = 0.029$; Fig. 3E–F). The period of diagnosis (1999–2008 vs 2009–2018, PFS/OS $p = 0.074/0.240$), sex (PFS/OS $p = 0.817/0.477$), age at diagnosis (< 7 years vs ≥ 7 years, PFS/OS $p = 0.500/0.477$), tumor dimension (< 4 cm vs ≥4 cm, PFS/OS $p = 0.168/0.353$), and extent of resection (GTR/NTR vs STR/Bx, PFS/OS $p = 0.481/0.189$) were not significantly associated with disease progression. In contrast, patients who received surgery and adjuvant radiotherapy had marginally better PFS and OS rates than did those who received surgery alone or surgery followed by intracystic interferon (PFS/OS $p = 0.124/0.112$; Fig. 3C–D).

Long-term visual and endocrine morbidities

Among the survivors ($n = 25$), 15 (60%) had chronic visual impairments, including reduced visual acuity in 12 and visual field

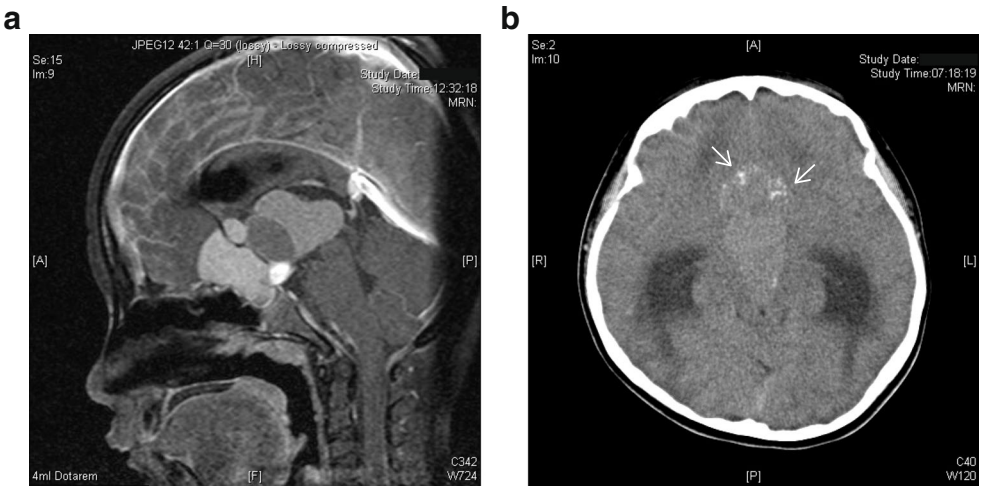


Fig. 1 Typical radiographic features of pediatric craniopharyngioma. (A) Post-contrast magnetic resonance imaging T1 sequences showing suprasellar mixed solid-cystic mass. (B) Plain computed tomography scan showing calcification within the tumor (white arrows)

loss with preserved visual acuity in 3 patients. Endocrinopathies were present in 23 (92%) patients, with adrenal insufficiency as the most common deficit ($n = 22$, 88%), followed by secondary hypothyroidism ($n = 21$, 84%), diabetes insipidus ($n = 19$, 76%), growth hormone deficiency ($n = 16$, 64%), and secondary hypogonadism ($n = 15$, 60%). Sixteen (64%) patients were overweight or obese at their last evaluation, with one patient requiring bariatric surgery (Fig. 2).

Discussion

We summarized the outcomes of children with craniopharyngioma treated in five pediatric oncology units in Hong Kong over the past 20 years. Frequent progression and a near-universal occurrence of tumor- and therapy-related toxicities characterized the disease course of our patients, consistent with other reports [11, 15]. Although our cohort size was small, we did not observe an effect of surgery on outcomes. This concurred with a systematic review of 109 studies of pediatric craniopharyngioma, showing similar PFS rates among patients treated with GTR or limited resection and radiation [10].

Aggressive surgery is associated with an increased risk of treatment-induced endocrinopathies and should be adopted with great caution in developing pediatric patients [16–20]. Using a reduced clinical target volume of < 5 mm gross tumor volume, Merchant et al. reported a 96% 5-year PFS rate for patients who received limited surgery and adjuvant conformal radiation [7]. The stark difference between this outcome and the outcomes of patients who received a similar treatment approach (radiation therapy after biopsy or STR) in our study is most likely multifactorial. Such factors may include the use

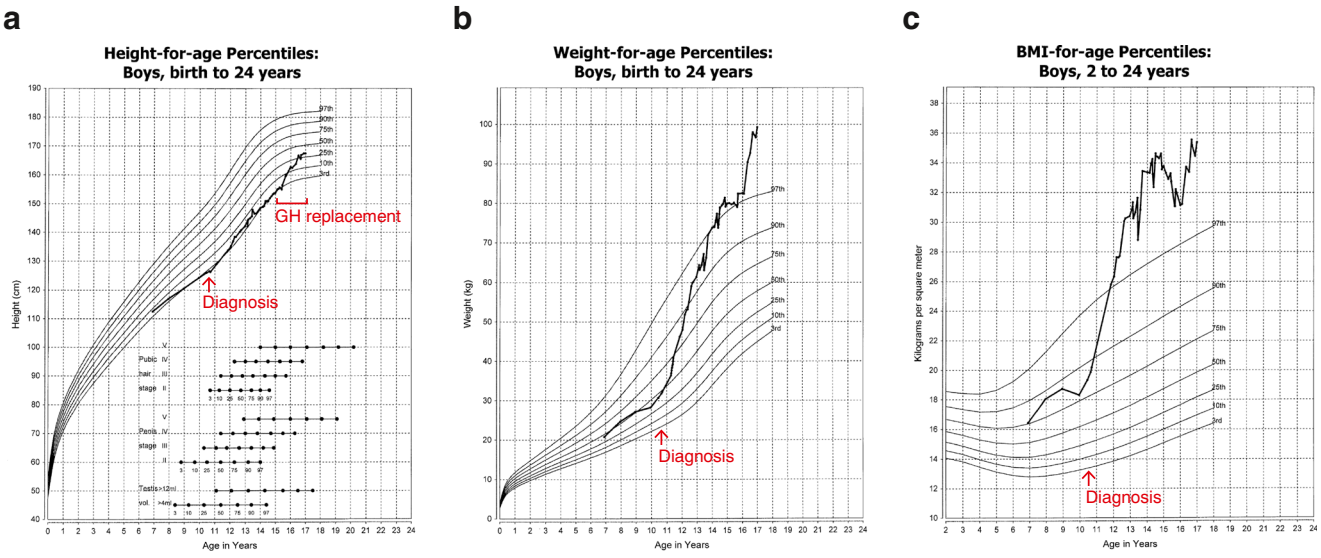


Fig. 2 Growth charts from a representative patient (Patient 17) experiencing panhypopituitarism and hypothalamic obesity, with complications including diabetes mellitus and obstructive sleep apnea. (A) Trend of body height with age showing stunted growth, which improved with growth hormone replacement. Note delayed administration of growth hormone because of diabetes mellitus. (B–C) Trend of body weight and body mass index showing morbid obesity as a result of hypothalamic insult

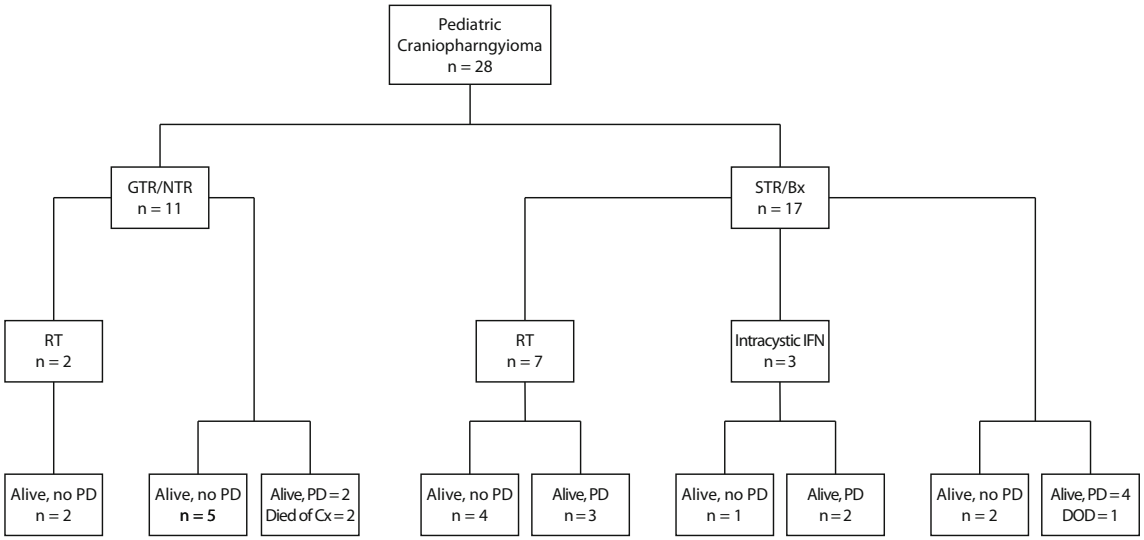


Fig. 3 Treatment approach and outcomes for children with craniopharyngioma in our study cohort. *Bx* biopsy; *Cx* complication; *DOD* died of disease; *GTR* gross-total resection; *IFN* interferon; *NTR* near-total resection; *PD* progressive disease; *RT* radiation; *STR* subtotal resection

of lower radiation doses, lack of routine on-treatment imaging to account for tumor cyst dynamics, and challenges with defining the volume at risk postoperatively [7]. Whether ethnicity contributes to this survival discrepancy remains a question to be addressed in larger studies with Chinese children [7]. Nevertheless, review and standardization of local radiation protocols for children with craniopharyngioma should be prioritized with the dual objectives of enhancing disease control and minimizing toxicity in healthy tissues.

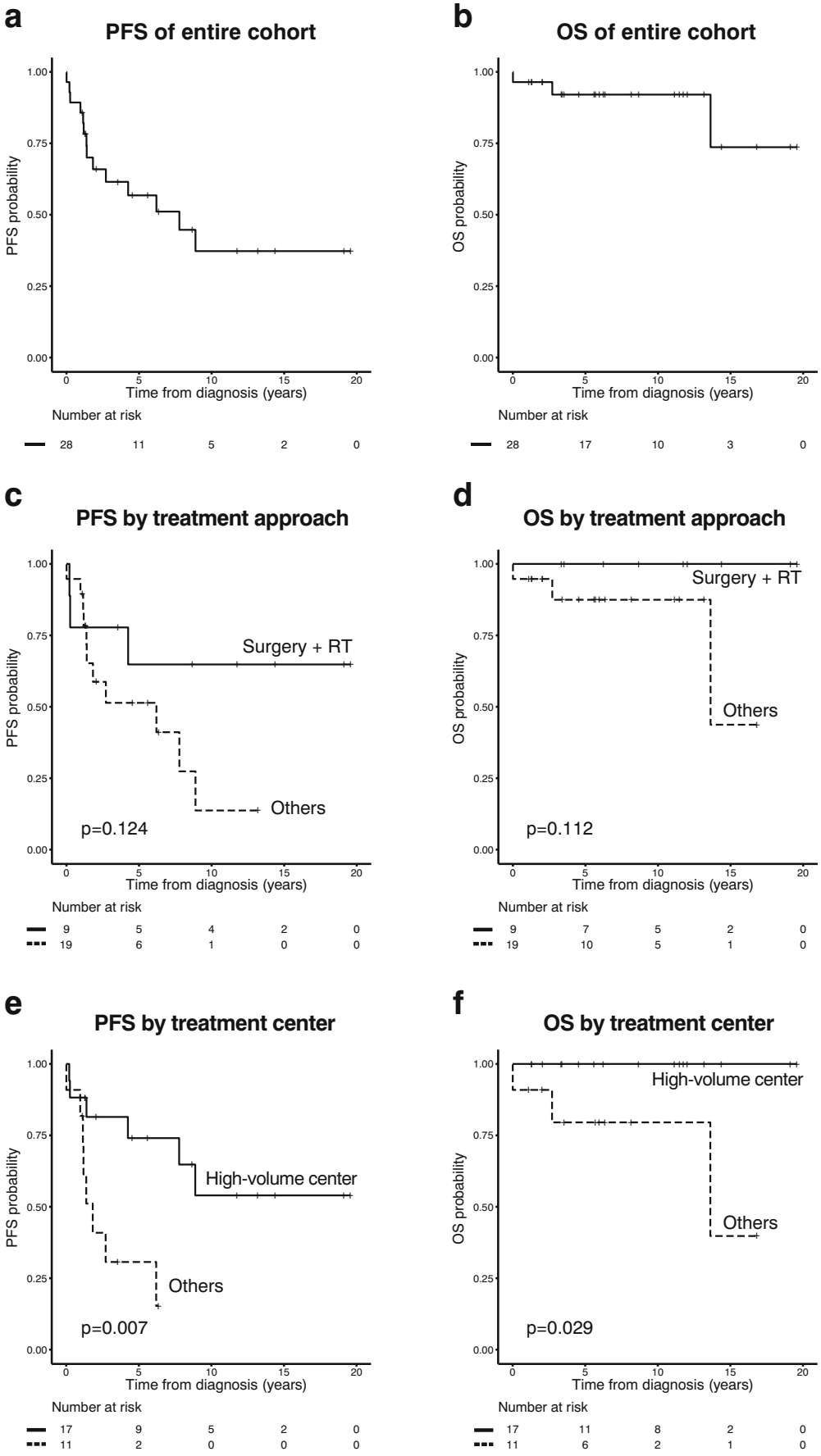
Recently, large cystic craniopharyngiomas have been treated with limited surgery and interval intralesional injections of interferon. The potential advantage of this approach is it can avoid complications from aggressive resection and radiation [6]. However, a protracted treatment course is necessary, and at times, such a regimen can become financially prohibitive because accessibility to interferon is challenging. Our patients treated with this approach had satisfactory disease control during therapy, but the lesions frequently recurred after stopping the injections.

More than 90% of the survivors in our cohort experienced chronic endocrinopathies requiring medical intervention, with two-thirds of patients being overweight or obese. Hypothalamic obesity is a well-described phenomenon in patients with craniopharyngioma [18, 20, 21]. Survivors are at an increased risk of increase cardiovascular events, including myocardial infarction and stroke [22]. Obesity at diagnosis and aggressive resection are predictors of hypothalamic obesity in survivors [18].

The lack of comprehensive endocrine evaluation in a large proportion of our patients hindered meaningful analysis of whether these endocrinopathies were tumor-induced or treatment-related. A British multicenter analysis compared the prevalence of pituitary hormone deficiencies in 85 pediatric patients with craniopharyngioma at diagnosis and last follow-up [17]. Anterior pituitary hormone deficiency was evident in 20% to 40% of patients, and 7% had diabetes insipidus at diagnosis. After completion of treatment, most patients suffered from deficiencies in growth hormone (93%), thyroid-stimulating hormone (86%), and adrenocorticotropic hormone (78%). Two-thirds of the patients had diabetes insipidus or gonadotrophin deficiency. Considerably fewer patients in the same study who were treated during an earlier period had gonadotrophin deficiency, diabetes insipidus, or panhypopituitarism, suggesting that changes in surgical practice affected long-term morbidities.

Our study revealed significant differences in PFS among centers, with better outcomes observed in the center with the highest patient volume. Centralization of service is prognostically important for highly complex and rare conditions such as pediatric brain tumors [23–26]. In the context of craniopharyngioma, Sughrue and colleagues described the association between study sample sizes and the risk of treatment-related complications [16]. Larger sample sizes, as a surrogate for high center volumes, are associated with reduced neurologic and endocrine complications. Locally, centralization of care for children with craniopharyngioma and other neuro-oncological conditions will be achieved in a timely manner by the recently established Hong Kong Children's Hospital, where all newly diagnosed pediatric oncology cases

Fig. 4 Progression-free survival (PFS) and overall survival (OS) of children with craniopharyngioma. Survival rates (A) of the entire cohort, (B) according to treatment approach, and (C) according to treatment center. *Bx* biopsy; *GTR* gross-total resection; *NTR* near-total resection; *RT* radiation; *STR* subtotal resection


a
PFS of entire cohort
PFS probability
1.00
0.75
0.50
0.25
0.00
0
5
10
15
20
Time from diagnosis (years)
Number at risk
28
11
5
2
0
b
OS of entire cohort
OS probability
1.00
0.75
0.50
0.25
0.00
0
5
10
15
20
Time from diagnosis (years)
Number at risk
28
17
10
3
0
c
PFS by treatment approach
PFS probability
Surgery + RT
Others
p=0.124
1.00
0.75
0.50
0.25
0.00
0
5
10
15
20
Time from diagnosis (years)
Number at risk
9
5
4
2
0
19
6
1
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d
OS by treatment approach
OS probability
Surgery + RT
Others
p=0.112
1.00
0.75
0.50
0.25
0.00
0
5
10
15
20
Time from diagnosis (years)
Number at risk
9
7
5
2
0
19
10
5
1
0
e
PFS by treatment center
PFS probability
High-volume center
Others
p=0.007
1.00
0.75
0.50
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Time from diagnosis (years)
Number at risk
17
9
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11
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f
OS by treatment center
OS probability
High-volume center
Others
p=0.029
1.00
0.75
0.50
0.25
0.00
0
5
10
15
20
Time from diagnosis (years)
Number at risk
17
11
8
2
0
11
6
2
1
0

will be managed by a dedicated, interdisciplinary team. Our current study will serve as a local benchmark for comparisons in the future.

Several limitations to our study should be noted. Although we examined a population-based cohort, our sample size remained small, undermining the statistical power of subgroup analyses. The lack of a territory-wide treatment protocol and the resulting variation in management approaches and practices at the technical level confounded interpretation of the outcomes based on treatment factors. Furthermore, the occurrence of morbidities such as endocrinopathies was not registered prospectively, precluding precise narration of their incidence and causal relations with specific treatments.

Conclusion

Children with craniopharyngioma in Hong Kong experience frequent disease progression and multiple long-term morbidities. Patient outcomes may be improved through service centralization and standardization.

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Compliance with ethical standards This study was approved by the University of Hong Kong/Hong Kong West Cluster Institutional Review Board, with the requirement for informed consent waived.

Conflict of interest The authors declare no conflicts of interest.

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