RESEARCH ARTICLE

Craniopharyngioma: A lower-middle-income-country epidemiology perspective

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Abstract

Objective: To quantify the frequency of craniopharyngiomas presenting to tertiary care neurosurgical centres, the demographics and mortality rate, and commonly presenting to neurosurgical practice.

Methods: Our study was a retrospective cross-sectional analysis of patients admitted at 32 neurosurgical centres between January 1, 2019, and December 31, 2019, with brain tumour. Kruskal Wallis analysis was used to determine normality; normally distributed variables were reported as means with standard deviation, while median with interquartile range was used for non-normally distributed variables.

Results: Of 2750 patients with brain tumours, 114 patients presented with craniopharyngioma. The median age at diagnosis was 18 years, with 42 (42.8%) patients below the age of 15, 40 (40.9%) patients aged 15-39, and 16 (16.3%) patients aged 40 and above. There were 70 (61.4%) males and 44 (38.6%) females in our cohort. Gross total resection was performed in 42(36.8%), 45 (39.5%) underwent subtotal resection, 9 (7.9%) underwent CSF diversion only, and 2 (1.8%) had a biopsy. Most of our patients 94(82.5%) presented to public hospitals, with 20 (17.5%) patients presenting to private hospitals (p=0.002). The overall survival at two years was 86.8% in patients with known outcomes, and only 10% of patients died within 30 days of surgery.

Conclusion: Craniopharyngiomas comprised a small portion of all brain tumours in our region. They are more common in males and in patients from the lower socioeconomic class. These patients mainly presented to public sector hospitals, and the three highest volume centres were all public sector institutions. The overall survival rate at two years in our region is lower than in other regions.

Keywords: Craniopharyngioma, Brain neoplasm, Retrospective study, Epidemiology, LMIC

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Introduction

Craniopharyngiomas are rare tumours of the central nervous system. Being virtually benign, they can cause symptoms ranging from headaches, visual disturbances, and nausea to endocrine disturbances. These tumours can be quite extensive. While they typically arise in the suprasellar region, they can involve the hypothalamus, optic chiasm, third ventricle, cranial nerves, and major blood vessels. These tumours are best treated in a multidisciplinary fashion with neurosurgeons, neurologists, medical and radiation oncologists, endocrinologists, ophthalmologists, and paediatricians working together and utilizing a multimodal treatment approach.

The incidence of craniopharyngiomas is 0.5 to 2 cases per million persons per year.[1] While generally considered a paediatric disease (1.2-4% of all intracranial tumours), almost half of craniopharyngiomas are found in adults. The age distribution is bimodal, with elevated incidence from 5-14 years and 50-74 years of age. Familial cases are sporadic, with only two reported families in literature. Gender, geographical location, and ethnicity have shown no significant difference in incidence.

There are two histopathological subtypes of craniopharyngioma, adamantinomatous craniopharyngioma (ACP) and papillary craniopharyngioma (PCP). These are now classified as distinct tumour types by the 2021 WHO classification.[1] ACPs usually present with bimodal incidence (peaking at 5-15 years and 45-60 years), whereas PCPs typically occur in the 50-60-year range. ACPs are characterized by somatic mutations in CTNNB1 (encoding β-catenin) and can be cystic in appearance in contrast to PCPs, which are usually solid and can have somatic BRAF mutations.[1-3] Classification schemes have been suggested for craniopharyngiomas based on tumour topography, degree of attachment or invasion of hypothalamic structures, infundibular involvement, and role of the diaphragm sellae. The WHO classification focuses on both molecular and

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morphological characteristics.[4-9]

The standard of care for craniopharyngioma is somewhat conflicted, with the goal being the lowest long-term co-morbidity. Treatment can be surgery only, surgery combined with radiation therapy or radiation therapy alone. If the tumour can be fully resected without significant vascular, visual, and hypothalamic damage, then surgery is preferred. More often, surgery is performed to reduce symptoms and may include subtotal resection, cyst fenestration, cerebrospinal fluid (CSF) diversion, or Ommaya reservoir placement. Radiation therapy is usually administered as an adjuvant after subtotal resection and can be either fractionated radiation, stereotactic radiosurgery, or proton beam therapy. Hypothalamic activity and obesity are common complications post stereotactic treatment, and pharmacologic and bariatric surgical interventions have shown no proven benefit in randomized trials so far.[2,10,11]

Methods

Our study was a national retrospective cross-sectional analysis of patients who were admitted at multiple neurosurgical centres between January 1, 2019, and December 31, 2019. These patients had a histopathological diagnosis of primary or secondary brain tumours. Thirty-five high-volume centres (more than 5 cases per year) with dedicated neurosurgical facilities participated in the study. Students, residents, and faculty collated data from electronic medical records specific to each centre, as well as paper charts. The overall sample size was not known due to incomplete literature from all the different centres; a sample size from a single tertiary care hospital was used to estimate a sample size of 300 cases.

The papers on methodology[12] and general findings[13] in this special supplement provide greater detail about the study process, parameters used, organization details, and the Pakistan Brain Tumour Consortium (PBTC) which made this effort possible. Socioeconomic Status (SES) used in this paper has been derived from employment status and the job type that the patients presented within their demographical history. The jobs were used to estimate socioeconomic brackets according to the classification by the Pakistan Bureau of Statistics supplement.[14]

Data were collected and divided into four types of variables. Demographics included age, gender, residence, socioeconomic class, and marital status. Surgical features were time to surgery, institutional characteristics, type of surgery done, and Karnofsky Performance Score (KPS).[1] Neoplastic features included type of tumour, grade, and tumour location. Treatment and outcome characteristics included the post-operative KPS, current status (deceased vs alive), and chemotherapy and radiotherapy completion status.

Statistical analysis was performed using Statistical Product and Service Solutions version 25 and STATA version 16. The complete sample of craniopharyngioma was analyzed, and normality was assessed using the Shapiro-Wilk test. Mean with standard deviation was calculated for continuous variables with normal distribution, while median with interquartile range was calculated for variables with non-normal distribution.

Results

In the study period, 2750 patients were diagnosed with brain tumours at the participating centres. Of these, 114 (4.14%) patients were found to have a craniopharyngioma. The median age at diagnosis was 18 (IQR= 10.0-32.3), with 42 patients below the age of 15, 40 patients aged 15-39, and 16 patients aged 40 (Figure-1). In the paediatric population (less than 18 years of age) with a total of 391 cases, 51(13%) tumours were craniopharyngioma, the third most common brain tumour, after medulloblastoma and glioma.

Amongst the 114 patients, 70 (61.4%) were males and 44 (38.6%) females. The socioeconomic status distribution of

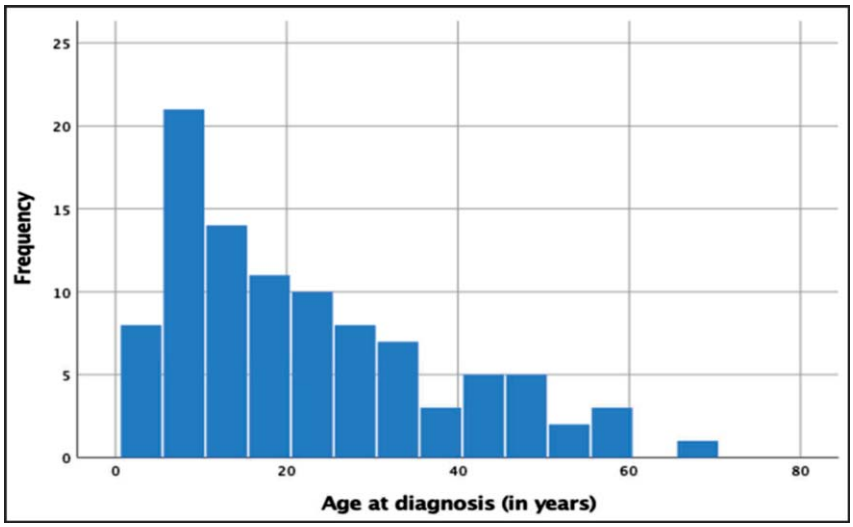

Figure-1: Distribution of age at diagnosis.

Table-1: Demographic characteristics of patients with craniopharyngioma.

Demographic characteristics		n	Percentage
Age at diagnosis (median)	18		
Gender	Male	70	61.4%
	Female	44	38.6%
Socioeconomic Status of Patient	Lower Class (e.g. blue-collar workers, labourers, daily wagers)	62	59.0%
	Middle Class (e.g. graduates, mid-level office workers, homeowners)	41	39.0%
	Upper Middle or Upper Class	2	1.9%
Marital Status of Patient	Unmarried	63	64.3%
	Married	33	33.7%
	Other	2	2.0%
Public or Private Hospital	Public	94	82.5%
	Private	20	17.5%
Hospital Annual Patient Load	Up to 100	60	52.6%
	More than 100	54	47.4%
Total Patients per Hospital (mean ± SD)		109 ± 63	
Current Status	Alive	66	86.8%*
	Deceased	10	13.2%*
	Lost to follow up	38	33.3%**
Overall survival at two years rate	≤30 days	98.7%	
	>30 days	88.2%	

*From patients with known outcomes
**From all patients.

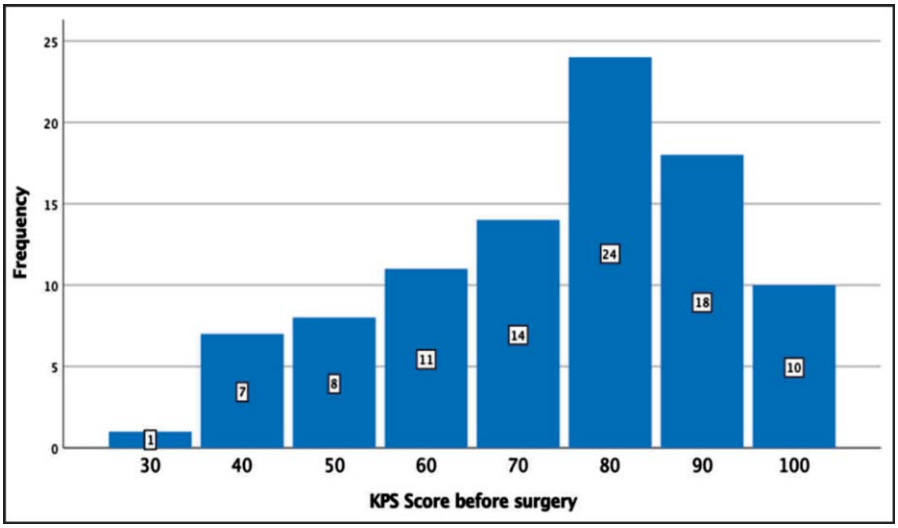

Figure-2: KPS score before surgery.

our patients showed that 62 were from a lower socioeconomic status, 41 were from a middle socioeconomic status, and two were from an upper socioeconomic status. 63 of our patients were unmarried, with 33 married patients and 18 of unknown marital status, which may be due to the division of age as younger patients are less likely to be married but may also contribute to the support available for older single patients.

Of the 32 centres, 27 centres had at least one craniopharyngioma surgery per year. Eleven institutions had three or fewer cases per annum, 13 had between 4-6 cases, 2 had 7-10 cases, and only one had more than 10 cases per year. Ninety-four cases (82.5%) were at public institutions, while only 24 (17.5%) were at private hospitals. In general, these patients presented at higher volume centres which had a median of 95 (Range= 212 days) brain tumour patients presenting per year.

Out of the 114 patients, 54 (47.4%) patients presented to hospitals with an annual volume of more than 100 cases per year and 60 (52.6%) patients presented to centres with 100 or lower cases per year (p=0.071). Most of our patients 94(82.5%) presented to public hospitals, with 20(17.5%) presenting to private hospitals (p=0.002). The median time to surgery was 41 (IQR= 154-3) days. The overall survival rate at two years was 86.8% in patients with known outcomes, and only 1 out of 10 patients died within 30 days of surgery. The demographics are summarized in Table-1.

All 114 patients underwent surgical intervention, with 17 undergoing further radiotherapy and 2 undergoing chemotherapy. Gross total resection was performed on 42(36.8%) patients, 45(39.5%) underwent subtotal

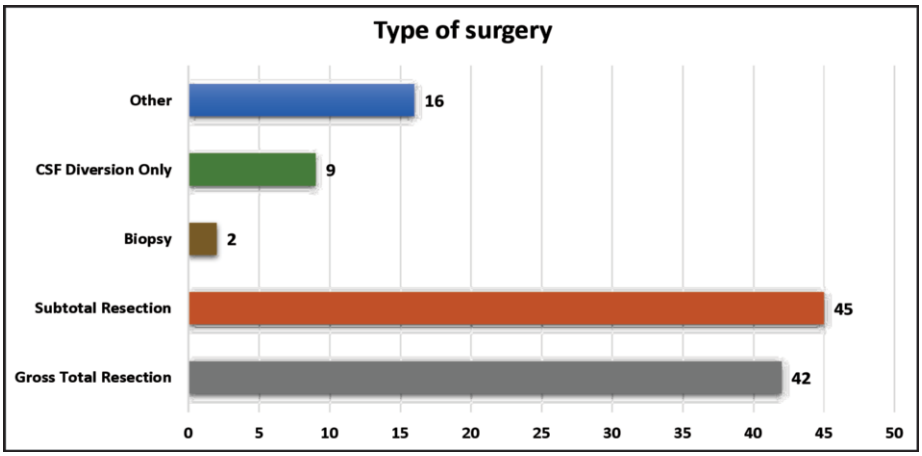

Figure-3: Type of surgery for patients with craniopharyngioma.

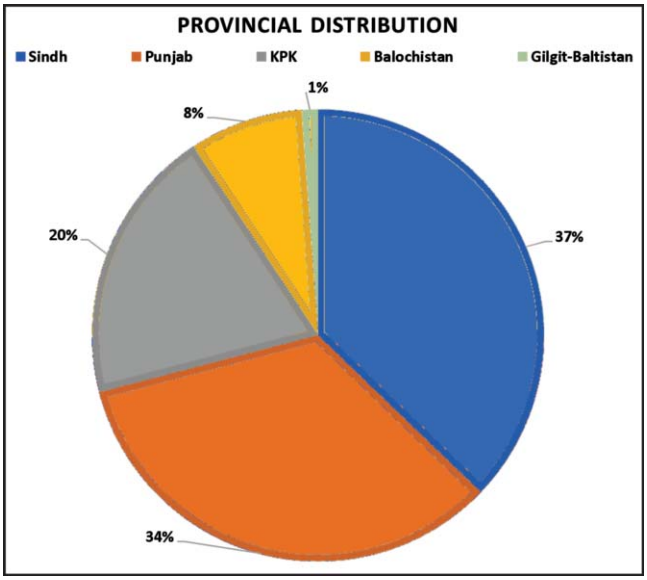

Figure-4: Provincial distribution of patients with craniopharyngioma.

resection, 9(7.9%) were subjected to CSF diversion only, 2(1.8%) had a biopsy (with subsequent surgery planned for later based on histopathological analysis), and 16(14%) underwent an unspecified surgery (reported as either craniotomy or other). The types of surgery are illustrated in Figure-2.

Sellar tumours numbered 92(74.2%) in our sample, with 32(25.8%) being extrasellar. Extension in the left or right para-sellar region (in hospital records) was observed in MRI, and a significant majority 59(51.8%) were midline, with 14(12.3%) being bilateral, 16 (14%) being right-sided, and 12 (10.5%) being left sided. Only 13 (11.4%) tumours had no reported extension into the para-sellar region in the hospital records. Tumour characteristics are summarized in Table-2.

In terms of functionality, ten patients presented with a KPS of 100, 18 patients with a KPS of 90, 24 patients with a KPS of 80, and 41 patients with KPS below 80. This information is summarized in Figure 2. The average (median) KPS score at presentation was 80, and post-surgery was 90, showing an increase of 10.

Sindh had the highest number of new cases of craniopharyngioma diagnosed across Pakistan in 2019, followed closely by Punjab. Sindh accounted for 32 (37%) patients, 29 (34%) were from Punjab, 17 (20%) from KPK, 7 (8%) from Balochistan, and 1 (1%) from Gilgit-Baltistan. The provincial distribution of cases is illustrated in Figure-3.

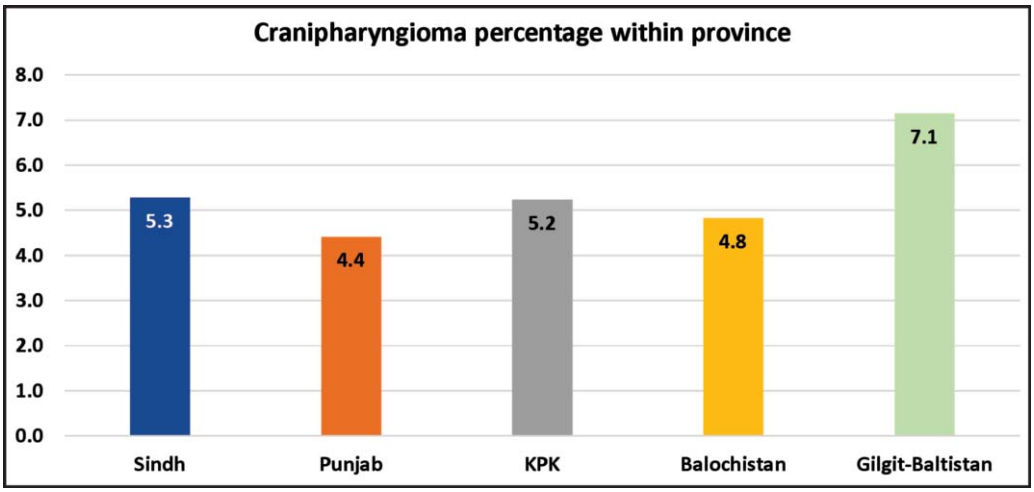

Figure-5: The percentage of craniopharyngioma from all brain tumours within each province.

Sindh had a total of 784 brain tumour cases in 2019, with 32(5.3%) being craniopharyngiomas. Punjab had the highest number of brain tumours amongst all the provinces at 927 cases but the lowest proportion of craniopharyngiomas with 29(4.4%) cases. KPK had 366 total brain tumours and 17 (5.2%) craniopharyngiomas. Balochistan had a total of 162 brain tumours, out of which 7 (4.8%) were

Table-2: Tumour characteristics.

		N	Percentage	p-value
Location	Sellar	92	74.2%	<0.01
	Extra-sellar	32	25.8%	
Extension in left or right para-sellar region	Left	12	10.5%	<0.01
	Right	16	14.0%	
	Bilateral	14	12.3%	
	Midline	59	51.8%	
	Unspecified	13	11.4%	

Table-3: Clinical characteristics of patients.

Clinical characteristics	Median
Time to surgery in days	41 (3, 153)
KPS score before surgery	80 (60, 90)
KPS score after surgery	90 (70, 100)

craniopharyngioma. Gilgit- Baltistan had only 14 reported brain tumours with one (7.1%) craniopharyngioma. Azad Jammu Kashmir had 12 brain tumours, but none of those reported were craniopharyngioma.

Discussion

Our study has provided new data about the incidence of craniopharyngioma in the Pakistani population. We noted a higher proportion of craniopharyngiomas (4.14%) in our population compared to the rate of 0.7% reported in studies from the United States.[15,16] Our region has previously had single-centre studies showing 41.5 cases per year on average at one tertiary care centre but no multi-centre studies were found for comparision.[17]

Within the paediatric population, craniopharyngioma was the third most common tumour after medulloblastoma and glioma, similar to The Central Brain Tumour Registry of the United States (CBTRUS).[15] The median age at diagnosis in our cohort was 18, which is higher than the worldwide age, which is bimodally distributed but more heavily skewed towards the paediatric population. Our study also demonstrated a bimodal distribution with a peak at 5-15 years and a smaller peak at 40-50 years (Figure-1). CBTRUS reported a median age of 44 (with 53.1% of patients above the age of 40) in the United States, and other studies show bimodal distributions as well, generally at 5-14 years and 50-75 years.[10,18,19] Most of our patients (64.3%) were unmarried at the time of diagnosis, which may be representative of the lower average age at diagnosis; however, in older populations, the marital status may also be an indicator of support at home which has been shown to influence outcomes in tumour care.[20] In our population, the median age for unmarried patients was 11 (range = 39), which shows that their marital status was due to age, while the median age for married patients was 35 (range = 39).

We noted a male-to-female ratio of 1.6:1, which is higher than the ratio reported in international data. In the US, the annual incidence in males was 322 and in females was 306, which demonstrates a ratio of 1.05:1, a figure significantly lower than our ratio.[15,21] There is no gender disparity reported in other literature either.[1,2,10,18,22] This may indicate that in our region, either female patients are unable to access care, are not diagnosed adequately, or there is a true disparity in tumour occurrence between the two genders.

Socioeconomic status is not commonly reported in the literature. In our study, most patients were from a lower socioeconomic status. This is reflective of the overall number of brain tumours within Pakistan, with the lowest socioeconomic class, which makes up most of the population in the region, having the highest incidence of brain tumours and the worst outcomes. Health expenditures in our region are largely out-of-pocket. Brain tumour care can be prohibitively expensive, even for patients belonging to the middle or higher socioeconomic status. This was reflected in the fact that the majority of our craniopharyngioma patients presented to public healthcare institutions which are government-funded and lower out-of-pocket expenses. Unfortunately, this often translates into lower quality of care, lack of a multidisciplinary approach, and subsequently poor long-term outcomes.

A large proportion (11 institutions) of our centres had three or fewer cases per year, while institutions with 4-6 craniopharyngioma cases per year were the majority (13 institutions). There were only three centres with more than 6 cases per annum, and all 3 of these centres had more than 70 cases of brain tumour surgeries per annum on average (with 2 exceeding 100 cases per annum). In addition, all 3 of these centres were public sector hospitals and teaching institutes. Overall, 94 of our 114 cases presented at public sector hospitals, with only 24 presenting at private hospitals, showing that the volume for craniopharyngioma is largely skewed towards the public-funded institutes.

Forty-two (36.8%) of our patients underwent subtotal resection (STR), followed closely by 45 (39.5%) patients with gross total resection(GTR). Literature reports that the extent of resection alone does not influence long-term survival outcomes and that STR with radiotherapy can have equal outcomes to GTR, with lesser morbidity.[23] Although all 114 patients received surgical intervention, only 17 underwent radiotherapy, which is an adjuvant

treatment in case of residual tumour or high risk of recurrence (supra- and subdiaphragmatic tumour locations and subtotal removal).[24] While chemotherapy is not part of standard care with craniopharyngioma, two patients also received chemotherapy with an unspecified agent, and this may identify the need for further investigation and education in centres where this happened. The overall survival at two years rate for patients within our cohort was 86.9% of all cases with known outcomes (with at least one follow-up). There was only one patient within our cohort who died within 30 days of surgery, although the cause of death was not confirmed. According to CBTRUS, five-year survival amongst predominantly non-malignant tumours was lowest in craniopharyngioma, which had five-year relative survival of 85.8%.[20] While we could not calculate 5-year survival due to our limited study time, we do plan to add follow-up over longer periods to future studies to address the metric.

Conclusion

Craniopharyngiomas are generally benign tumours that can behave in a malignant fashion due to their proximity to important neurovascular structures. A multidisciplinary approach at high-volume centres is necessary to achieve the best possible outcomes. We noted a higher incidence of craniopharyngiomas in our population compared to international literature, but this may be a limitation of the patient cohort included in our paper. Further systematic studies will be conducted to better understand the regional incidence of craniopharyngiomas, treatment methodology utilized, socioeconomic impact, and long-term outcomes.

Limitations of the Study

The study was retrospective, cross-sectional in nature and was limited by the data available in hospital records. The hospitals included in the study were not a comprehensive list of all neurosurgical centres in Pakistan, as some centres did not consent to sharing data. However, these centres were generally lower-volume centres (less than 5 cases per year). The centres selected for this study were all surgical institutions, and patients who present outside neurosurgical clinics or practices in other centres (such as private clinics) may not be captured in our study, particularly those with metastatic brain tumours.

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Conflict of Interest: None to declare.

Funding Disclosure: None to declare.

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