RESEARCH ARTICLE

Ependymoma: an epidemiological perspective from a low- and middle-income country

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Abstract

Objective: To enumerate the burden of ependymoma in our region and identify the demographic, tumoural, surgical, clinical characteristics, and outcomes of patients diagnosed with ependymoma.

Methods: This retrospective cross-sectional study included patients admitted under neurosurgical service between January 1 and December 31, 2019. The inclusion criterion for the study was a histopathological diagnosis of the brain lesion. The experience of the ependymal brain tumours observed at the 32 participating sites in Pakistan is presented.

Results: A total of 2750 patients with brain tumours were seen in 2019 at our centres of whom 58(2.1%) had a histopathological diagnosis of ependymoma. The median age at diagnosis was nine (IQR= 4.5-24.5) years. The median time to surgery from date of radiological diagnosis was 38.5 (IQR= 4-93.8) days. The median KPS score at presentation was 70 (IQR= 60-80), and post-surgery was 90 (IQR= 70-100), showing an average increase of 20. Our population's overall mortality rate for ependymoma was 31.1%, with the 30-day mortality rate being 2.2% (lower than the 4.5% on average for all brain tumours in our cohort).

Conclusion: Ependymomas were predominantly found in the paediatric population in the presented cohort. While gender distribution and histopathological grading seemed to follow international trends, this study had a much higher mortality rate and a much lower gross total resection rate than centres in high-income countries.

Keywords: Ependymoma, Brain neoplasm, Retrospective study, Epidemiology, LMIC.

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Introduction

Ependymomas are relatively rare CNS tumours with an annual incidence of 0.43 patients per 100,000 people, according to the Central Brain Tumour Registry of the United States (CBTRUS).[1] Originating from glial cells, ependymal tumours account for 0.8% and 1.8% of all primary CNS tumours internationally and in the US, respectively. It has been shown to have a predisposition towards the male gender (1.3:1) and the paediatric population. They are the third most common brain tumours in children globally.[2,3]

The grading of ependymoma by the WHO incorporates site and molecular characteristics as well as histopathological features.[4] Ependymomas can now be defined by anatomic location and molecular alteration (with a NOS suffix). This is a welcome change as resource constraints often mean that molecular analysis is unavailable for brain tumours in our region. The recent 2021 WHO classification of CNS tumours has reclassified Myxopapillary ependymoma as WHO grade 2 rather than grade 1 as previously.[5]

Literature generally shows significant variance in the utility of ependymal tumour grade as a prognostic marker due to confounding by the anatomical compartment; however, the use of WHO grade in stratification of adult patients with supratentorial ependymomas in specific is well established.[6,7] There is no longer an "anaplastic ependymoma" term in the 2021 WHO CNS tumour classification, as the three distinct gradings are WHO grade 1, 2, and 3.[5] Tumour prognosis is associated with age, tumour grade, tumour location, and molecular genetics.[8]

The mainstay for ependymal tumour therapy is surgical resection and follow-up radiotherapy if needed. The role of chemotherapy is largely unproven, even as new molecular targets are identified in recent literature.[7,9-11] However, despite optimal management, a large number

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of ependymoma do recur, particularly in the paediatric population.

Methods

The study followed a retrospective cross-sectional model and included patients who were admitted at a neurosurgical centre between January 1, 2019, and December 31, 2019. The only inclusion criterion of the study was the presence of histopathological diagnosis of the brain tumour. The centres selected for inclusion were the highest volume centres in the country and had existing dedicated neurosurgical facilities. A total of 32 centres participated in the study and reported data from hospital records, and filled out the standardised questionnaire.

Time to surgery was defined as the time in days between the radiological diagnosis and the date of surgery. Hospitals with an annual volume of more than 100 brain tumour cases per year were designated as high-volume centres, and those with 100 or lower cases per year were designated as low-volume centres. Since the data was collected in 2019 before the revised WHO 2021 guidelines for the classification of brain tumours, the 2016 WHO classification of brain tumours was used.

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 demographic history. The jobs were used to estimate socioeconomic brackets according to the classification by the Pakistan Bureau of Statistics supplement.[14] The lower socioeconomic class included blue-collar workers, labourers, and daily wagers. The Middle socioeconomic class included graduates, mid-level office workers and homeowners. The upper and upper-middle socioeconomic class included landowners and business owners.

The data were tested for normal distribution using the Shapiro-Wilk test. Continuous variables are presented as mean and standard deviation with frequencies and percentages, whereas continuous variables are presented as medians due to the low sample size and non-normal distribution of data. Statistical evaluation was performed using STATA version 16.

Results

A total of 58 patients presented with ependymoma in the centres enrolled in our study in 2019. Thus 2.1% of all patients with brain tumours in 2019 at our centres had a histopathological diagnosis of ependymoma. The median age at diagnosis was nine years, with 32 (61.5%) patients below the age of 15 years, 15 (28.9%) patients aged 15-39 years, and 5 (9.6%) patients aged 40 years and above; the age distribution is illustrated in Figure-1. There were 35 males (58.3%) and 25 females (41.7%) in our cohort. The socioeconomic status distribution of our patients showed that 28 (56%) were from a lower socioeconomic status, 20 (40%) were from a middle socioeconomic status, and 2 (4%)

Table-1: Demographic Characteristics of patients diagnosed with ependymoma.

Demographic characteristics		n	Percentage (within group)
Age at diagnosis (median)		9	
Gender	Male	35	58.3%
	Female	25	41.7%
Time to surgery in days (median)		38.5	
KPS score before surgery (median)		70	
KPS score After surgery (median)		90	
Socioeconomic Status of Patient	Lower Class	28	56%
	Middle Class	20	40%
	Upper Middle or Upper Class	2	4%
Marital Status of Patient	Unmarried	40	69%
	Married	12	20.7%
	Other	6	10.3%
Public or Private Hospital	Public	40	69%
	Private	18	31%
Hospital annual Patient Load	Up to 100	35	60.3%
	More than 100	23	39.7%
Total Patients per Hospital (median)		110.5	
Current Status	Alive*	31	68.9%*
	Deceased*	14	31.1%*
	Lost to follow up**	13	22.4%**

*From patients with known Outcomes
**From all patients.

Table-2: Tumour characteristics.

		n	Percentage
Type of ependymoma[22]	Myxopapillary	1	1.7%
	Subependymoma	1	1.7%
	Other WHO Grade 1	1	1.7%
	WHO Grade 2	7	12.1%
	WHO Grade 3	13	22.4%
	WHO Grade 4	2	3.4%
	Not specified	33	56.9%
Laterality of Tumour	Right	7	12.1%
	Left	11	19.0%
	Bilateral	7	12.1%
	Midline	31	53.4%
	Not specified	2	3.4%
Tumour location	Supratentorial	29	50%
	Infratentorial	29	50%

Table-3: Adjuvant treatment.

		N	Percentage
Radiotherapy	Received	11	19.0%
	Not received	21	36.2%
	Lost to follow up	26	44.8%
Chemotherapy	Received	2	3.4%
	Not received	22	37.9%
	Lost to follow up	34	58.6%

Table-4: Mortality according to characteristics.

		Mortality rate
Mortality Rate	≤30 days	2.2%
	>30 days	28.9%
Hospital Facility	Public	41.4%
	Private	12.5%
Hospital volume	>100 cases per year	44.4%
	<100 cases per year	22.2%
Tumour location	Infratentorial	23.8%
	Supratentorial	33.3%

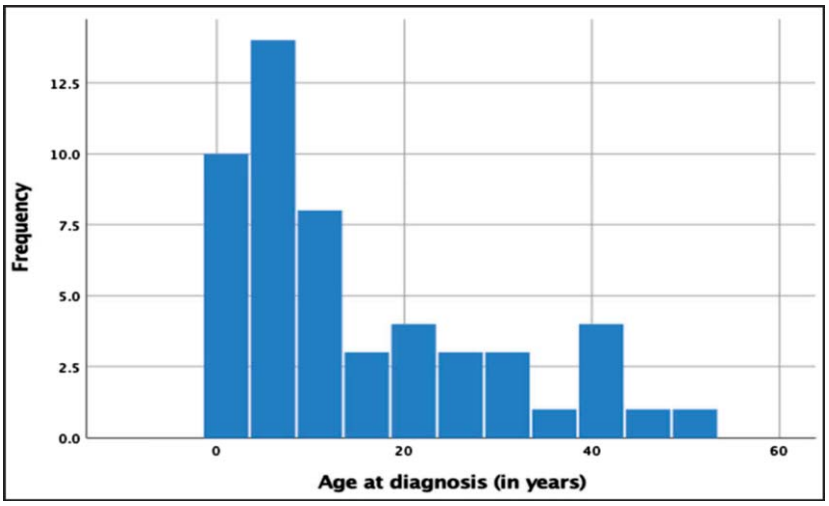

Figure-1: Age distribution amongst patients with ependymoma.

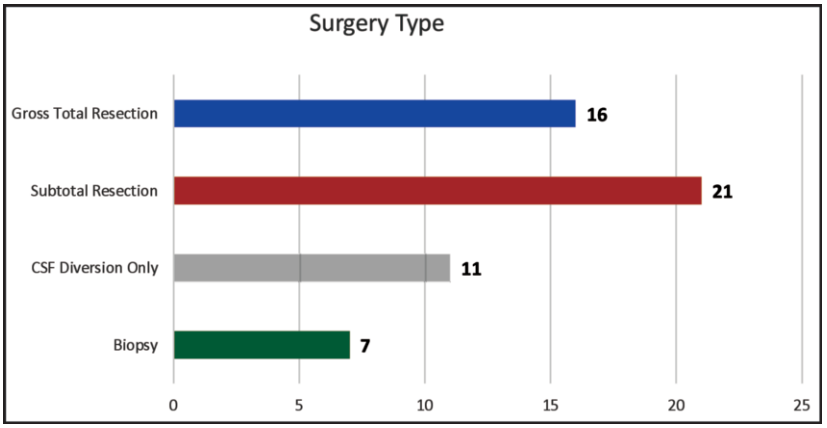

Figure-2: Surgery type done for patients with ependymoma.

were from an upper socioeconomic status 40 of our patients were unmarried, with 12 married patients and 6 of unknown marital status. The average (median) KPS score at presentation was 70 (IQR=20), and postoperative was 90 (IQR=30), which was statistically significant (t-test, p<0.001).

The median time to surgery was 38.5 (IQR= 4-93.8) days These patients usually presented at higher volume centres which had a median of 111 brain tumour cases presenting per year. Out of 58 patients, 35 (60.3%) patients presented to high-volume hospitals and 23 (39.7%) patients presented to low-volume centres. Most of our patients (n=40, 69%) presented to public hospitals, with 18 (31%) patients presenting to private hospitals (p=0.885). The overall mortality and the demographics of our patients are summarized in Table-1.

Ependymomas were divided into four types as per WHO classification 2016. Sub ependymomas (Grade 1) and Myxopapillary ependymomas both numbered one each with an additional grade 1 unspecified tumour. There were seven Grade 2 ependymomas and 13 grade 3 (anaplastic) ependymomas. Thirty-five tumours did not have histopathological grading available. Eleven of these tumours presented on the left side, seven were bilateral, and 31 were midline tumours, with only two tumours missing laterality information. Twenty-nine (50%) of the tumours were infratentorial, with the remaining 29 (50%) supratentorial. These findings are summarized in Table-2.

Gross total resection was performed in 16(29.1%) patients with 21(38.2%), undergoing subtotal resection, 11(20%) had CSF diversion only, and 7 (12.7%) were subjected to biopsy with surgical intervention planned in the future. Figure-2 demonstrates these findings.

Around 11 (19%) of our patients received postoperative radiotherapy, with 17 (36.2%) not receiving radiotherapy and 22(44.8%) lost to follow-up. Two (3.4%) of our patients received chemotherapy (1 in the public sector and 1 in the private sector), with 18 (37.9%) not receiving chemotherapy and 28 (58.6%) lost to follow-up. These findings are summarized in Table-3.

The overall mortality rate for ependymoma in our population was 31.1%, with the 30-

day mortality rate being 2.2% (lower than the 4.5% on average for all brain tumours in our cohort). Public hospitals had a higher mortality rate than private hospitals (41.1% and 12.5%, respectively), and hospitals with more volume (more than 100 cases per year) had double the mortality rate of hospitals with less volume. Supratentorial tumours had a higher mortality rate than infratentorial tumours (33.3% and 23.8%, respectively). Table-4 shows the mortality rate according to time from discharge, type of institution, average neurosurgical volume, and tumour location.

Discussion

A higher proportion of ependymoma was observed in our population with CNS tumours compared to that in the US or globally.[2,3,15] Most of our patients belonged to the paediatric age group, whereas ependymoma was the fifth most common tumour (11.1%) in the paediatric population of our total cohort. Our median population age was higher than the worldwide average as well, with our median being nine years vs five years in the CBTRUS.[1]

In a study of 43 paediatric patients in Pakistan, Qurni et al. observed/reported ependymomas to be the most common paediatric brain tumour (28%).[16] He observed most (64%) of the ependymoma were graded 3, similar to our patients. Most of the tumours in our population were midline, and the majority were present in the cerebellar region. The most common location for ependymoma reported in the literature is infratentorial in about 60% of cases.[17]

In our cohort of patients diagnosed with ependymoma, 60% were from the paediatric age group (0-18 years). Paediatric ependymoma is generally considered a separate biological entity due to advances in epigenomic profiling and transcriptomic analysis. Therapy may be tailored even for histologically similar tumours due to biological subtypes based on age, anatomical position, and clinical outcomes.[18] There is, however, still a need to differentiate aggressive variants of ependymoma, including the supratentorial RELA fusion subtype and the posterior fossa groups.[9]

The male-to-female ratio in our population was 1.4:1, which is similar to the ratio reported by the CBTRUS (1.3:1).[1,3] These results reflect the predisposition of ependymoma in the male population, which has been widely reported in several studies.[2,15] However, some textbooks may still refute any gender predilection in ependymoma cases.[19] This warrants more systematic analyses of the present literature to conclude if the male gender is a significant risk factor for the development of ependymoma.

LMICs usually lack centralised healthcare systems. Due to poor facilities and lack of satisfaction, patients often prefer private hospitals over publicly funded healthcare facilities to receive quality healthcare. This incurs considerable out-of-pocket costs for these patients, as insurance systems are not very popular in the region.[20] Our patients mostly presented to high-volume centres and public hospitals that may be unable to provide quality or timely management of the disease, possibly contributing to the higher mortality observed. Public healthcare centres constitute some of the highest volumes, and therefore there is higher mortality in public centres as well due to the higher overall volume.

Most of our patients were also from either the lower socioeconomic stratum (56%) or the middle economic stratum (40%). The mortality rate amongst patients with known outcomes in our population was 31.1% which is much higher than the 1-year mortality rate reported by studies in other parts of the world.[21,22] Most of these deaths were beyond 30 days of surgery, as only one patient died within 30 days of surgery. Five-year mortality for ependymomas reported in the literature remains high at about 65%.[2]

Age less than 40 years and the extent of surgery are related to a better prognosis, while tumour location and grade may also be indicative of better outcomes.[17] Surgery is the definitive treatment for these tumours, and postoperative radiotherapy is indicated for high-grade ependymoma, regardless of the degree of resection, while low-grade ependymomas also benefit from radiotherapy if there is subtotal resection (which should be confirmed by postoperative MRI). At this point, postoperative chemotherapy does not appear to be efficacious in improving outcomes.[9,10] In our cohort, eleven patients underwent adjuvant radiotherapy, which is recommended for grade 2 and grade 3 tumours, but a surprising two patients were also reported as receiving chemotherapy which is not currently advised in the guidelines.[23] Due to resource constraints and personnel shortage, records are often physical, and these findings may not reflect the actual landscape of adjuvant treatment in ependymomas in Pakistan. Poor record keeping and lack of a centralized database to collate patient information and follow their treatment and diagnosis across different centres limits the available knowledge about patients receiving chemotherapy or radiotherapy. A central registry would be useful to track inter-hospital transfer and chain of care.

Conclusion

Ependymomas were predominantly found in the paediatric population in our cohort. While gender distribution and histopathological grading seemed to follow international

trends, our patients had a much higher mortality rate and a much lower gross total resection rate than centres in high-income countries. This study illustrates the need for specialized training and resource allocation, as well as better patient tracking mechanisms to improve surgical outcomes in patients diagnosed with ependymoma.

Limitations of the Study

The study was dependant on the available records at the participating tertiary care institutions and the catchment area to each centre catered. These could be deficient. The healthcare system is composed of public and private healthcare facilities, with rural areas having District and Tehsil Headquarter hospitals as their primary and secondary care centres. The reported brain tumours in our region are lower than expected, which may be due to the limited population being diagnosed and presenting at a tertiary care centre. Some patients also could have consulted a medical oncologist or radiation oncologist without a neurosurgical consult (although a neurosurgeon being part of the team is recommended). Sampling method used was consecutive non-randomized sampling which is also a limitation as it was not explicitly calculated. However, since this study was meant to estimate incidence and prevalence there was no accurate way to gauge a sample size nationwide.

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Conflict of Interest: None to declare.

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