RESEARCH ARTICLE

The Pakistan Brain Tumour Epidemiology Study

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Abstract

Objective: To provide information about brain tumour epidemiology in Pakistan and potential associated risk factors due to family, medical and social characteristics.

Methods: A retrospective cross-sectional nationwide study was designed by the Pakistan Society of Neuro-oncology, to include patients diagnosed with brain tumours in Pakistan retrospectively, from January 1, 2019-December 31, 2019. The study intended to involve data from all age groups for all brain tumour cases, irrespective of histopathology which would determine the national prevalence and incidence of these tumours.

Results: A total of 2750 brain tumour cases were recorded, of which 1897 (69%) were diagnosed in the public sector. MRIs were a more common radiological study compared to CT scans. Gliomas were the most common tumours 778 (28.29%), while pineal tumours were the least common 19 (0.69%). The median age at diagnosis for males was 36 (24-49), while the median age at diagnosis for females was 37 (24-48). Hypertension was the most common co-morbidity in patients diagnosed with a brain tumour, 524 (51.89%), and smoking was the most frequent social behaviour, 355 (62.02%). Findings indicate a low metastasis frequency and few females seeking care.

Conclusion: The PBTES and the PBTC have presented an opportunity and platform for hospitals and health professionals to work together to strengthen cancer care health systems, ensure implementation of treatment guidelines and conduct regular cancer registration.

Keywords: brain neoplasms, registries, retrospective studies, epidemiology, Neuro-oncological surgery.

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Introduction

The Global Action Plan for the Prevention and Control of Non-communicable Disease 2013-2020 recommended that countries establish disease registries to develop a better understanding of regional and national needs.[1] Registries can help determine disease patterns and can drive health policy decisions on evaluation, management, and planning of health care services for disease control. Cancer is the second most common noncommunicable disease (NCD), and therefore, creating registries for various cancers is crucial for improving cancer care.

Several countries of various income settings have successfully established brain tumour registries to collect and analyse epidemiological data. The most prominent of these is the Central Brain Tumour Registry of the United States (CBTRUS), a population-based tumour registry which records annual histological data for primary and secondary central nervous system tumours.[2] Currently, Pakistan does not have a centralised brain tumour epidemiology repository that can determine national incidence or prevalence. A study conducted on the global incidence of malignant CNS tumours reported that no data was available for Pakistan.[3] In the spirit of promoting global neuro-oncology research and care, the Pakistan Society of Neuro-oncology (PASNO) conducted a nationwide study to assess brain tumour distribution. PASNO subsequently laid the foundation for the Pakistan Brain Tumour Consortium (PBTC), which formed the basis of the research group for the Pakistan Brain Tumour Epidemiology Study (PBTES). The purpose of this study was to provide information about brain tumour epidemiology in Pakistan and potential associated risk factors due to family, medical and social characteristics. This study has authentic data from across the entire country to provide a holistic picture of brain tumour epidemiology to pave the way for building a prospective brain tumour registry for Pakistan.

Methods

A retrospective cross-sectional study was designed to

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include patients diagnosed with brain tumours in Pakistan retrospectively from January 1, 2019- December 31, 2019. The study involved data from all age groups for all brain tumour cases, irrespective of histopathology. Patients, both alive and deceased, with a radiological diagnosis of a brain tumour were included. The patient or household occupations were recorded and used as a proxy for socio-economic class as a social determinant of health - these categories were based on the Pakistan Standard Classification of Occupations (PSCO).[4] Data were recorded on a comprehensive online database between August 2020 and February 2021. A comprehensive study protocol on the multi-institutional experience of the PBTES has been included in this supplement.[5]

Ethical approval was obtained from the Aga Khan University Hospital's Ethics Review Committee (Ref: 2020-3529-10977). Since data collection was planned for hospitals and neurological centres across Pakistan, approval from the National Bioethics Committee was also requested and provided (Ref: No.4-87/NBC-487/20/749).

Data were recorded from 32 hospitals across the country, in both the public and private sectors. Currently, in Pakistan, there is no centralized mechanism for logging patients that visit both neurosurgical centres and radiology centres, so to ensure that no patients were duplicated, data was only collected from neurosurgical centres. Data were analyzed using SPSS Version 25.0 and STATA Version 16.0.

Results

Hospital Distribution: The hospitals from which medical records were collected were both from the public sector (n = 23) and private sector (n= 12). The highest number of brain tumour cases were recorded at the Punjab Institute of Neuroscience (n= 365), which is a public sector hospital. Figure 1 shows details of the brain tumour cases at all the centres included in the study.

Social and Demographic Data: A total of 2750 records were obtained — these were patients that presented to one of the 32 neurosurgical centres above with a brain tumour from January 1, 2019, to December 31, 2019. The distribution for gender was 1605(58.4%) male and 1142(41.5%) female, and for 0.1%, this information was not recorded. The median age at diagnosis for males was 36 (24-49), while the median age at diagnosis for females was 37 (24-48). The median age at diagnosis by brain tumour subtype has been provided in Figure-2.

Residential information showed that 2259 patients were from Pakistan. The remaining had travelled from Afghanistan, Syria, Oman and Sudan. In Pakistan, patients were from various districts across the country, and in terms of provincial and territorial distribution, 783 (34.66%) lived in Sindh, 925 (42.14%) in Punjab, 120 (5.31%) in Balochistan, 377 (16.69%) in Khyber Pakhtunkhwa, 14 (0.62%) in Gilgit-Baltistan and 13 (0.58%) were from Azad Jammu and Kashmir (Figure-3).

The occupations for 2494 (90.69%) of the patients were recorded and used as a proxy for socio-economic class as a social determinant of health. Hypertension was the most common co-morbidity in patients diagnosed with a brain tumour, with 524 (51.89%) reported cases, and smoking was the most common social behaviour observed in 355 (62.02%) patients.

Table-1: Patient Characteristics.

Category	Subcategory	Total	% of Total Category
Facility Type	Public	1897	69
	Private	853	31
Age Groups	<15 years	287	10.4
	15-19 years	133	4.8
	20-39 years	868	31.6
	40-59 years	776	28.2
	60+	212	7.7
	Not specified	474	17.2
Gender	Male	1605	58.4
	Female	1142	41.5
	Not specified	3	0.1
Marital Status	Currently Married	1694	61.6
	Never Married	746	27.1
	Other	38	1.4
	Not specified	272	9.9
Socio-economic	Lower Class SES	1321	48.0
Status-SES	Middle Class SES	1007	36.6
(Determined by	Upper Middle SES	145	5.3
Occupation)	Upper Class SES	21	0.8
	Unknown	256	9.3
Social History	Alcohol	8	1.40
	Gutka	16	3.32
	Paan	70	12.24
	Niswar	122	21.33
	Smoking	355	62.02
	Opioids	1	0.002
Co-morbidities	Hypertension	524	51.89
	Diabetes	308	30.50
	Ischaemic Heart Disease	96	9.50
	Epilepsy	7	0.69
	Pulmonary	9	0.009
	Renal	4	0.004
	Hepatitis	12	1.19
	Other Neoplasms	6	0.59
	Endocrine	15	1.49
	Mental Health	4	0.40
	Tuberculosis	3	0.30
	Other	19	1.88

Table-2: Radiology.

Radiology	n (%)
MRI or MRI and CT Scan	26623 (96.8)
CT Scan Only	63 (2.3)
Not specified	24 (0.9)

Table-3: Histopathology by Age Group.

Age Category	Tumour
Children (<15 years)	Medulloblastoma (24%)
	Glioma (21.3%)
	Craniopharyngioma (14.6%)
Adolescents (15-19 years)	Glioma (27.8%)
	Pituitary Adenoma, Craniopharyngioma (9%)
	Meningioma (8.3%)
Young Adults (20-39 years)	Glioma (34.7%)
	Meningioma (16%)
	Pituitary Adenoma (12.6%)
Middle-aged Adults (40-59 years)	Glioma (27.7%)
	Meningioma (20.5%)
	Pituitary Adenoma (12.1%)
Older Adults (>60 years)	Glioma (16%)
	Meningioma (17%)
	Pituitary Adenoma (9.4%)

Table-4: Patient Characteristics without a Specified Histopathology.

Category	Subcategory	Total	% of Total Category
Facility Type	Public	330	17.4
	Private	207	24.3
Age Groups	<15 years	37	12.8
	15-19 years	27	20.3
	20-39 years	137	16.8
	40-59 years	149	19.2
	60+	63	29.7
	Not specified	124	26.1
Socio-economic Status	Lower Class SES	266	20.1
	Middle Class SES	189	18.8
	Upper Middle SES	38	26.2
	Upper Class SES	2	9.5
	Unknown	42	16.4
Surgery Type	Biopsy	16	7.4
	Gross Total Resection	100	8.2
	Subtotal Resection	36	6.0
	CSF Diversion Only	22	17.4
	Other	45	17.4
Radiation Therapy	Radiation Administered	91	19.0
	Radiation Not Administered	84	11.0
	LTFU for Radiation	304	20.2
Chemotherapy	Chemotherapy Administered	13	7.5
	Chemo Not Administered	64	7.9
	LTFU for Chemotherapy	369	21.0

Radiological Studies and Surgeries: In Pakistan, Magnetic Resonance Imagining (MRI) and Computed Tomography (CT) scanning are used to carry out initial screening and to make preliminary diagnoses. Out of the 2750 records, 1345 (48.9%) had only MRIs, 63 (2.3%) had only CT scans, and 1318 (47.9%) had both MRIs and CT scans (Table-2). The radiological investigations for 24 (0.9%) of those visiting medical facilities for brain tumour care were not reported.

At least one surgery was performed on 2,419 patients, and 344 patients went on to undergo second and third surgeries (Figure-4). Most people, 1218 (50.35%). underwent gross total resection (GTR) of the tumour

Main Histopathological Findings: The main brain tumour types that were recorded included meningiomas, craniopharyngiomas, gliomas, brainstem gliomas, ependymomas, medulloblastomas, haemangioblastomas, pituitary adenomas, lymphomas, pineal tumours, vestibular schwannomas and other brain neoplasms. The five most

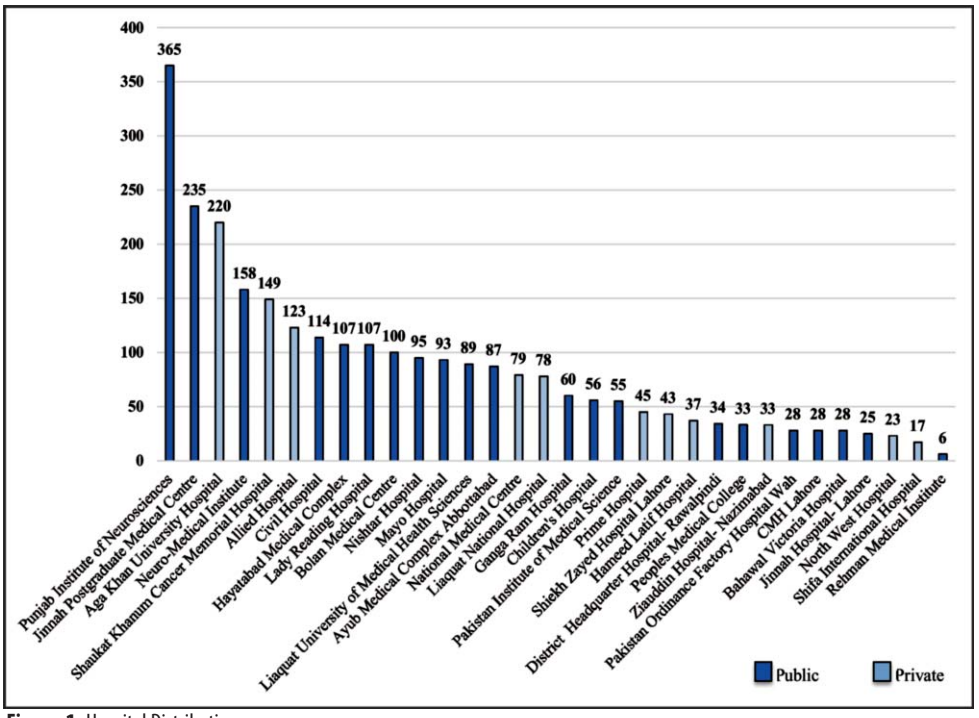

Figure-1: Hospital Distribution.

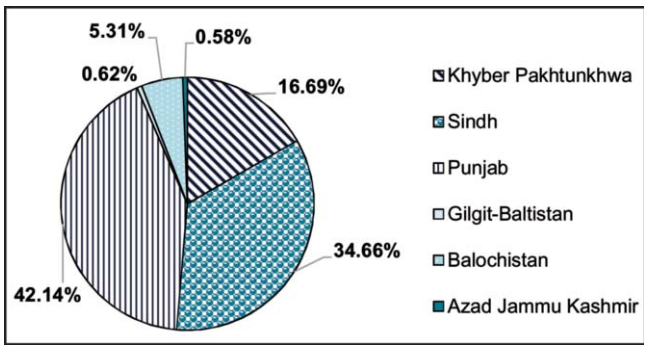

Figure-3: Distribution of Patients from Pakistan.

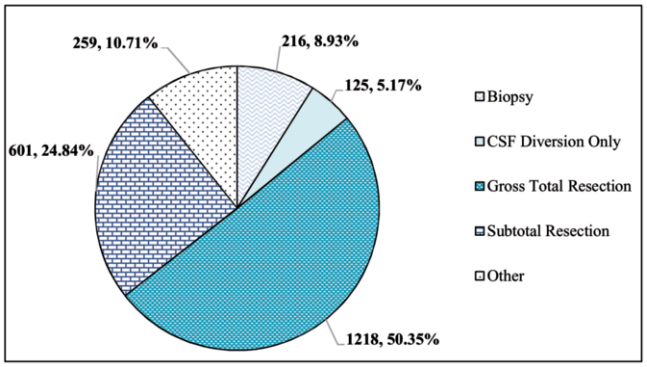

Figure-4: Extent of Resection.

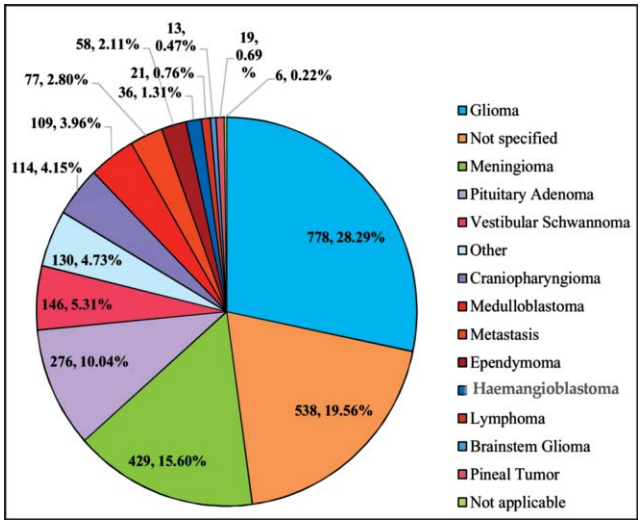

Figure-5: Histopathological Distribution.

common brain tumours being treated in Pakistan are gliomas (28.29%), meningiomas (15.60%), pituitary adenomas (10.04%), vestibular schwannomas (5.31%), and craniopharyngiomas (4.15%) (Figure-6). The median age by By age group, Table-3 shows the tumours that were most common.

Patients presenting at the participating neurological centres for brain tumours underwent adjuvant

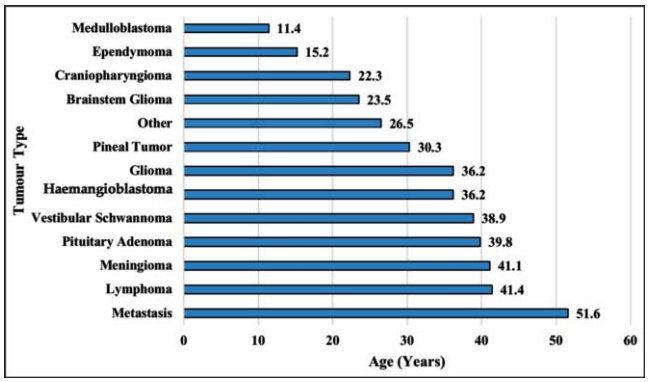

Figure-6: Median Age at Diagnosis by Tumour Type.

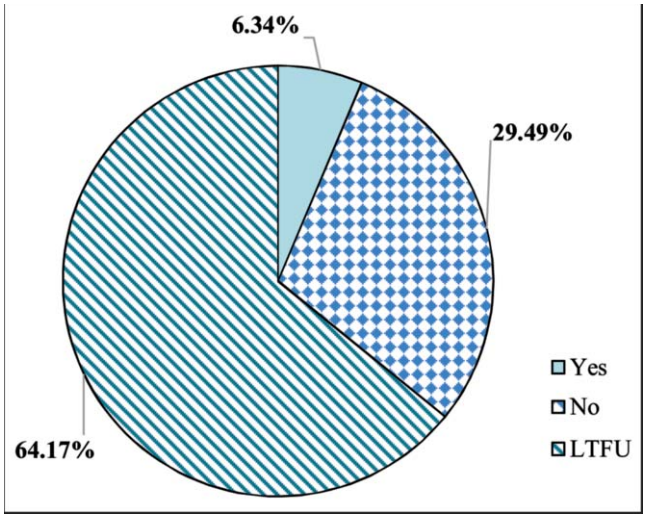

Figure-7: Chemotherapy.

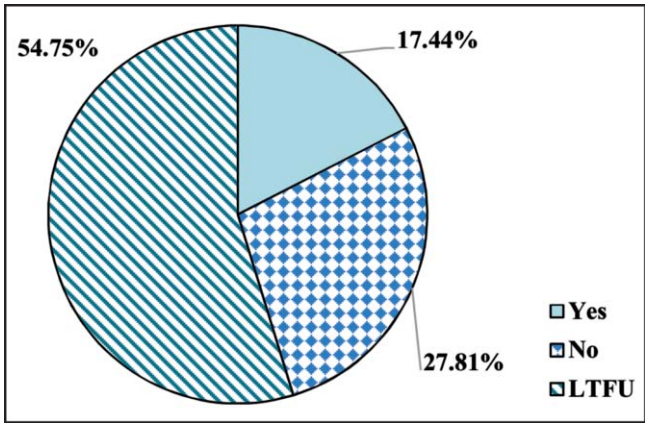

Figure-8: Radiation Therapy.

chemotherapy (6.34%) and radiation therapy (17.44%) (Figures-7 and 8). However, a significant proportion of patients (chemotherapy (64.16%; radiation therapy = 54.75%) were lost to follow-up for adjuvant treatment.

At the last follow-up, 850 (44.81%) of patients were alive

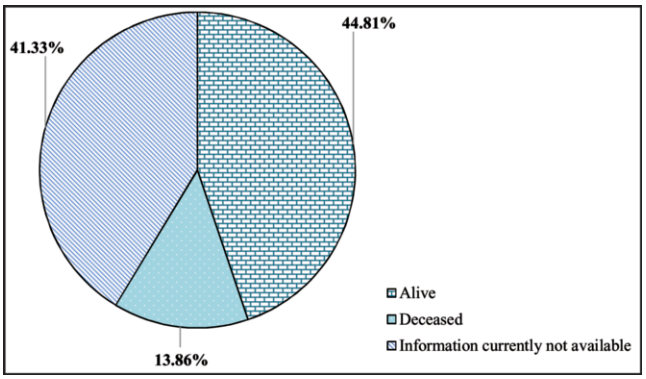

Figure-9: Current Status.

post-surgery, while the records for 263 (13.86%) of patients indicated that they were deceased (Figure-9). Almost half of the patients recorded in the PBTES were lost to follow-up, and the status of these individuals is unknown. The 30-day mortality for brain tumour patients covered by PBTES was 4.04%.

Brain tumours without specified histopathology accounted for 330 (24.3%) of tumours being operated on in the private sector and 207 (17.4%) of all tumours being operated on in the public sector (Table-4). Tumours that did not have specified histopathology were found in 63 (29.7%) patients over the age of 60 years. Radiation and chemotherapy were provided to 91 (19%) and 13 (7.5%) patients with unknown histopathology, respectively.

Discussion

Brain tumour epidemiology has been examined on a small scale in Pakistan, mostly in single-centre studies and as part of general cancer registries. A single centre cross-sectional study on brain tumour epidemiology conducted in Khyber Pakhtunkhwa had shown that during a five-year period (2008-2013), with 761 registered cases, the most common type of brain tumour was a tumour in the neuroepithelial tissue and that lymphomas and haematopoietic neoplasms were the least common,[5,6] Furthermore, the Pakistan Atomic Energy Commission (PAEC) found in its 2018-2019 annual report that tumours of the CNS were the fourth most common tumours overall, the sixth most common tumours among males and the eighth most common tumours among females.[6,7] Intracranial tumours were not singled out in this analysis.

Paediatric tumours have also been examined at single centres in Pakistan; a public tertiary care hospital in Karachi scrutinized pathology records from 1989-1998, which showed that paediatric brain tumours were most common between the ages of 5 and 9, with the most common tumour type being a primitive neuroectodermal tumour.[7,8] A similar retrospective study carried out at a public sector hospital in Islamabad examined data from 1998 to 2013 showed that brain tumours were diagnosed mostly primarily among children aged 6-8 and that medulloblastomas were the most common type of cancer.[8,9]

However, these studies are either limited by catchment area and age group or are not restricted to brain tumours. The PBTES presents results from the first national hospital-based study in Pakistan using the WHO 2016 histological classification of tumours of the central nervous system.[9,10] The results from PBTES indicate severely fragmented care and a lack of standardised brain tumour reporting standards in Pakistan. Demographic data such as date of birth or age at diagnosis, date of diagnosis, socio-economic status, and/or current living status were not available. Further, many discrepancies were found in the methods of recording and reporting diagnoses and histopathology. This raises questions about whether this is due to the lack of adequate record keeping or truly due to gaps in treatment and a breach in the continuity of care. A standardized record keeping method is recommended to ensure that a complete set of patient characteristics are reported at the place of presentation, which will remedy the gaps in this technology. To establish continuity of care for brain tumour patients and reduce the loss to follow-up, it is important to implement treatment guidelines in their entirety — frequent tumour board discussion and accountability are recommended to ensure safe surgery and appropriate adjuvant chemoradiotherapy.

Distance and Lost-to-follow-up: Full addresses were provided for 2367 of the 2750 patients. Of these, the median distance travelled across the country was 104 km, which did not adhere to global guidelines suggesting a cut-off of 50 km distance from a major hospital as an acceptable limit in cancer patients for optimal follow-up and outcomes.[10,11] Only 41% of patients had access to brain tumour surgical care within 50 km of their primary address. Travelling to a private sector hospital was associated with better overall survival in comparison to public hospitals, regardless of the distance travelled. Patients travelling more than 50 km for brain tumour surgery had better pre- and post-surgery Karnofsky performance[11,12] scores and overall survival in comparison with patients travelling less than 50 km.[13] The distance travelled to a hospital dictates a patient's access to continuity of care through adjuvant chemoradiotherapy and regular follow-ups. This can be disrupted if patients cannot overcome the barriers due to extensive distances travelled.

Of 2750 patients presenting in 2019, 1140 (41.45%) were lost to follow-up (LTFU) at various stages of care. Patients from a lower socio-economic status (SES) had significantly higher odds of being LTFU. Similarly, patients from the adult population (19-49) had significantly higher odds of not following up, as opposed to paediatric and elderly populations, and patients receiving care at public institutions were LTFU more often than patients visiting private institutions. Married patients also had greater odds of being LTFU than unmarried patients.[14] Current literature indicates that patients who are elderly (>50 years), unmarried, of low socio-economic status, or from rural areas are less likely to follow up in clinics.[12,15] In comparison, our data shows that adults, who are married, from lower SES (daily wage workers), or those receiving care at public hospitals, are at a higher risk for being LTFU in an LMIC. It is noteworthy that some patients who were LTFU may be receiving care at another centre. However, there is no consolidated record of these patients.

Age, Gender, and Socio-economic Status: Globally, paediatric tumours are documented vigorously, as paediatric patients and their families typically present to and are diagnosed at specialized centres or are referred to specialized care facilities from other medical centres.[13,16] However, a proportion of tumours reported to the PBTES, particularly in the paediatric age group, did not have histopathological confirmation of the diagnosis. In Pakistan, the paediatric population makes up 43.4% of the total population, followed by the 20-39 age group, which makes up 27.33% of the population. PBTES has shown that brain tumours in the 20-39 years age group are most common with paediatric tumours being the third most common. Interestingly, while the 40-59 age group consists of only 13.3% of the total Pakistani population, it consists of 28.2% of all brain tumours, the second highest age group to be diagnosed with a tumour.

In the United States, the median age at diagnosis for all primary CNS tumours between 2014 and 2018 was 61 years.[2] In Pakistan, PBTES found that patients with brain tumours mostly presented between the ages of 20 and 39 years, with the median age at presentation being 36 years. This is in line with that of LMIC populations, which often have larger youth and working-age individuals.. Further, patients presenting and being recorded were 58.4% male and 41.5% female, and for 0.1%, the gender was not recorded. The gender imbalance highlights the need to ensure access to safe, quality surgical care for women with brain tumours, as well as widespread cancer outreach and awareness programmes that are targeted towards women, particularly in rural settlements. It is, however, noteworthy that although fewer women are diagnosed than men, there is no statistical difference in the median age of the two genders. This implies that women who are able to access health care for brain tumours can do so in a timely manner.

PBTES data suggests that 48% of patients undergoing surgery were from a low socio-economic background based on using occupation as a social determinant as a proxy for socio-economic background. Professions from this stratum of the society include blue-collar workers, labourers and daily wage workers. These patients typically reside in rural areas and travel long distances to receive care at specialized neurosurgical centres in urban hubs. Further, brain tumour care can pose a high financial cost to these patients — while this has not been formally assessed from the PBTES's 2019 findings, it opens avenues for further research for health-seeking behaviour, direct and indirect out-of-pocket expenditure for brain tumour care and value of treatment studies.

Medical History, Surgery, and Histopathology: Various co-morbidities were found in brain tumour patients in Pakistan, with the most prominent being hypertension and diabetes mellitus. A 2012 meta-analysis assessed diabetes mellitus as a risk factor for brain tumours and concluded that while diabetics and non-diabetics alike have a similar risk, there was a significant positive correlation associated with brain tumours and diabetes mellitus in females but not in males.[14,17] No associations have been found between brain tumours and hypertension.

In terms of surgery for brain tumours in Pakistan, we found that 50.53% of our patients underwent gross total resections. However, postoperative radiology to determine if the entire tumour was removed was not carried out, and true gross total resection was not objectively determined in many cases. Our findings are self-reported, and this underlines the need for transparency while verifying the extent of resection. An MRI forty-eight hours post-surgery is recommended as the standard practice to assess and confirm the extent of resection.[15,18] Additionally, a postoperative MRI can assist in determining the reoccurrence of glioblastomas and can subsequently inform treatment options.[16,19]

Metastatic brain tumours are considered the most common type of intracranial tumours.[17,20] However, PBTES shows that metastatic lesions to the brain make up less than 3% of operated tumours in Pakistan. This may be because patients in advanced stages of the disease may refuse to visit medical centres and instead opt for in-home palliative care. However, this may also indicate a gap in the detection and treatment of brain metastases,

which is further telling of the lack of accurate health information collection and reporting standards for medical care for brain tumours in Pakistan. Globally, meningiomas are the most common primary brain tumour. However, PBTES shows that most of our patients are glioma cases. It is speculated that this is due to the aggressive symptoms of glial tumours, which are easier to detect even by non-medical professionals, and therefore are the cases that are most frequently brought into healthcare facilities for diagnosis and treatment.

Registry Development: Cancer registries across the world are crucial for monitoring cancer incidence, mortality and survival.[1] Population-based registries provide a holistic representation of the landscape of brain tumour epidemiology and can also provide evidence to inform policy, aid in decision-making and prioritisation, and offer causal associations between behaviour and brain tumour diagnosis.[13,16] However, population-based registry development in LMICs, like Pakistan, must overcome grave roadblocks such as poor health infrastructure and referral systems, gaps in record keeping, the lack of continuity of care, disputed census data and insufficient post-mortem reports. Cancer registration in Nigeria has faced similar issues, citing funding and institutional commitment, lack of education and training, incomplete data and sustainability as the main challenges faced whilst creating a cancer registry. Recommendations from the Nigerian experience include consistent and adequate government focus on making cancer a registrable disease, using this registration as a basis for government cancer care and control policies and programmes, and sustainable funding for cancer registration.[18,21]

The first step toward population-based registries to assess the burden of disease of brain tumours is to document cases coming into hospitals through a multi-hospital-based registry. This is what the PBTES has achieved and, by doing so, has become a seminal piece of work for clinical brain tumour epidemiology in Pakistan, a basis for further registry building and a guide for decision making. Even when not adhering to international registration standards, cancer registration exercises in LMICs show the weaknesses in health systems and provide opportunities to improve data and quality indicators.[18,21] Our findings are representative of the lack of emphasis put on cancer care and surgical health systems, which is valuable to drive policy change and close the knowledge and practice gaps in cancer treatment and management in Pakistan. With due attention from public and private structures and institutions and viable funding, cancer registration can become standard protocol in Pakistan.

The PBTES demanded that all hospitals enter data in a preformed study tool to ensure consistency. However, due to differences in internal hospital record keeping, there were many differences and discrepancies in the reported data. To create a stronger hospital-based registration system that can culminate into a population-based registry, consistency in the methods of recording treatments using international standards are important to implement and enforce, such as those established by the International Classification of Diseases (ICD-10).[19,22] A coordinated and robust method of recordkeeping and data sharing is vital for monitoring diagnostic findings, treatment strategies and patient outcomes, in addition to being useful for ensuring smooth communication among health professionals and informing hospital and public health policy.[20,23] In future, for registry-building initiatives, it is imperative that symptoms be meticulously documented both pre-and post-surgery and adjuvant treatment to better assess the efficacy of treatment protocol for various tumours and tumour subtypes. Follow-up mechanisms must also be founded and be made compulsory to ensure holistic and continuous care.

In Pakistan, patients typically have physical copies of their hospital records, and these are often the only official documentation of disease. This can result in low incidence and prevalence data, as hospitals do not retain records of patients that they have referred to other medical facilities and often have incomplete data of patient referral history prior to presenting at their centre. Consistent and reliable institutional memory for each presenting patient is necessary to develop a stronger hospital-based registry and population-based registration system. Ensuring strong institutional recordkeeping of patient treatment and follow-up will lead to coordinated, continuous care and can better health outcomes and palliative care management.

Conclusion

The PBTES and the PBTC have presented an opportunity and platform for hospitals and health professionals to work together to strengthen cancer care health systems, ensure implementation of treatment guidelines and conduct regular cancer registration.

Disclaimer: None to declare.

Conflict of Interest: None to declare.

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