

RESEARCH ARTICLE

Gender disparities in brain tumours: A Pakistan brain tumour epidemiology study analysis

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Abstract

Objective: To explore the differences in demographic, surgical, and prognostic characteristics between the two genders in patients with brain tumours in Pakistan.

Methods: This study was a retrospective cross-sectional analysis of patients with a histopathological brain tumour diagnosis across 32 high-volume hospitals in Pakistan. The study period was from January 1, 2019, to December 31, 2019. There were no restrictions on inclusion apart from time.

Results: From 2750 patients enrolled in the study, 1605 (58.4%) were male, and 1142 (41.6%) were female. The median age amongst males was 36 (24-49), while the median age amongst females was 37 (24-48). The ratio of married to unmarried patients was 2.7:1 for females and 1.3:1 for males. Surgical treatment was carried out for 1430 (58.1%) males and 1013 (41.9%) females. The median time to surgery was 25 (4-107) days for males and 31 (5-98) days for females. The greatest disparity in tumour malignancy was in grade IV gliomas.

Conclusion: Males generally have a higher incidence of brain tumours in our experience, apart from meningiomas, which favour females. The mortality rate and glioblastoma incidence rate are both higher amongst males. However, post-treatment cure is also witnessed. Sociocultural norms play a prominent role in accessing healthcare. Women are generally at a disadvantage compared to their male counterparts, which may impact reporting of brain tumour cases and treatment outcomes.

Keywords: Brain neoplasms, Epidemiology, Gender equity, Retrospective study
(JPMA 72: S-79 [Suppl. 4]; 2022) DOI: <https://doi.org/10.47391/JPMA.11-S4-AKUB13>

Introduction

Differences in ageing, physiology and disease pathology according to gender are well-established constituents of medical theory and practice. How they differ are important for the diagnosis and prognosis of all diseases, including cancer. Literature shows a significant difference between males and females in cancer incidence and prognosis, depending on the tumour type.¹ Globally, males have a higher cancer prevalence and are less responsive to therapy, with lower overall survival.^{2,3} The greater incidence of these tumours in males, regardless of region, age, and other demographic characteristics, suggests that gender serves an important role in tumour pathophysiology. Only by investigating the molecular, transcriptomal, and cellular characteristics of these tumours in both genders can we address each need with tailored equitable treatment

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according to the disease burden.

Brain tumours, while relatively rare, carry high morbidity and mortality, and for many brain tumours, the mortality rate has not changed much over the past couple of decades. Current research primarily focuses on oncogenesis and molecular biology of brain tumours to identify pathways to overcome treatment resistance and develop new therapies.⁴⁻⁶

Literature has demonstrated a significant difference in treatment response to different types of tumours between males and females. Nimela et al. report that female patients with gliomas had a significantly worse functional state (measured by the Karnofsky Performance Scale (KPS)) and significantly more distress (measured by the Health Measurement Questionnaire (HMQ)) compared to patients with other tumours.⁷ However, there were no differences noticed in males. This study explored the gender-related differences in our region's demographic, surgical, and prognostic characteristics of patients with brain tumours.

Methods

This study was a retrospective cross-sectional analysis of patients with a histopathological brain tumour diagnosis across 32 neurosurgical centres in Pakistan. The study period was from January 1, 2019, to December 31, 2019. There were no restrictions on inclusion apart from time.

The papers discussing detailed methodology and general findings 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^{8,9} included in this supplement.

Data included demographics, treatment methods, adjuvant chemoradiotherapy and lost to follow-up, which was declared if medical records at the primary surgical care centre did not reflect follow-up at the same centre with the same surgeon. Socioeconomic status was determined using occupation as a proxy.

Data were analyzed using the Statistical Package for Social Sciences version 25 and STATA Statistical Software Package version 16. Chi-square and Fischer's Exact tests were used to calculate significance as the data were not normally distributed.

Results

Of the total 2750 patients enrolled in the study, 1605 (58.4%) were male, and 1142(41.6%) were female. Three patients did not have their gender logged at the hospital they had presented. The median age amongst males was 36 (24-49), while the median age amongst females was 37 (24-48). More males were present in each age category than females reflecting their larger overall frequency.

Table-1: Demographic Characteristics (n=2747).

		Gender			
		Male	%	Female	%
Age group	Unspecified	283	60.0	189	40.0
	Children (<15 years)	162	56.4	125	43.6
	Adolescent (15-19 years)	86	64.7	47	35.3
	Young Adult (20-39 years)	514	59.2	354	40.8
	Middle-aged adults (40-59 years)	429	55.4	346	44.6
	Older adults (60-99 years)	131	61.8	81	38.2
SES	Lower (e.g. blue-collar workers, labourers, daily wagers)	788	59.7	532	40.3
	Middle (e.g. graduates, mid-level office workers, homeowners)	554	55.1	451	44.9
	Upper Middle or Upper	98	59.0	68	41.0
	Unknown	165	64.5	91	35.5
Patient Marital Status	Unmarried	470	63.1	275	36.9
	Married	944	55.8	749	44.2
	Other	191	61.8	118	38.2

SES (Socioeconomic Status).

Table-2: Hospital Characteristics.

		Gender of Patient		
		Male	Female	Ratio (M: F)
Hospital annual volume	Up to 100	674	505	1.3
	More than 100	931	637	1.5
Hospital type	Public	1092	802	1.4
	Private	513	340	1.5
Lost to follow-up in radiotherapy		898	604	1.5
Lost to follow-up in chemotherapy		1048	709	1.5
Distance Travelled	<50 km	549	424	1.3
	50-500 km	603	416	1.4
	>500km	228	144	1.6

Table-3: Surgical Characteristics.

		Male	%	Female	%
Was the patient admitted and surgery done?	Yes	1403	58.1	1013	41.9
	No	202	61.0	129	39.0
Type of surgery	GTR	699	57.4	518	42.6
	STR	352	58.7	248	41.3
	Biopsy only	140	64.8	76	35.2
	CSF diversion only	70	56.0	55	44.0
	Other	344	58.4	245	41.6
Time to surgery in days (median)		25	IQR: 4-107	31	IQR: 5-98

Similarly, there was a larger number of males in each socioeconomic category, with males and females predominantly being from the lower socioeconomic strata. Most of our patients were married in both age categories, but the ratio of married to unmarried was larger in females at 2.7:1 compared to 1.3:1 for males. The demographic characteristics and the percentage of each gender within its category are tabulated in Table-1.

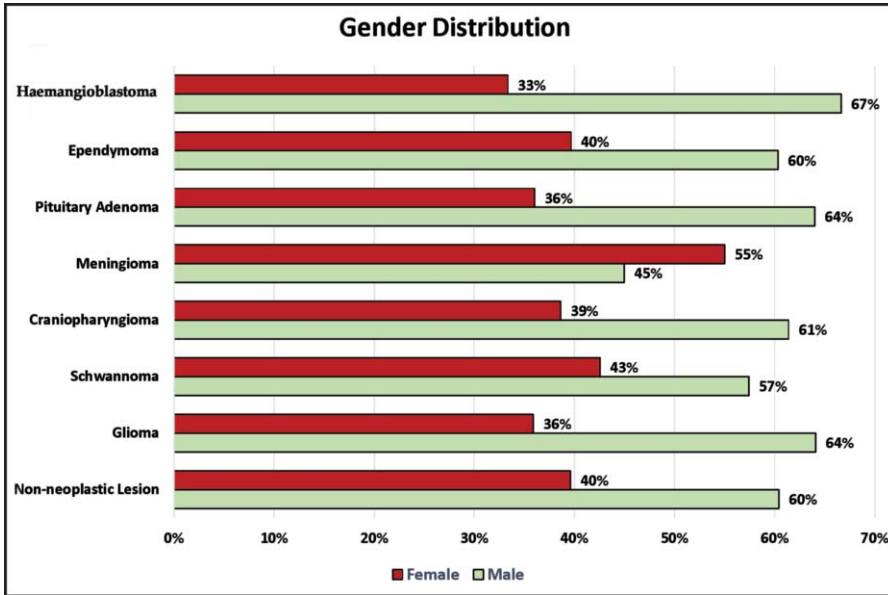


Figure-1: Gender Distribution.

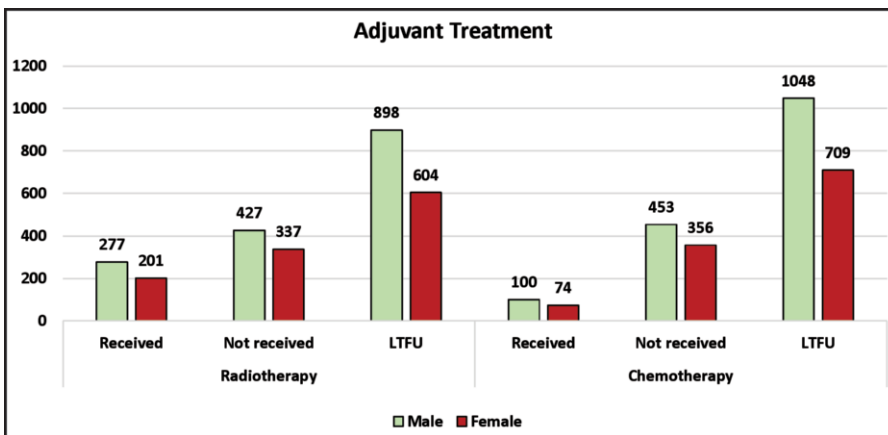


Figure-2: Adjuvant Treatment.

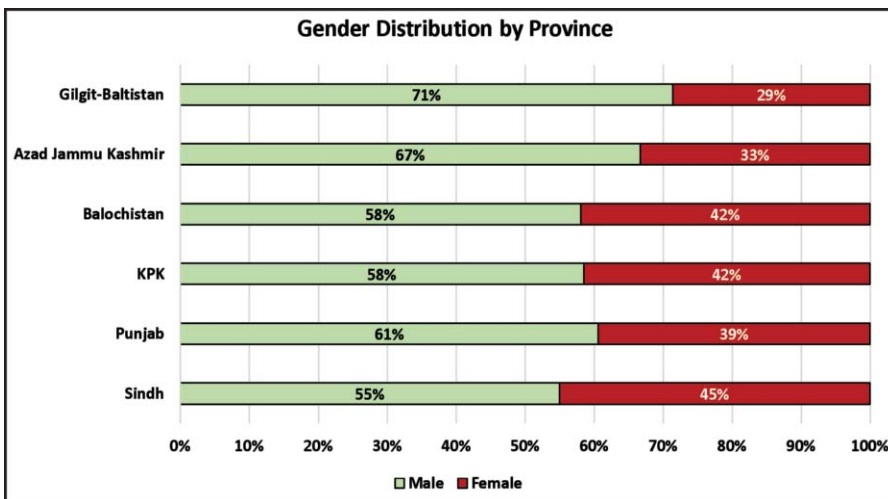


Figure-3: Gender Distribution by Province.

The ratio of male-to-female patients was roughly equal across hospitals with more than 100 cases of brain tumours annually (M: F ratio= 1.3) and those with less than 100 cases per year (M: F ratio= 1.5). Similarly, the ratio of males and females in public and private hospitals was 1.4 and 1.5, respectively. The lost to follow-up ratio was the same between radiotherapy and chemotherapy at 1.5 each. As the distance travelled by patients to their surgical institution increased, the male-to-female ratio also increased. At a cutoff of fewer than 50 km, the M: F ratio was 1.3, at 50-500 km, the ratio was 1.4, and at more than 500 km, the ratio was 1.6, demonstrating that males were more likely to travel a larger distance for treatment than females. The data are summarised in Table-2.

Gender distribution across different tumour types was also analysed. Higher tumour prevalence was seen in males across all tumour types. The gender distribution in numerical form is illustrated in Figure-1.

A total of 478 patients received radiotherapy post-surgery (M: 277 (57.9%), F: 201 (42.1%). Four hundred twenty-seven males did not receive radiotherapy, 337 females did not receive radiotherapy, and 898 males were lost to follow-up, while 604 females were lost to follow-up with no radiotherapy information available. Of the 174 patients that received chemotherapy, 100 (57.45%) were male, and 74 (42.53%) were female. Four hundred fifty-three males and 356 females did not receive chemotherapy. One thousand forty-eight males and 709 females had no information available regarding chemotherapy. Figure-2 illustrates the adjuvant treatment.

The median pre-op KPS, which measures functionality,⁸ was 80 for males and 90 for females, while the median post-op KPS was 90 for males,

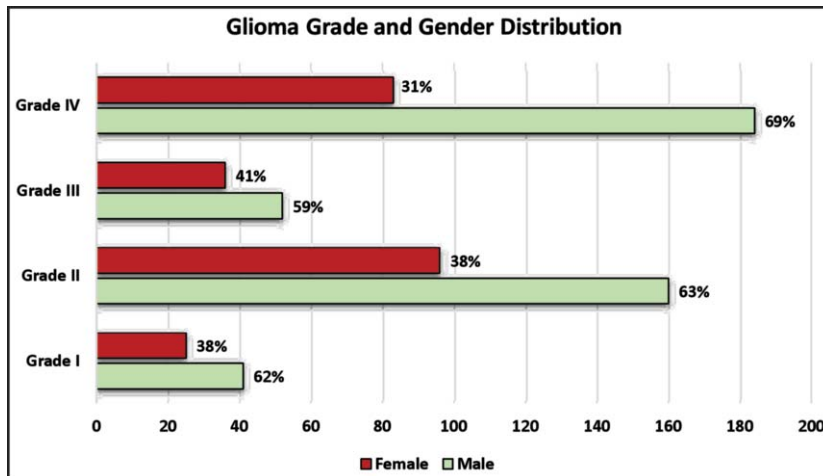


Figure-4: Glioma Grade and Gender Distribution.

Table-4: Outcomes.

		Male	Female
Pre-op KPS (median)		80 (60-90)	80 (70-90)
Post-op KPS (median)		90 (80-100)	90 (80-100)
		Males	Females
Status	Alive	713	551
	Deceased	210	134
	LTFU	682	457
		%	%
		56.4	43.6
		61.0	39.0
		59.9	40.1

KPS (Karnofsky Performance Scale).

Table-5: PBTES and CBTRUS Gender Ratios by Tumour Type.

Tumour type	PBTES	CBTRUS	Ratio (PBTES: CBTRUS)
Non-neoplastic Lesion	1.53	0.63	2.42
Glioma	1.79	1.32	1.35
Schwannoma	1.35	0.89	1.52
Craniopharyngioma	1.59	1.05	1.52
Meningioma	0.82	0.37	2.21
Pituitary Adenoma	1.78	1.12	1.59
ndymoma	1.52	1.31	1.16
Haemangioblastoma	2.00	0.86	2.33

PBTES (Pakistan Brain Tumour Epidemiology Study), CBTRUS (Central Brain Tumor Registry of the United States).

which showed an improvement on average and 90 for females, which showed no change on average. Two hundred ten males (61%) and 134 (39%) females expired before the conclusion of the study. The 30-day mortality rate was 3.7% for males and 4.5% for females. Amongst the patients known to be alive, 713 were males, and 551 were females. Overall, males made up 59.9% of the LTFU group, while females made up 40.1% of the group. Table-4 summarizes the outcomes according to gender group.

The mean distance travelled by males was 252 ± 371.5 kilometres, and the average distance travelled by females

was 223 ± 374 kilometres (p=0.036). Males accounted for 431 patients from Sindh, 562 from Punjab, 214 from KP, 94 from Balochistan, eight from Azad Jammu and Kashmir, and ten from Gilgit-Baltistan. Females accounted for 353 (45%) patients from Sindh, 365 (39%) from Punjab, 152 (42%) from KP, 68 (42%) from Balochistan, 4 (33%) from Azad Jammu and Kashmir, and 10 (29%) from Gilgit-Baltistan. Figure-3 shows the gender distribution according to province.

The disparity between males and females with regard to tumour grade in glioma patients is illustrated in Figure-4. The greatest difference is in grade IV gliomas, with a ratio of 2.2 (68.9 % of grade IV gliomas were males). Thus, males appear to have a disproportionately higher number of highly malignant gliomas. Figure-4 shows the frequency of males and females diagnosed with each grade of glioma at our centres.

Discussion

In our population, the ratio of incidence of brain tumours in males and females was 1.4, which matches the United States, where the incidence ratio is also 1.4. The annual incidence of primary malignant brain tumours in the US is 2.6 per 100,000 for females and 3.7 per 100,000 for males, according to the Central Brain Tumor Registry of the United States (CBTRUS).^{10,11} High-income countries generally have higher rates of brain tumours, with males having 5.8 per 100,000 and females having 4.1 per 100,000, while low-and- middle-income countries (LMICs) often report having lower incidence rates, with males having three per 100,000 and females having 2.1 per 100,000.^{12,13} Our incidence rates are lower overall than those reported in other LMICs (1.25), but our data is based on limited centres in Pakistan (and only neurosurgical centres), which may not represent the true burden of disease. Different regions also have differing male-to-female population ratios. Pakistan's (where the Pakistan Brain Tumour Epidemiology Study, or PBTES, is based) is 1.05, while the US's (where CBTRUS is based) is 0.98. Caucasian males seem to have the highest risk for non-malignant brain tumours and primary malignant brain tumours in the US. Females had higher rates of non-malignant tumours, particularly meningiomas, while males had higher rates of primary malignant brain tumours.^{1,13,14}

In the presented cohort, there were 236 (55%) females and 193 (45%) males diagnosed with meningioma. Both

males and females predominantly presented between 36 and 44 years of age. However, no females 75 years or older presented with brain tumours at any neurological centres in Pakistan. Meningiomas have shown a great disparity in incidence in literature as well, with females aged 30 to 70 more than twice as likely to develop the disease, although they are more likely to have low-grade tumours, while males are more likely to have malignant meningiomas. The reason for this may be linked to hormonal levels; meningiomas are known to be sensitive to progesterone and estrogen, with hormone replacement therapy increasing the risk of occurrence rises. Additionally, there have been reported cases of rapid meningioma growth during pregnancy when estrogen levels are high. In men with low testosterone levels, the risk for meningioma is higher, and some cases report the presence of luteinizing hormone-releasing hormone receptors. This may indicate that testosterone plays a protective role against the tumour.^{1,3}

The highest disparity in our hospital-based incidence was in haemangioblastoma with a male to female ratio of 2, followed by glioma with a ratio of 1.79, then pituitary adenomas with a ratio of 1.78. According to CBTRUS, the male-to-female ratio is 1.1 for pituitary adenomas in the United States.¹⁵ Haemangioblastomas do not have a difference in incidence between genders in literature, a fact that also applies to several other tumours in which we do see a disparity in the male to female ratio. This may be accurate or an indication of gaps in diagnosis or presentation in the female gender. Table 5 illustrates the gender ratio in our study and the CBTRUS database.

Ependymomas generally do not show a predilection for gender, but some subtypes, such as the supratentorial ependymoma, have demonstrated oncogenes that are twice as likely to be present in males.¹ The male-to-female ratio in our population was 1.52:1, which is higher than the ratio reported by the CBTRUS (1.3:1).^{10,11} Previous studies in Pakistan report an incidence ratio of 3:1 in ependymomas in the paediatric age group. Other regions report lower figures (for all age groups), with Japan having a ratio of 1.1:1, China having a ratio of 1.3:1, Sweden reporting a 1:1 ratio, 1.38:1 in the United Kingdom, 1.3:1 and in France.^{16,23}

Gliomas generally have a higher incidence in males in literature; specifically, mesenchymal subtypes show the greatest disparity in the male to female ratio. Our data showed that males were more likely to have gliomas than females and more than twice (2.2 times) as likely to have grade IV gliomas, in particular, than females in our population. CBTRUS also demonstrates a higher incidence of gliomas in males, particularly higher-grade gliomas,

with the ratio of males to females with GBM being 1.58 in adults.^{9,10} The male to female ratio of patients with GBM in the paediatric population in Pakistan (in another study by Ahmed et al.) was 2:1; in Japan, it was 1.25:1 (for all age groups), in Iran, it was 2:1, and 1.75:1 in the United Kingdom.^{16,17,19,20,23} Our ratio is the highest reported around the world; this may be due to a truly higher predisposition of the male gender to develop GBM in our population or an underrepresentation of the female patients with GBM who do not receive care and go undiagnosed.

Males were 1.4 times more likely to receive surgery than females, comprising 58.1% of the surgical cohort (they also made up 61% of the cohort that did not receive surgical intervention). They were also 1.5 times more likely to be lost to follow-up, making up 59.9% of the patients that did not follow up at the centre where they had undergone surgery. Inter-hospital patient tracking was not possible due to the lack of a centralized registry or uniform patient identification number.

For our cohort, the mortality rate amongst males with known outcomes was 22.7%, and for females was 19.6% for all brain tumours. Males had a higher mortality rate which may correspond to the higher ratio of malignant tumours in that group. The mortality rate amongst males internationally is 3.57% and for the female gender is 2.79%.^{2,3,12} Our mortality rates are comparatively much higher than internationally, and the difference in mortalities is also higher than reported in literature worldwide. There was no change in KPS in females post-operative, while in males, the KPS rose by 10 to a median of 90, indicating that functionality, on average, is improved in males post-surgery but not females.

Male patients travelled a significantly longer distance of 29 km on average, and the highest disparity in presentation was in the province of Punjab, where the ratio of males to females presenting was 1.5, followed by KP, where the ratio was 1.4. While a general culture does exist within the region due to shared religion, there are important differences in the subculture and norms within each province. Women living in some provinces face greater difficulties in accessing healthcare, and a large portion of them may go undiagnosed or be unable to complete proper treatment. Further, males are likely able to travel further for treatment due to the autonomy that they have, whereas females often do not have the resources nor the decision space to do so. While the underlying sociocultural concerns require complex and cross-cutting solutions, practical stopgap measures include establishing and equipping more hospitals in regions with greater disease burden (particularly for

chemoradiotherapy) and sending surgical missions from urban centres to rural settlements to provide surgery.

Women have generally been marginalized in many spheres of health care, with brain tumour care being one of them.^{1,2,13,14} Part of this is linked with males being the traditional breadwinners of the family. However, in Pakistan, there are other factors at play as well, including cultural, religious, and societal pressures that cause women to be at a disadvantage in receiving healthcare. Without addressing the unmet burden of care or alternatively disproving its existence, it will be difficult for a policy to address the disparities and inequities in the health policy. By informing policy based on gender, race, religion, or other demographic characteristics, neuro-oncological care will be better suited to treating women and other underserved populations.

Conclusion

Males have an overall higher frequency of nearly all brain tumours, apart from meningioma, which favour females. The mortality rate and glioblastoma incidence rate are both higher amongst males. However, they do see greater improvement post-treatment also. Sociocultural norms play a large role in accessing healthcare, and women are generally at a disadvantage compared to their male counterparts, which may impact reporting of brain tumour cases and treatment outcomes.

Disclaimer: None to declare.

Conflict of Interest: None to declare.

Funding Disclosure: None to declare.

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