RESEARCH ARTICLE

Metastatic brain tumours in Pakistan: An epidemiological overview

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Abstract

Objective: To quantify the metastatic brain tumour burden presenting to tertiary care neurosurgical centres, the demographics and mortality rate, and the type of metastatic tumours commonly presenting to neurosurgical practice.

Methods: A cross-section retrospective study was conducted on patients diagnosed with brain tumours from 32 neurosurgical centres across Pakistan between January 1, 2019, to December 31, 2019. At least one neurosurgical resident and one neurosurgical faculty member were recruited from each centre as members of the Pakistan Brain tumour consortium. Mean with standard deviation or median with interquartile range was reported as variables.

Results: Of 2750 patients in this cohort, 77 (2.8%) were diagnosed with metastatic brain tumours. The median age of these patients was 52 (IQR= 43-60) years; 9 (14%) adults were aged 20-39 years, 37 (57%) were aged 40-59, and 19 (29%) were aged 60 and above. There were 62 (82.7%) married patients with 4% unmarried. The median KPS score both pre and post-surgery was 80 (IQR= 60-90, 70-90 respectively), and 43 (55.8%) patients were lost to follow-up. The mortality rate for patients that followed up was 50%, 17 patients were alive, and 17 were deceased at the end of the study period. The 30-day mortality rate amongst our patients was 11.8% (n=4).

Conclusion: The number of patients presenting to neurosurgical care with brain metastases is much lower than the expected incidence of metastatic brain lesions. Multidisciplinary integration and the establishment of a registry to track patients diagnosed with brain tumours is the first step in ensuring better care for these patients.

Keywords: Brain Metastases, Epidemiology, LMIC, Neuro-oncological surgery,

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Introduction

Brain metastasis are the most common intracranial neoplasm and is present in around 98,000 to 170,000 patients, making up roughly 50% of all brain tumours with an incidence of 8.3 per 100,000.[1,2] Of all malignant tumours, around 10% to 26% develop brain metastasis, the most common ones being lung, breast, and melanoma.

In recent years, the incidence of metastasis has seen a sharp rise, primarily due to longer survival in patients with metastatic cancer and advancement in imaging modalities.[3] Small asymptomatic metastatic lesions are now diagnosable through increasingly sensitive MRI techniques[4]. Prognostic predictors of metastatic brain tumours include age, size of metastasis and number, site of the primary tumour, radiosensitivity or chemosensitivity of the tumour and the presence of other systemic metastasis.[5-7] For some cancers, such as small-cell lung cancer, cranial irradiation is generally the preferred therapy due to the high likelihood of spread to the brain.[8]

Metastatic disease, making up a considerable portion of the brain tumour burden, should then be common in neuro-oncological surgery clinics. However, in resource-constrained settings like LMICs, the burden of metastatic disease is even higher, with the low availability of palliative care programmes, supporting societies and social structures, and the high cost of end-of-life treatment. A major problem with defining the exact scope of the issue lies with the lack of epidemiological data available regarding brain metastasis. This study aimed to quantify the surgical metastatic brain tumour burden and the epidemiological characteristics of patients presenting with these tumours.

Methods

A nationwide cross-sectional and retrospective study was conducted from 2020 to 2021 Data from January 1, 2019 to December 31, 2019 was examined, Inclusion criteria were patients with a histopathological diagnosis of brain

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tumour across 32 neurosurgical centres in Pakistan. Centres included were required to have a minimum of 5 annual brain tumour surgeries per year, and data was collected from the physical and online records available at these institutions. Data collectors were residents, research associates, and medical students with supervision and coordination by neurosurgical faculty at each institution, which were part of the Pakistan Brain Tumour Consortium (PBTC). Patients who presented to surgeons at participating centres were enrolled in the study retrospectively, regardless of whether they had surgery or not. Patients without a formal histopathological diagnosis were excluded from the study.

The Pakistan Brain Tumour Consortium (PBTC) was established with at least one neurosurgical attending and one resident from each participating neurosurgical centre. The purpose of the group was to collect cases and establish future collaboration for an eventual national registry for brain tumours. 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.

Definitions: Patients lost-to-follow-up were defined as patients who had been diagnosed with the tumour with histopathological and radiological studies and then discontinued clinical follow-up at the institute where the first surgery was done at any point within two years from the initial visit.

Socioeconomic status was determined through patient employment status and profession. The Pakistan Bureau of Statistics supplement[11] was used to estimate the economic subset of the patients and categorize them into lower socioeconomic class (e.g. blue-collar workers, labourers, daily wagers), middle class (e.g. graduates, mid-level office workers, homeowners), and upper/upper-middle class (e.g. businessmen, landowners, politicians).

The WHO 2016 guidelines were used to classify tumour type, as those were the most recent guidelines available at the time of data collection.[12]

Centres were divided into high and low-volume centres based on their annual brain tumour surgery volume. High volume centres were those with up to 100 brain tumour surgeries per year, while low volume centres were those with less than 100 brain tumour surgeries per year.

Data analysis was carried out using the Statistical Package for the Social Sciences (SPSS) version 25 by IBM. Initially, the Shapiro-Wilk test was used to assess the normality of the data. For the normally distributed data, means with standard deviation were reported for continuous variables, and for non-normally distributed data, median and range were reported. In all cases $p < 0.005$ was considered significant.

Results

From a total of 2750 patients in our cohort, 77 (2.8%) were diagnosed with metastatic brain tumours. The median age of these patients was 52 (IQR= 43-60) years; 9 (14%)

Table-1: Demographic characteristics of patients.

Variables		N	Percentage (Within Group)
Age At Diagnosis (Median)		52	
Gender	Male	37	56.1%
	Female	39	59.1%
Time To Surgery In Days (Median)		21	
KPS Score Before Surgery (Median)		80	
Socioeconomic Status of Patient*	Lower Class	39	60.9%
	Middle Class	20	31.3%
	Upper Middle or Upper Class	5	7.8%
Marital Status of Patient	Unmarried	3	4%
	Married	62	82.7%
	Other	12	16%
Public Or Private Hospital	Public	41	53.2%
	Private	36	46.8%
Hospital Annual Patient Load	Up to 100	37	48.1%
	More than 100	40	51.9%
Total Patients Per Hospital (Median)		100	

*As defined in methods according to Pakistan Bureau of Statistics.[11]

Table-2: Treatment modalities.

Variables		N	Percentage
Surgery Type	CSF Diversion Only	2	2.6%
	Biopsy	20	26.0%
	Subtotal Resection	22	28.6%
	Gross Total Resection	24	31.2%
	Not specified	9	11.7%
Was chemotherapy done?	Yes	20	26.0%
	No	13	16.9%
	LTFU	44	57.1%
Was radiotherapy done?	Yes	31	40.3%
	No	9	11.7%
	LTFU	37	48.1%

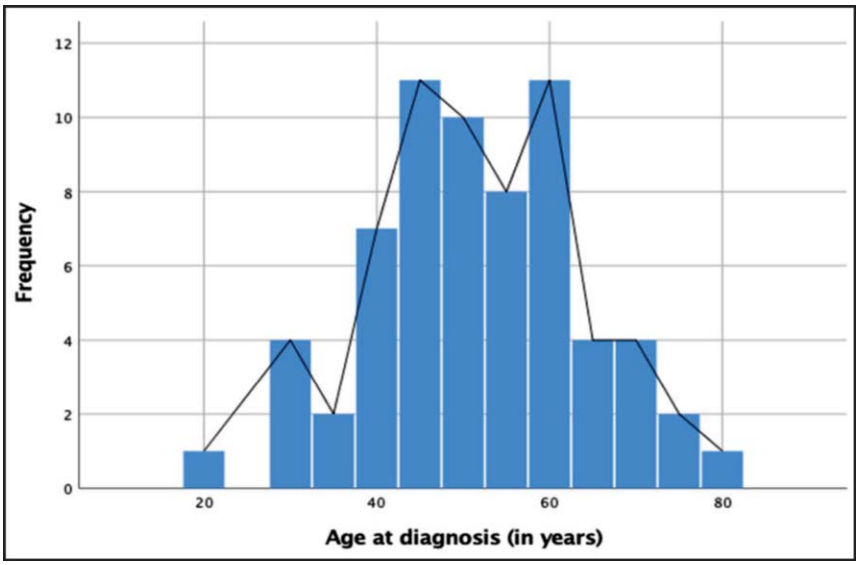

Figure-1: Age distribution of the patients presenting with metastatic brain lesions.

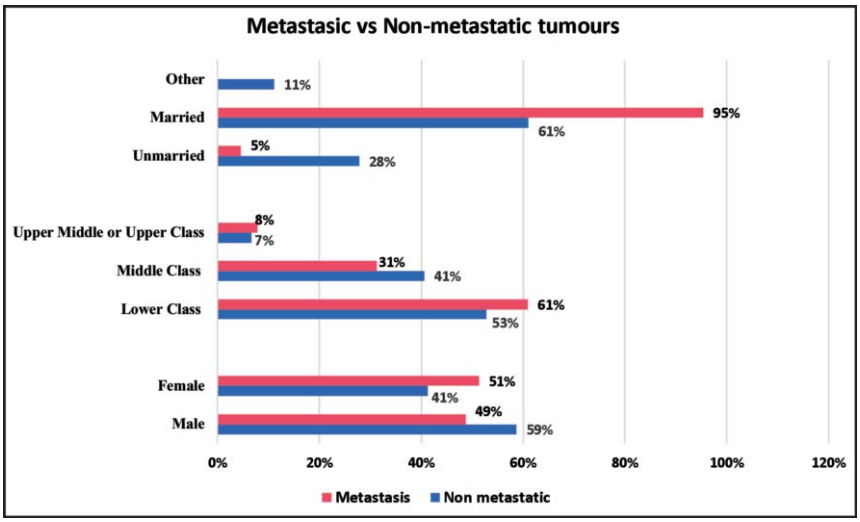

Figure-2: Metastatic lesion and non-metastatic lesion distribution by demographic groups.

Table-3: Patient outcomes.

Variable		N	Percentage
KPS Score Before And After Surgery (Median)		80	
Current Status	Alive	17	22.1%
	Deceased	17	22.1%
	Lost to follow up	43	55.8%

patients were aged 20-39 years, 37 (57%) were aged 40-59, and 19 (29%) were aged 60 and above. There were no patients aged below 20 with a metastatic brain lesion. The age distribution is illustrated in Figure-1.

In our cohort, 37(56.1%) patients were male, and 39(59.1%) were female. The median time to surgery was 21 (IQR= 3.5-64.5) days. Of the 77 patients, 39(60.9%) were from the lower socioeconomic class, 20 (31.3%) were from the middle socioeconomic class, and 5 (7.8%) were from the upper middle or upper socioeconomic class. In terms of marital status, 62 (82.7%) patients were married, 3 (4%) were unmarried, and 12 (16%) were either divorced, widowed, or preferred not to specify.

Our patients presented almost evenly to public and private centres at 41 (53.2%) and 36 (46.8%), respectively, and 37 (48.1%) presented to high volume centres with 40 (51.9%) presenting to low volume centres. The median surgical volume for all centres combined was 105 (IQR=78-149) cases. The demographic distribution of the patients is summarized in Table-1.

The distribution of metastatic vs non-metastatic lesions according to socio-demographics varied significantly in our cohort; we had more females than males in the metastatic group as opposed to more males than females in the non-metastatic group as well as in the overall data. Figure 2 illustrates the comparison of socioeconomic class between metastatic tumours and non-metastatic brain tumours in our cohort.

Of all the tumours, 10(56%) lesions were predominantly in the frontal lobe, 4 (22%) in the temporal lobe, 3(17%) in the parietal lobe, and one tumour was in the cerebellar region. These findings are illustrated in Figure-3. The primary site of these tumours was not specified for 13(16.9%) tumours. Of those with a confirmed primary cancer outside the cerebrum, 21 (27.3%) were breast cancers, 13 (16.9%) were lymphomas, 12 (15.6%) were lung cancers, 7 (9.1%) were renal tumours, 4 (5.2%) were colonic tumours, 2 (2.6%) were thyroid cancers, and there were one each of melanoma, multiple myeloma, and undifferentiated sarcoma. These findings are illustrated in Figure-4.

Most patients (n=75) underwent surgical intervention, with only two not receiving surgical therapy. Twenty-four patients underwent gross total resection, 22 received a subtotal resection, 20 were biopsied only, and 2 underwent a CSF diversion procedure. Nine patients were subjected to an unspecified surgical procedure. Of the 77

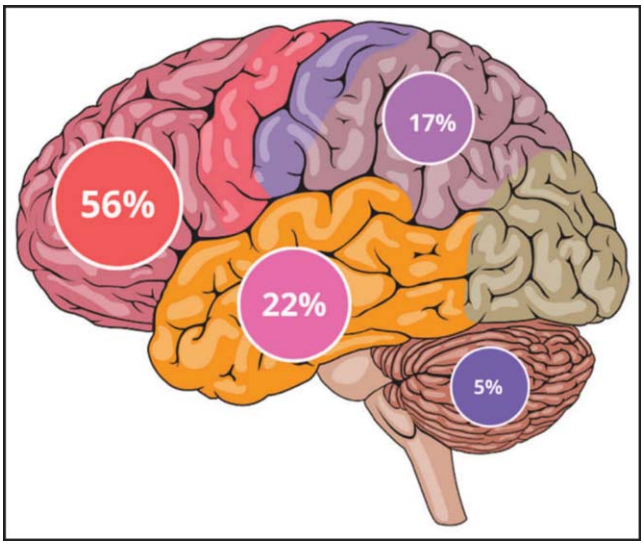

Figure-3: Distribution of metastatic lesion according to lobe.[13]

patients, 20 received chemotherapy, 13 did not, and 44 were lost to follow-up. From the radiotherapy cohort, 31 patients received radiotherapy, nine did not, and 37 were lost to follow-up. These figures and their respective percentages are summarized in Table-2.

The median KPS scores pre- and post-surgery were 80 (IQR= 60-90, 70-90 respectively), and 43 (55.8%) patients were lost to follow-up. The mortality rate amongst patients with known outcomes was 17 (50%) patients at one year follow-up, with 17 alive at the end of the study period. The 30-day mortality rate amongst our patients (with known outcomes) was 4 (11.8%); thus, 4 (23.5%) of all patients that were confirmed to be deceased had died within 30 days of surgery. Table-3 shows the Mean KPS score after surgery and the mortality rate among our patients.

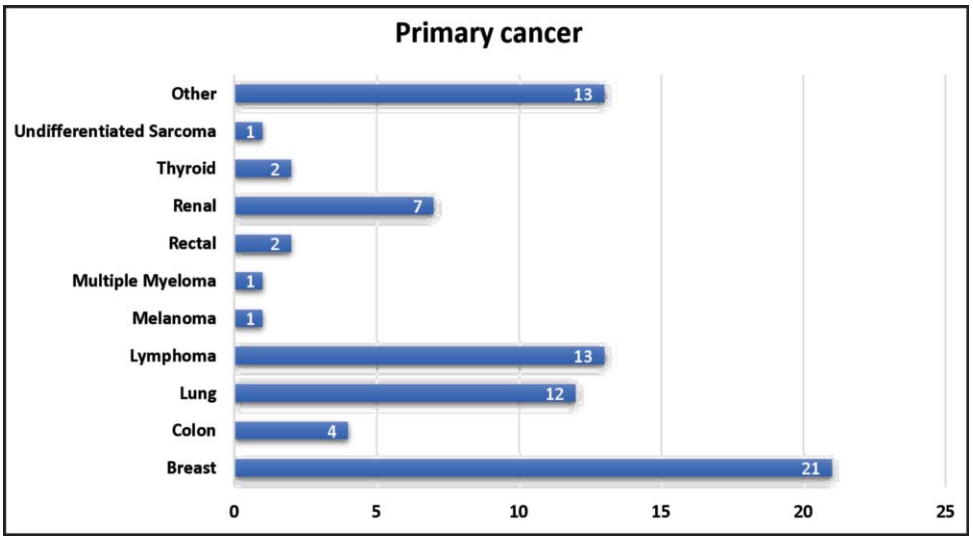

Figure-4: Primary cancer types for brain metastases.

Discussion

Amongst all the brain tumours in our cohort, 2.8% were diagnosed with metastatic brain lesions. While it is not known which proportion of patients with metastases present to neurosurgical practice, international data shows that more than half of all brain tumours (51% or more) are usually metastatic lesions.[10,14] Ahmed et al. reported that in their study on patients from a single tertiary centre, they found that 10.27% of their cohort had metastatic brain lesions, a finding corroborated by Kashif et al.[15,16] However, both studies were on patients with specific tumour types (breast and hepatocellular cancers) and were not representative of all metastatic tumours. Our data showed that only a very small portion of these patients present to neurosurgical practice, which may impair their treatment options. Several reasons for this may include lower referral to neurosurgical practice due to patients being moved towards end-of-life care, decreased overall survival for most cancers compared to high-income countries, and a lower number of patients being diagnosed with a metastatic lesion due to scarcity of resources.[9,17-19] The socioeconomic status of our patients shows that almost 70% were from the lower socioeconomic class, which may also factor into the presentation rate. Since our patients all received surgical therapy, it might also be preferential reporting of cases that were surgically viable from our participating centres.

There is no difference in incidence between the different genders internationally, and our data also reflect an almost equal distribution of metastases amongst males and females.[2,5,8,20] There is little to no data currently available corresponding to the marital status and socioeconomic class in brain metastases; our data shows that a majority of our patients were married, which corresponds to the age distribution since most of our patients were adults and due to sociocultural norms cohabitation is less common without marriage than in western states.[21,22] It also raises the question of economic responsibilities as married people, in general, have greater economic ties than unmarried people and thus may choose to forego care to

extend life and instead focus on quality of life with palliation.

Brain metastases occur in 10% to 30% of adults with systemic malignancies but only in 6% to 10 % of children internationally.[2,5] In our population, we had no paediatric cases; only adults aged 20 and above presented with brain metastases. The median age of incidence was 52, and more than half of our patients were in the 40-59-year age group. The average age at presentation of patients with the primary lesions reported is generally higher, which corresponds with the average age in our group.[9,17-19]

In our cohort, the most common primary tumour was breast cancer (27.3%), followed by lymphoma and then lung cancer. We had 2 cases of rectal cancer and 1 of melanoma which is generally ubiquitous in literature. The most common primary brain tumours internationally are cancers of the lung, breast, kidney, colorectal region, and melanoma.[23,24] Breast cancer-related brain metastases has an incidence of 16-20%, renal cell carcinoma has the second highest incidence at 7-10%, and melanoma at 7%. Spread is usually haematogenous, and thus, watershed areas and junctions of grey and white matter in the cerebrum are common locations of metastasis due to narrow arteries. The blood flow and relative weight can be good predictors of the frequency of metastasis; cerebral hemispheres have 80% of brain metastases, 15% are in the cerebellum, and 5% are in the brainstem.[10,14] The type of tumour may also show a predilection for certain areas, with pelvic, gastrointestinal, and breast tumours metastasizing more commonly to the posterior fossa. In our case, the number of cases was not sufficient to definitively comment on the distribution of metastatic lesions according to location for each type of original cancer.

Patients with a single metastatic lesion can be treated with either surgery or stereotactic radiosurgery combined with whole brain radiation therapy (WBRT).[3] Solitary lesions with quiescent primary disease, symptomatic lesions, radiotherapy resistance, and good accessibility are preferred for surgical resection. Patients with systemic disease progression, newly diagnosed cancer, and significant neurological deficits are generally deferred to other treatment modalities. For patients with multiple metastases, surgery is less common, although it may still be considered for those with one symptomatic accessible region (for palliative reasons), multiple resectable lesions or no identifiable primary cancer (biopsy).

Most patients on presentation have more than one metastatic lesion, and treatment is generally whole brain radiation therapy (WBRT). However, the benefit of WBRT must be weighed against likely neurocognitive side effects leading to poor functionality, due to which some may prefer steroid therapy alone. The role of chemotherapy is currently restricted to salvage and experimental treatment. These patients require an interdisciplinary team with an oncologist, palliative care specialist, neurosurgeon, neurologist, pain consultant, and radiation therapist. Due to limited life expectancy and generally poor physical condition, aggressive treatment is not sought; rather, quality of life and pain control is generally prioritized.[7] The general life expectancy amongst untreated patients is one month, two months with steroids alone, and 3-6 months for steroids with WBRT.

Almost all our patients underwent surgical therapy, which generally has the highest performance outcomes when compared with other surgical modalities such as WBRT. This is likely due to our selection criteria which had targeted the major surgical centres within the country with dedicated neurosurgical facilities. Thirty-one patients received radiotherapy, and 20 patients also received chemotherapy. Chemotherapy is not currently recommended for metastatic lesions, and it is unclear whether the chemotherapy was targeted toward the brain lesion or primary cancer in our cohort. For radiotherapy, options generally include stereotactic radiosurgery and whole brain radiotherapy (WBRT). WBRT is generally used in patients with poor KPS or larger metastatic load, it has more debilitating neurocognitive effects, and recent studies suggest that steroid therapy might be as efficacious without the side effect profile.[25,26]

Out of 77 patients, survival data were not available for 55.8% of the cohort. The remaining patients were equally divided (n=17) amongst the deceased and alive groups at the end of our study (December 31 2019). 11.8% of our patients with metastases had died within 30 days of surgery, much higher as compared to non-metastatic brain tumours, for which the 30-day mortality was 4.5%. In general, the effectiveness of any treatment for brain metastases is determined by control of the primary cancer. Several scales exist for graded prognostic assessment, which measure median survival (typically less than two years).[27] There is a clear survival benefit in patients receiving surgery or stereotactic radiosurgery combined with WBRT.[28,29] Greater care needs to be taken to track patients with brain metastases and ensure that they receive a neurosurgical evaluation as part of standard treatment, which current data suggests is not being done.

Conclusion

The number of patients presenting to neurosurgical care with brain metastases is much lower than the expected incidence of metastatic brain lesions. All the patients were adults, peaking around the mid-50's age, and a large number were reported to receive chemotherapy which is concerning if done for metastatic tumours. Half of the patients with known follow-up died within the year despite receiving surgical intervention, and the 30-day mortality rate was more than twice that of non-metastatic brain tumours. Multidisciplinary integration in care and strengthening follow-up is the first step in ensuring better care for these patients.

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Conflict of Interest: None to declare.

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