Predictors of Survival in Patients with Metastatic Brain Tumors: Experience from a Low-to-Middle-Income Country

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Abstract

Objective The interplay of static factors and their effect on metastatic brain tumor survival, especially in low-to-middle-income countries (LMICs), has been rarely studied. To audit our experience, and explore novel survival predictors, we performed a retrospective analysis of brain metastases (BM) patients at Shaukat Khanum Memorial Cancer Hospital (SKMCH), Pakistan.

Materials and Methods A retrospective review was conducted of consecutive patients who presented with BM between September 2014 and September 2019 at SKMCH. Patients with incomplete records were excluded.

Statistical Analysis SPSS (v.25 IBM, Armonk, New York, United States) was used to collect and analyze data via Cox-Regression and Kaplan–Meier curves.

Results One-hundred patients (mean age 45.89 years) with confirmed BM were studied. Breast cancer was the commonest primary tumor. Median overall survival (OS) was 6.7 months, while the median progression-free survival (PFS) was 6 months. Age ($p = 0.001$), gender ($p = 0.002$), Eastern Cooperative Oncology Group ($p < 0.05$), anatomical site ($p = 0.002$), herniation ($p < 0.05$), midline shift ($p = 0.002$), treatment strategies ($p < 0.05$), and postoperative complications ($p < 0.05$) significantly impacted OS, with significantly poor prognosis seen with extremes of age, male gender (hazard ratio [HR]: 2.0; 95% confidence interval [CI]: 1.3–3.1; $p = 0.003$), leptomeningeal lesions (HR: 5.7; 95% CI: 1.1–29.7; $p = 0.037$), and patients presenting with uncal herniation (HR: 3.5; 95% CI: 1.9–6.3; $p < 0.05$). Frontal lobe lesions had a significantly better OS (HR: 0.5; 95% CI: 0.2–1.0; $p = 0.049$) and PFS (HR: 0.08; 95% CI: 0.02–0.42; $p = 0.003$).

Conclusion BM has grim prognoses, with comparable survival indices between developed countries and LMICs. Early identification of both primary malignancy and metastatic lesions, followed by judicious management, is likely to significantly improve survival.

Keywords
- metastatic brain tumors
- brain metastasis
- management strategies
- overall survival
- progression-free survival

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Introduction

Metastases to the brain constitute one-third of all brain tumors and are construed as the most fearful complication of systemic malignancies.[1] Solid primary malignancies metastasize to the brain at some point in their lives in about 15 to 40% of the patients, with the incidence reported to range from 100,000 to 300,000 patients per year.[2,3] A history of poor prognoses and high mortality dictates their management recommendations. In the past, few landmark studies have sought to evaluate prognostic systems and their clinical applicability. In 1997, Gaspar et al developed three prognostic classes for brain metastases (BM) using the recursive partitioning analysis. These constituted Karnofsky Performance Status, primary tumor status, presence of extracranial metastases, and age.[4] This was later upgraded to the Graded Prognostic Assessment, where the "number of brain metastases" replaced "primary tumor status" as a valid prognostic predictor.[5]

Existing literature is usually noted to either evaluate the aforementioned prognostic models or different management strategies, for prognoses and overall survival (OS).[6–9] However, the interplay of several other static factors such as tumor location, radiologic heterogeneity between patients, postoperative complications, and their effect on the survival outcomes is yet to be studied. Moreover, only limited data from a few centers exist on evaluating the effect of these prognostic models on recurrence or progression of metastatic brain tumors.[10]

Herein, we report our experience with the patients presenting with BM to our center. Our aim is to understand survival trends in metastatic brain tumor patients and the impact of multiple factors on our patient population. This will allow us to assess the quality of metastatic brain tumor care provided by our institution within the context of being in a state with poor health metrics and outcomes.

Materials and Methods

Study Design and Patient Selection

This is a retrospective review of patients from a combined neurosurgical/radiation oncological patient population; all patients were treated with either surgery, radiation, or both, except three patients who did not undergo any treatment at all. Data was collected from the largest cancer hospital in Pakistan, the Shaukat Khanum Memorial Cancer Hospital, Lahore. The cases included in the present study encompassed all consecutive patients who presented to our center with metastatic brain tumors, from September 2014 till September 2019. Patients who had already been treated at an outside facility and had only presented for a second opinion or those with missing or incomplete records were excluded.

Data Collection

Data was collected using a self-designed proforma after reviewing the literature. Variables recorded included patient demographics—gender, age, primary malignancy type, Eastern Cooperative Oncology Group performance score (ECOG), presence of extracranial metastases, and brain metastases free interval (BMFI); radiological characteristics—side, lobe involved, tentorial location, ventricular involvement (if any), tumor location, number of intracranial metastasis, size of metastasis, and the presence of herniation, edema, midline shift and postoperative hydrocephalus; treatment type—surgery, radiation, or both; and survival data—OS, and progression-free survival (PFS). Time intervals were calculated as follows: BMFI as the time between diagnosis of primary tumor and first BM; PFS as the time from first surgery, or first radiation if the surgery was not contemplated, till tumor recurrence, or progression of residual disease; and OS as the time of first diagnosis of BM to death or censorship. Patients were censored at their date of death if available, or otherwise at date of last encounter before September 1, 2019.

Statistical Analysis

Data were entered and analyzed and visualized using IBM SPSS (v.23). Categorical variables were expressed as numbers and percentages. Continuous variables were reported using mean, median, and standard deviation. Variables were cross-tabulated to obtain the mean and median survival outcomes. Univariate survival analyses were performed using the Cox proportional hazards model and Kaplan–Meier method. Variables were cross-tabulated for survival rates between groups, and the log-rank test was used to determine statistical significance of the variables' impact on survival indices: OS and PFS. Finally, the Kaplan–Meier curves were used to visualize cumulative survival and hazard differences between groups. All levels of significance were set at p-value less than 0.05, at a confidence level of 95%.

The study was approved by the institutional review board (IRB) at our institution. Patient consent was not required as this was a retrospective chart review, and no patient identifiers were disclosed.

Results

Patient Characteristics

A total of 142 patients were identified. Twenty-two patients were excluded because they presented for a second opinion after being treated once already at another facility, and an additional 20 patients had insufficient data available for our analysis. The final analysis was performed on 100 patients. ►**Table 1** shows the baseline clinical and demographic characteristics of the patients. There were 38 (38%) males and 62 (62%) females enrolled in our study. The mean age was 45.89 years at the diagnosis of primary tumor. The most common primary malignancy was breast cancer (49%; $n = 49$), followed by colorectal cancer in 11 patients (11%). Most patients presented with the ECOG performance score of 1 ($n = 37$; 37%). Mean BMFI was 21.4 months, with a median of 17.8 months. Radiological characteristics are summarized in ►**Table 2**. In 62 patients (62%), extracranial metastases were present at the time of the diagnosis of BM. Sixty-nine patients (69%) presented with a single metastatic lesion, most commonly solid in consistency ($n = 54$; 54%) and with a mean size of 41.89 mm ($\pm$14.24 mm). Ninety-six lesions (96%) were

Table 1 Patient demographics and clinical characteristics, and their association with survival

Overall survival							Progression-free survival				
			Log-rank test	Cox Regression univariate analysis				Log-rank test	Cox Regression univariate analysis	
	Frequency ($n = 100$)	Mean | median (mo)		*p*-Value	HR (95% CI)	*p*-Value	Mean | median (mo)		*p*-Value	HR (95% CI)	*p*-Value
Age				= 0.001					< 0.05		
< 18 y	1	0.50	0.50		0.56 (0.03–9.7)	= 0.694	0.50	0.50		0.49 (0.03–8.60)	= 0.628
18–49 y	54	9.09	6.15		0.04 (0.004–0.38)	= 0.005	8.36	5.85		0.039 (0.004–0.35)	= 0.004
50–64 y	44	13.2	9.25		0.03 (0.003–0.27)	= 0.002	11.9	6.50		0.034 (0.004–0.31)	= 0.003
> 64 y	1	0.30	0.30		Reference		0.30	0.30		Reference	
Gender				= 0.002					= 0.167		
Male	38	7.28	4.98		2.0 (1.3–3.1)	= 0.003	6.0	4.33		1.7 (0.7–3.8)	= 0.174
Female	62	12.8	11.2		Reference		12.1	8.05		Reference	
Primary cancer				= 0.176					= 0.787		
Breast	49	12.3	8.00		1.1 (0.6–1.9)	= 0.202	11.5	7.30		1.01 (0.4–2.3)	= 0.977
Testicular	11	5.99	3.00		2.2 (1.0–4.7)	= 0.809	5.95	3.00		1.08 (0.2–5.2)	= 0.915
Colorectal	7	6.25	4.10		1.4 (0.5–4.1)	= 0.055	6.19	3.70		0.69 (0.1–5.6)	= 0.731
Lung	2	5.85	5.85		2.5 (0.6–10.9)	= 0.580	5.85	5.85		0.00	= 0.991
Prostate	7	6.73	5.80		2.1 (0.9–5.1)	= 0.225	6.72	5.80		0.00	= 0.98
Others	24	12.3	10.0		Reference		10.3	6.05		Reference	
ECOG				< 0.05					= 0.015		
0	13	28.1	25.0		0.01 (0.001–0.07)	< 0.05	26.9	25.0			= 0.055
1	37	10.0	9.50		0.17 (0.09–0.34)	< 0.05	9.33	6.00		0.1 (0.01–2.17)	= 0.155
2	17	11.5	11.3		0.23 (0.10–0.48)	< 0.05	8.68	8.00		0.8 (0.1–6.7)	= 0.860
3	18	5.39	4.42		0.52 (0.26–1.03)	= 0.061	5.30	3.88		2.2 (0.3–17.0)	= 0.463
4	15	2.77	1.50		Reference		2.75	1.50		Reference	
Extracranial metastases				= 0.101					= 0.245		
1	24	9.88	11.3		1.48 (0.8–2.7)	= 0.209	8.74	8.10		1.3 (0.7–2.3)	= 0.442
2	27	7.79	5.70		1.94 (1.1–3.4)	= 0.029	7.21	5.40		1.7 (0.9–3.2)	= 0.092
Multiple	11	8.44	5.25		2.0 (0.98–4.17)	= 0.057	8.42	5.00		1.9 (0.9–4.1)	= 0.099
None	38	14.0	7.40		Reference		12.7	6.00		Reference	

(*Continued*)

Table 1 (*Continued*)

Overall survival						Progression-free survival					
			Log-rank test	Cox Regression univariate analysis			Log-rank test	Cox Regression univariate analysis			
	Frequency ($n = 100$)	Mean | median (mo)		HR (95% CI)	*p*-Value	Mean | median (mo)		HR (95% CI)	*p*-Value		
BMFI			= 0.843				= 0.674				
< 18 months	52	10.6	8.25	1.1 (0.2–8.2)	= 0.910	9.83	6.05	0.37 (0.04–2.91)	= 0.346		
18–2 y	18	15.0	8.50	1.0 (0.1–7.6)	= 0.994	13.5	6.15	0.27 (0.03–2.47)	= 0.244		
> 2–4 y	25	8.51	3.25	1.3 (0.2–9.8)	= 0.802	7.57	3.25	0.41 (0.05–3.60)	= 0.427		
> 4–6 y	3	8.00	0.50	1.9 (0.2–18.6)	= 0.579	8.00	0.50	0.00	= 0.979		
> 6 y	2	6.38	6.38	Reference		6.25	6.25	Reference			

Abbreviations: BMFI, brain metastasis free interval; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

extraventricular, mostly right sided ($n = 46$; 46%) and involving the frontal lobe ($n = 28$; 28%). Anatomically, 61 lesions (61%) were present on the gray–white junction, followed by 19 (19%) dural-based lesions. Forty-three patients (43%) presented with brain herniation, most commonly of the tonsillar type ($n = 18$; 18%). Midline shift was observed in 44 patients (44%), with a mean midline shift of 4.36 mm ± 5.82 mm. The largest midline shift of 17 mm was observed in four patients. Ninety-two patients (92%) had perilesional edema on neuroimaging at presentation.

►**Table 3** summarizes the management and postmanagement course of the patients. Forty-nine people (49%) underwent both surgery and radiation, while three people (3%) received no treatment. Twenty-two patients developed postoperative hydrocephalus, followed by hemorrhage as the commonest postoperative complication ($n = 8$; 8%). Progression or recurrence was observed in 27 patients (27%), with 77 patients (77%) dead at the time of censorship.

Survival Analysis

Kaplan–Meier analysis determined the impact of variables on survival indices (OS and PFS). The results generated by the log-rank test, as well as the mean and median survival times are listed in ►**Tables 1–3**. The mean/median OS and PFS were 10.7/6.7 months and 9.8/6 months, respectively. Three people had the longest OS of 59 months, which was also the longest PFS these patients. Age was associated with an essentially longer OS and PFS ($p = 0.001$ and $p < 0.05$, respectively), where of all age groups, middle age (50–64 years) had a longer mean survival of 13.2/9.25 and 11.9/6.50 months, respectively. Gender significantly affected the OS ($p = 0.002$), with males having a lesser mean/median OS of 7.28/4.98 months. People with breast cancer had a longer mean/median OS and PFS of 12.3/8 and 11.5/7.3 months, compared to the rest of the group. Type of primary malignancy, however, did not significantly affect the OS and PFS ($p = 0.176$; $p = 0.787$, respectively). Patients who presented with the ECOG performance score of 0 had the greatest mean/median OS and PFS of 28.1/25 and 26.9/25 months. This was versus a mean/median OS and PFS of only 2.77/1.50 and 2.75/1.50 months in patients with ECOG 4, with ECOG as a significant predictor of both the survival indices (OS: $p < 0.05$; PFS: $p = 0.015$). While the absence of extracranial metastases resulted in a longer mean OS of 14 months, it did not significantly impact survival ($p = 0.101$). Anatomic location of the lesions significantly impacted survival (OS: $p = 0.002$; PFS: $p = 0.03$), where leptomeningeal lesions had the worst mean/median OS and PFS of 1.84/1.30 and 1.79/1.30 months in both, respectively. Lobar location of the lesion also played a vital role in PFS of the patient ($p = 0.001$).

Significant impact of brain herniation at presentation was observed on OS ($p < 0.05$). Patients who did not present with herniation had a higher mean/median OS of 14.2/12.0 months as compared to those who did, with the worst OS observed in patients with tonsillar herniation (mean: 5.3 months; median: 3.75 months). Midline shift was associated

Table 2 Radiological characteristics and their association with survival

	Overall survival					Progression-free survival				
			Log-rank test	Cox Regression univariate analysis			Log-rank test	Cox Regression univariate analysis		
	Frequency ($n = 100$)	Mean | median (mo)		*p*-Value	HR (95% CI)	*p*-Value	Mean | median (mo)		*p*-Value	HR (95% CI)	*p*-Value
No. of BM				= 0.118					= 0.074		
1	69	11.6	7.50		0.6 (0.3–1.0)	= 0.046	10.8	6.10		0.37 (0.15–0.90)	= 0.029
2	14	9.28	8.80		0.8 (0.4–1.7)	= 0.559	8.40	7.75		0.60 (0.19–1.90)	= 0.394
Multiple	17	8.17	5.60		Reference		6.71	3.60		Reference	
Size of BM				= 0.543					= 0.596		
10–30 mm	24	9.07	6.00		0.73 (0.3–1.5)	= 0.422	8.23	5.55		1.3 (0.4–5.1)	= 0.658
> 30–40 mm	25	8.96	6.20		0.66 (0.3–1.4)	= 0.291	8.44	5.70		0.9 (0.2–3.5)	= 0.850
> 40–50 mm	25	9.78	5.80		0.76 (0.4–1.6)	= 0.470	8.99	5.00		0.8 (0.2–3.3)	= 0.790
> 50–60 mm	16	18.3	10.1		0.48 (0.2–1.1)	= 0.097	16.7	7.15		0.5 (0.1–2.3)	= 0.363
> 60–70 mm	10	9.2	7.00		Reference		7.06	4.50		Reference	
Tumor consistency				= 0.094					= 0.401		
Solid	54	8.52	5.65		0.9 (0.4–1.8)	= 0.746	7.98	5.00		0.98 (0.21–4.39)	= 0.975
Cystic	13	10.64	11.2		0.7 (0.3–1.6)	= 0.350	9.36	8.10		1.78 (0.37–8.58)	= 0.474
Solid-cum-cystic	21	18.43	12.0		0.4 (0.2–1.0)	= 0.044	17.4	11.0		0.71 (0.14–3.61)	= 0.688
Hemorrhagic	12	7.10	3.43		Reference		5.10	3.43		Reference	
Side				= 0.08					= 0.254		
Right	46	8.94	6.20		0.6 (0.4–1.1)	= 0.096	7.99	5.35		0.53 (0.20–1.41)	= 0.208
Left	34	14.8	11.3		0.5 (0.3–0.9)	= 0.016	14.2	10.9		0.46 (0.17–1.22)	= 0.119
Both	20	7.73	5.30		Reference		6.49	4.30		Reference	
Lobe involved				= 0.075					= 0.001		
Frontal	29	15.3	7.00		0.5 (0.2–1.0)	= 0.049	15.0	6.10		0.08 (0.02–0.42)	= 0.003
Parietal	24	9.39	8.45		0.8 (0.4–1.6)	= 0.516	7.18	5.55		0.94 (0.35–2.55)	= 0.908
Occipital	5	4.83	1.90		1.6 (0.6–4.5)	= 0.380	3.43	1.90		1.29 (0.15–11.04)	= 0.815
Temporal	5	10.9	13.1		0.6 (0.2–1.8)	= 0.368	10.9	13.1		0.00	= 0.981
Cerebellum	23	9.62	8.00		0.5 (0.2–1.0)	= 0.066	9.12	7.50		0.42 (0.13–1.34)	= 0.142
Cerebellar frontal	14	7.24	5.40		Reference		6.41	5.40		Reference	
Anatomic site				= 0.002					= 0.310		

(*Continued*)

Table 2 (*Continued*)

		Overall survival					Progression-free survival				
				Log-rank test	Cox Regression univariate analysis				Log-rank test	Cox Regression univariate analysis	
	Frequency ($n = 100$)	Mean | median (mo)		*p*-Value	HR (95% CI)	*p*-Value	Mean | median (mo)		*p*-Value	HR (95% CI)	*p*-Value
Dural based	19	9.67	9.00		0.9 (0.2–4.1)	= 0.902	8.34	7.50		1.0 (0.2–4.6)	0.953
Cortical	6	10.6	10.7		1.1 (0.2–5.5)	= 0.944	9.36	7.15		0.88 (0.16–4.86)	0.884
Gray–white junction	61	11.7	6.20		1.0 (0.3–4.3)	= 0.951	10.9	6.00		0.85 (0.2–3.5)	0.824
Deep	6	12.3	9.20		1.2 (0.2-6.1)	= 0.809	10.3	7.40		0.6 (0.1–3.3)	0.517
Leptomeningeal	6	1.84	1.30		5.7 (1.1–29.7)	= 0.037	1.79	1.30		3.9 (0.7–21.1)	0.112
Calvarial	2	13.2	13.2		Reference		13.2	13.2		Reference	
Tentorial location				= 0.221					= 0.121		
Supratentorial	61	12.1	7.00		0.6 (0.3–1.2)	= 0.170	10.9	6.00		0.37 (0.14–1.00)	= 0.049
Infratentorial	25	9.34	8.00		0.5 (0.3–1.1)	= 0.103	8.88	7.50		0.48 (0.16–1.45)	= 0.196
Both	14	7.24	5.40		Reference		6.41	5.40		Reference	
Ventricular involvement				= 0.410					= 0.261		= 0.399
Intraventricular	3	8.91	6.40		0.40 (0.04–3.95)	= 0.435	7.70	5.00		0.2 (0.01–2.76)	= 0.213
Extraventricular	96	10.84	7.15		0.30 (0.04–2.24)	= 0.243	9.93	6.00		0.3 (0.04–2.39)	= 0.269
Both	1	2.50	2.50		Reference		2.50	2.50		Reference	
Herniation				< 0.05					= 0.173		
Tonsillar	18	5.27	3.75		3.1 (1.6–5.7)	< 0.05	4.65	2.90		2.6 (0.9–7.3)	= 0.064
Subfalcine	17	6.37	1.90		3.0 (1.3–6.9)	= 0.008	5.88	1.90		2.0 (0.4–8.7)	= 0.371
Uncal	8	6.91	2.20		3.5 (1.9–6.3)	< 0.05	6.56	2.20		2.2 (0.7–6.6)	= 0.169
None	57	14.2	12.0		Reference		13.0	9.30		Reference	
Midline shift				= 0.002					= 0.071		
Yes	44	7.78	4.53		2.1 (1.3–3.3)	= 0.001	7.00	4.33		1.98 (0.93–4.24)	= 0.078
No	56	13.0	11.3		Reference		12.0	8.50		Reference	
Edema				= 0.366					= 0.841		
Yes	92	10.9	6.25		1.6 (0.6–4.4)	= 0.354	9.90	12.2		1.15 (0.27–4.90)	= 0.842
No	8	8.95	7.40		Reference		8.52	4.99		Reference	

Abbreviations: BM, brain metastasis; CI, confidence interval; HR, hazard ratio.

Table 3 Association of survival with treatment modalities and postoperative complications

		Overall survival					Progression-free survival				
				Log-rank test	Cox Regression univariate analysis				Log-rank test	Cox Regression univariate analysis	
	Frequency ($n=100$)	Mean | median (mo)		*p*-Value	HR (95% CI)	*p*-Value	Mean | median (mo)		*p*-Value	HR (95% CI)	*p*-Value
Treatment type				< 0.05					< 0.05		
Surgery	19	3.26	0.80		0.40 (0.1–1.4)	$= 0.155$	2.81	0.80		0.4 (0.1–1.5)	$= 0.18$
Radiation	29	9.03	6.40		0.13 (0.03–0.46)	$= 0.002$	8.12	5.70		0.1 (0.04–0.47)	$= 0.002$
Both	49	15.2	11.4		0.07 (0.02–0.23)	< 0.05	14.0	9.50		0.07 (0.02–0.25)	< 0.05
None	3	1.08	0.50		Reference		1.07	0.50		Reference	
Postoperative hydrocephalus				$= 0.004$					$= 0.706$		
No	78	12.2	9.25		0.5 (0.3–0.8)	$= 0.005$	11.0	6.20		0.8 (0.3–2.4)	$= 0.708$
Yes	22	5.58	2.50		Reference		5.35	2.50		Reference	
Complications				< 0.05					< 0.05		
Hemorrhage	8	7.61	9.00		1.8 (0.9–3.9)	$= 0.115$	7.51	8.75		1.5 (0.7–3.7)	0.324
Cognitive decline	6	9.87	11.3		1.2 (0.5–3.1)	$= 0.669$	8.81	8.10		1.0 (0.4–3.0)	0.890
Cerebral edema	2	2.50	2.50		3.9 (0.9–17.0)	$= 0.063$	2.50	2.50		3.7 (0.9–15.7)	0.080
Shunt malfunction	1	0.30	0.30		29.5 (3.3–266.6)	$= 0.003$	0.30	0.30		28.2 (3.1–255.4)	0.003
Others	16	7.86	4.67		1.4 (0.8–2.7)	$= 0.273$	7.06	4.35		1.4 (0.7–3.6)	0.370
None	67	12.2	7.50		Reference		11.1	6.00		Reference	
Recurrence/progression				$= 0.986$					N/A		
Yes	27	11.9	11.4		1.0 (0.6-1.6)	$= 0.986$	N/A	N/A		N/A	N/A
No	73	10.3	5.7		Reference		N/A	N/A		N/A	N/A

Abbreviations: CI, confidence interval; HR, hazard ratio; N/A, not available.

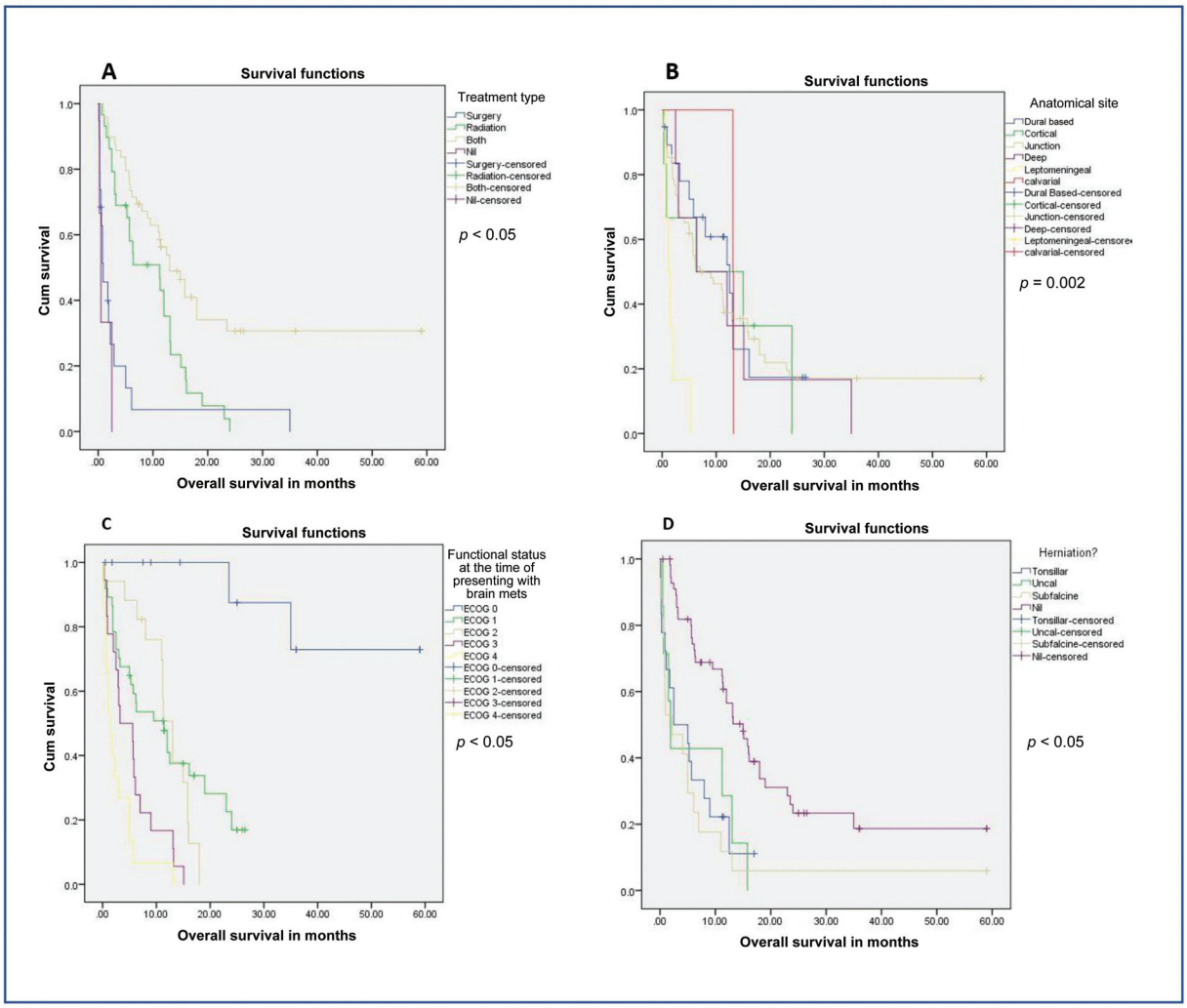

Fig. 1 Kaplan–Meier curves for overall survival; (**A**) treatment type; (**B**) anatomical site; (**C**) Eastern Cooperative Oncology Group (ECOG) functional status at the time of presentation; (**D**) brain herniation.

with significantly decreased mean OS ($p = 0.002$; 7.78 vs. 13 months in patients with no midline shift). Treatment strategies played an essential role in OS and PFS ($p < 0.05$ in both, respectively). Patients who underwent adjuvant therapy with radiation after surgery tended to live longer (-mean/median OS: 15.2/11.4 months) and without recurrence (mean/median PFS: 14/9.5 months) than those undergoing other management strategies. Postoperative hydrocephalus ($p = 0.004$) and other complications ($p < 0.05$) were also statistically significant predictors for OS. BMFI, number of BM, tumor consistency, and tumor locations other than the anatomic type did not significantly impact survival indices. ►**Fig. 1** shows the survival curves for OS. ►**Fig. 2** shows the hazard function curves for PFS.

Cox Proportional Univariate Analyses

The hazard ratios for OS and PFS according to all variables in the univariate Cox proportional hazard model are listed in ►**Tables 1–3**. Favorable prognostic models for OS included the age group of 50 to 64 years (hazard ratio [HR]: 0.03; 95% confidence interval [CI]: 0.003–0.270; $p = 0.002$), ECOG 0 (HR: 0.01; 95% CI: 0.001–0.07; $p < 0.05$), presence of a single metastatic brain lesion (HR: 0.6; 95% CI: 0.3–1.0; $p = 0.046$), solid-cum-cystic tumor consistency (HR: 0.4; 95% CI: 0.2–1.0; $p = 0.044$), frontal lobe lesions (HR: 0.5; 95% CI: 0.2–1.0; $p = 0.049$), left-sided lesions (HR: 0.5, 95% CI: 0.3–0.9; $p = 0.016$), adjuvant therapy (HR: 0.07; 95% CI: 0.02–0.23; $p < 0.05$), and absence of postoperative hydrocephalus (HR: 0.5; 95% CI: 0.3–0.8; $p = 0.005$). Significantly poor prognostic factors for OS included male gender (HR: 2.0; 95% CI: 1.3–3.1; $p = 0.003$), presence of 2 extracranial metastatic lesions (HR: 1.94; 95% CI: 1.1–3.4; $p = 0.029$), leptomeningeal lesions (HR: 5.7; 95% CI: 1.1–29.7; $p = 0.037$), uncal herniation at presentation (HR: 3.5; 95% CI: 1.9–6.3; $p < 0.05$), and postoperative shunt malfunction (HR: 29.5; 95% CI: 3.3–266.6; $p = 0.003$). Factors that were essentially associated with PFS were the age group of 50 to 64 years (HR: 0.034; 95% CI: 0.004–0.310; $p = 0.003$), single metastatic lesion (HR: 0.37; 95% CI: 0.15–0.90; $p = 0.029$), lesions of the frontal lobe (HR: 0.08; 95% CI: 0.02–0.42; $p = 0.003$), supratentorial location (HR: 0.37; 95% CI: 0.14–1.00; $p = 0.049$), adjuvant radiation (HR: 0.07; 95% CI: 0.02–0.25; $p < 0.05$), and postoperative shunt malfunction (HR: 28.2; 95% CI: 3.1–255.4; $p = 0.003$).

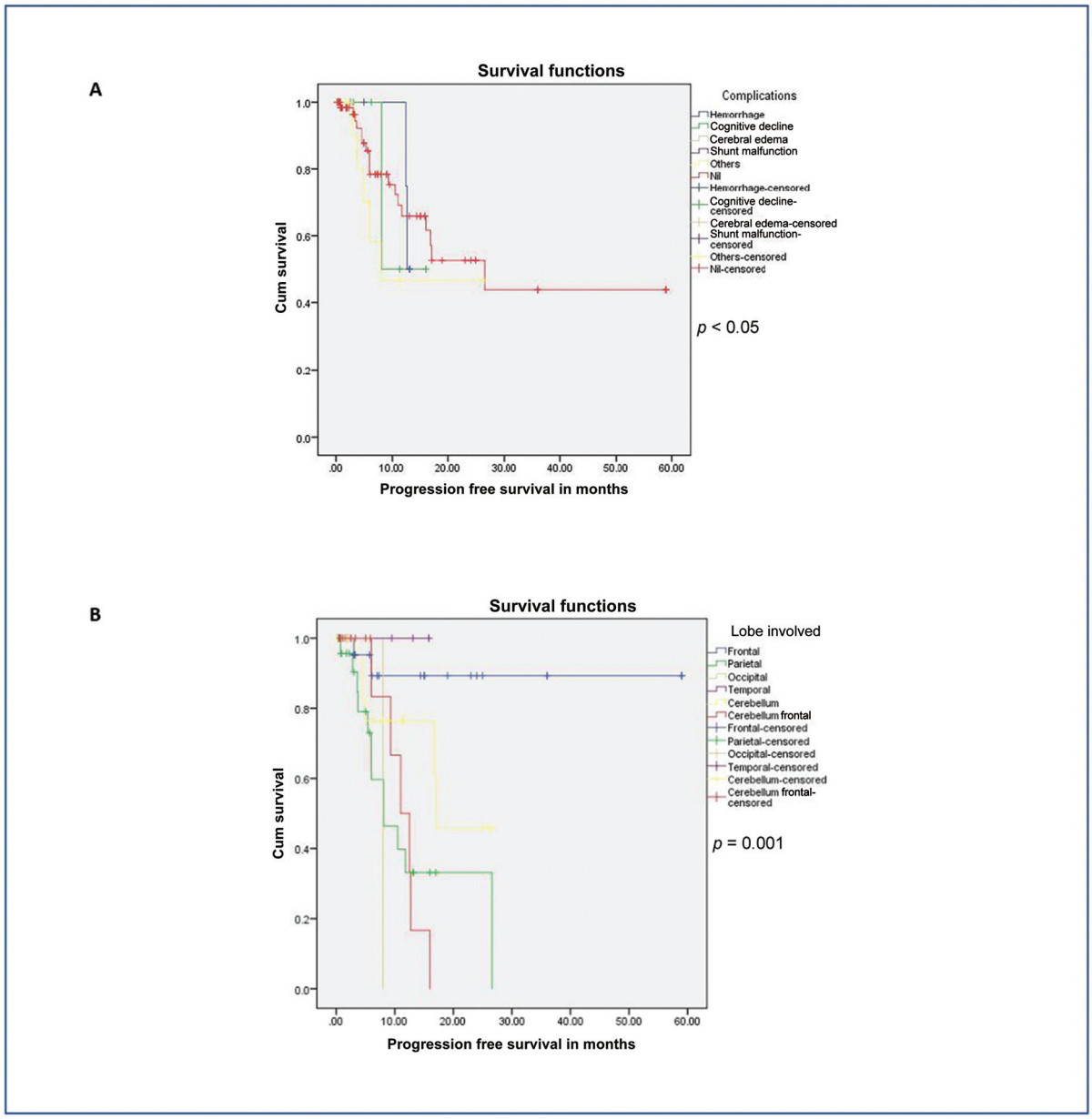

Fig. 2 Hazard function curves for progression-free survival; (**A**) complications; (**B**) lobe involved.

Discussion

Several facets of metastatic brain tumor care remain unexplored. Age, performance status at presentation, presence of extracranial metastases, number of BM, and site of primary tumor[1,2,8,10–12] have all been linked to survival in previous studies. However, assessment of these factors in low-middle income patient populations, as well as identification of other static factors and their association with survival indices, is rarely reported. Our principal finding was that survival in metastatic brain tumors is influenced by elements pertaining to patient, tumor, and management factors.

Comparable to previous studies,[10–12] our results were significant for the shortest overall and PFS of patients over 64 years of age. Our results also showed decreased survival at the other end of the spectrum, that is, under 18 years of age, which, to the best of our knowledge, was rarely reported previously. Suki et al, in their study on pediatric patients only, did report an extremely poor prognosis because of advanced intracranial disease at diagnosis, which supports our results.[3] However, our results are based on a small sample, and may represent a statistical outlier. Our findings of low median OS and PFS of 6.7 and 6 months, respectively, also corroborated with the literature, where they ranged from 3.4 to 12.8[1,3,8,10–13] and 6.91 months,[10] respectively.

Most authors agreed that the female gender was a strong prognostic factor for increased survival,[1,10,14] which was comparable to our results. This can perhaps be explained by significantly better outcomes reported for BM from breast cancer,[1,11] which predominantly occurs in females. While

recent literature reported lung tumors as the commonest primary tumors in their patients,[1,7,8,14,15] a major caveat in our series concerns the fact that the most common solid tumor was breast. This may be explained by the fact that most patients presenting to us were female, unlike other studies, which showed males to have a higher incidence of BM.[7,13] In fact, lung cancer comprised only 2% of primary tumors in our series. However, our institution is a major national referral center for cancer and thus, the referral pattern to our center, rather than the true population distribution, would dictate the distribution of the primary sites responsible for the BM in our study.[10] We also found worst outcomes with BM from lung tumors, with an overall survival of 5.85 months, closely followed by testicular and prostate cancers, which explains why our series reported poor survival indices for males. Other common primary tumors include malignant melanomas, colon cancer, and sarcomas.[3,7,8,13,15] However, primary systemic disease did not significantly impact survival in our study.

Suki et al suggested that the effective treatment of the primary malignancy and an increase in survival in recent years may have resulted in an increased incidence of BM. This notion was not similar to our results, as well as previous studies, where BM-free interval did not significantly impact survival.[16] In fact, literature showed longer OS and PFS with metachronous lesions, or those with a BMFI greater than 6 months, when compared to synchronous metastatic lesions.[1,10,11] Our study also reported a significantly shorter OS was with more than 1 extracranial metastasis, which was comparable to the literature findings.[2,12] Since extracranial disease is generally a contraindication to surgery for BM, this may add to the reason for bad prognoses. Morikawa et al reported a median OS of only 3.5 months with leptomeningeal metastases.[17] This was in harmony with our results, where anatomic location of the tumor affected survival, with leptomeningeal disease significantly decreasing the OS. This may be due to the local inflammation and impaired cerebrospinal fluid (CSF) resorption that occurs secondary to the invasion of the leptomeninges, which can then obstruct CSF flow and cause hydrocephalus and/or increased intracranial pressure.[18] The latter also showed significant association with a shorter OS, postoperatively, in our study. Once in the subarachnoid space, tumor cells can seed multiple areas of the CNS such as the basilar cisterns, via CSF circulation, increasing tumor burden, and further worsening prognosis.[19–21]

Our results showed most lesions to be frontal, parietal, or cerebellar, with significantly increased OS and PFS reported with frontal metastases. This may be due to most of our cases being right-sided—right frontal lobe is majorly noneloquent, and hence, more amenable to surgery. While not much correlation with lobar location was found in the literature, a few studies were comparable with our series.[11,13] D'Andrea et al reported lesions to occur more frequently on the right,[13] which concorded with our results. However, no correlation has been made with the survival indices in the literature, to the best of our knowledge. Left-sided lesions proved to be an important novel prognostic factor in our series, and significantly decreased survival when compared to right-sided lesions. This can perhaps be explained by the presence of eloquent structures on the left, which surgery and/or radiation can significantly damage, subsequently affecting the functional outcome in patients. Other radiologic findings which proved to be significant predictors of survival in our analysis, and were novel, to the best of our knowledge, included brain herniation, with uncal herniation having the poorest survival outcomes, presence of a midline shift, and postoperative hydrocephalus. Close follow-up of the primary tumor and early detection of BM can help prevent the former two, whose association with dismal prognoses is secondary to mass effect. Postoperative shunt malfunction drastically reduced both OS and PFS in our series, perhaps because the malfunctioning shunt caused hydrocephalus, and consequently, raised intracranial pressure—the latter detrimental to an already compromised postoperative brain.

Treatment strategies comprise the few prognostic factors that have been widely discussed in the literature, and significantly impacted survival in our study as well. Surgery and adjuvant radiation were the treatment of consensus, and our results corroborated with the present evidence, where surgery, followed by whole-brain radiation therapy (WBRT), significantly increased the median OS.[1,8,10,11,13] In fact, in an analysis of factors affecting survival, adjuvant WBRT was the only significant factor that was reported by Sivasanker et al in 2018.[10] While our population also consisted of patients who solely underwent radiation therapy, not all authors agreed with the approach, deeming neurosurgery necessary, to resolve symptoms arising from intracranial hypertension due to mass effect and perilesional edema.[13,22] However, unique challenges such as low health literacy, sparse distribution of tertiary care centers, resigned attitudes to terminal illness,[23] and lack of financial support determined how the patients presenting to our center were managed.

Recent studies show an improvement in the survival potential of metastatic brain tumor patients, especially those with metastatic malignant melanoma and nonsmall cell lung cancer, through targeted therapies against mutated BRAF proteins, and immunotherapeutic agents.[24,25] The use of intrathecal methotrexate for BM, both prophylactically and therapeutically, was also hypothesized to improve survival, but did not yield significant results.[3,24,26] Presently, stereotactic radiosurgery has become commonly utilized and has contributed significantly to decreased toxicity, prolonged quality of life, and general improvement in outcomes of patients with BM.[27] Globally, the development of enhanced recovery after surgery guidelines for craniotomy for brain lesions in general, in an effort to reduce perioperative morbidity and improve postoperative surgical outcomes, is currently an area of academic interests.[28]

Limitations of our study stem from its retrospective nature and our relatively small patient cohort, which may result in statistical outliers, and prevent the development of definitive guidelines regarding optimization of survival outcomes in metastatic brain tumors.

Conclusion

Patients with BM have dismal prognoses. Heightened awareness, prompt identification of both the primary malignancy and intracranial metastatic lesion, and utilization of novel treatment paradigms are necessary to optimize outcomes. More comprehensive analyses and clinical trials are required to test for significance of the relatively novel prognostic factors reported in our study, as well as develop new treatment strategies to counter this deadly disease. This will allow addition to a refined current pool of global knowledge and help improve clinical decision making for these patients.

Authors' Contributions

SBA contributed to study conceptualization, data collection and analysis, and approval of the final manuscript. UHT helped in data collection and analysis, literature review, and developing and finalizing the manuscript. IY was involved in study supervision and conceptualization, approval of the final manuscript.

Ethical Review

The study was approved by the IRB at Shaukat Khanum Memorial Cancer Hospital, Lahore, Pakistan.

Note

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None.

Conflict of Interest

None declared.

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