Article published online: 2022-08-24

Comparison of Glioblastoma Outcomes in Two Geographically and Ethnically Distinct Patient Populations in Disparate Health Care Systems

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AJNS 2022;17:178–188.

Abstract

Introduction Variations in glioblastoma (GBM) outcomes between geographically and ethnically distinct patient populations has been rarely studied. To explore the possible similarities and differences, we performed a comparative analysis of GBM patients at the University of Kentucky (UK) in the United States and the Aga Khan University Hospital (AKUH) in Pakistan.

Methods A retrospective review was conducted of consecutive patients who underwent surgery for GBM between January 2013 and December 2016 at UK, and July 2014 and December 2017 at AKUH. Patients with recurrent or multifocal disease on presentation and those who underwent only a biopsy were excluded. SPSS (v.25 IBM, Armonk, New York, United States) was used to collect and analyze data.

Results Eighty-six patients at UK (mean age: 58.8 years; 37 [43%] $<$ 60 years and 49 [57%] $>$ 60 years) and 38 patients at AKUH (mean age: 49.1 years; 30 (79%) $<$ 60 years and 8 (21%) $>$ 60 years) with confirmed GBM were studied. At UK, median overall survival (OS) was 11.5 (95% confidence interval [CI]: 8.9–14) months, while at AKUH, median OS was 18 (95% CI: 13.9–22) months ($p = 0.002$). With gross-total resection (GTR), median OS at UK was 16 (95% CI: 9.5–22.4) months, whereas at AKUH, it was 24 (95% CI: 17.6–30.3) months ($p = 0.011$).

Conclusion Median OS at UK was consistent with U.S. data but was noted to be longer at AKUH, likely due to a younger patient cohort and higher preoperative Karnofsky's performance scale (KPS). GTR, particularly in patients younger than 60 years of age and a higher preoperative KPS had a significant positive impact on OS and progression-free survival (PFS) at both institutions.

Keywords
- glioma
- glioblastoma
- survival
- population heterogeneity
- health care system
- Pakistan

DOI https://doi.org/10.1055/s-0042-1750779.
ISSN 2248-9614.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Glioblastoma (GBM) is the most common primary malignant brain tumor which is uniformly fatal. Maximal safe resection followed by the Stupp protocol remains standard of care.[1] Variations in outcomes in geographically and ethnically distinct patient populations in disparate health care systems has been seldom studied.[2] Specifically, a direct comparison has not been conducted between a North American and South Asian patient population.

The incidence of GBM, extent of resection (EOR), and its impact on survival has been extensively studied in North American and European populations.[3–9] In the United States, the incidence is estimated to be 3.19 per 100,000 population.[10] According to one study looking at regional incidence rates, the South has the highest rate of 24.31 per 100,000/year and the lowest median survival at 7 months. Interestingly, Kentucky is noted to have the highest age-adjusted incidence and death rates per 100,000 person years (7.9) for malignant brain tumors.[11]

The incidence of brain tumors in Pakistan, specifically GBM, is unknown. Limited data from few centers suggest that high-grade gliomas are the most common brain tumors, whereas intracranial metastases are rather infrequent.[12–15] Similarly, only one comprehensive study has been conducted with a 2-year follow-up, depicting outcomes at par with international literature.[16] There are several hurdles to good quality surgical care for brain tumors in Pakistan, specifically for high grade gliomas which require multidisciplinary collaboration and have a significant associated cost.[17]

In this study, we have compared patients undergoing surgery for GBM at two large academic tertiary-care centers as follows: (1) The University of Kentucky (UK) in the United States, and (2) The Aga Khan University Hospital (AKUH) in Pakistan. Our aim is to understand the variability in demographics, extent of resection, and patient survival in these two distinct patient populations and contrasting health care systems.

Materials and Methods

Patient Population

A retrospective review was conducted of consecutive patients who underwent surgery for high grade glioma between January 2013 and Dec 2016 at UK, and July 2014 and December 2017 at AKUH. Once these patients were identified, exclusion criteria were applied as follows: patients who had prior surgical intervention at another hospital; patients with recurrent tumor or multifocal disease on presentation; and patients who underwent only a biopsy, either stereotactic or open. Furthermore, to have a uniform cohort for comparison at both institutions, only patients whose final histology was consistent with GBM were included in the study.

Data Collection and Analysis

Statistical Package for Social Sciences (SPSS v.25 IBM, Armonk, New York, United States) was utilized to record and analyze data. Variables included patient demographics (gender, age, comorbidities, common presenting symptoms, seizures, and Karnofsky's performance scale [KPS]), imaging (intracranial side, lobar location of the tumor, and presumed preoperative diagnosis based on imaging alone), extent of resection (EOR; divided into gross-total resection [GTR], near-total resection [NTR], subtotal resection [STR], and gross residual disease [GRD]; NTR was classified as $> 95\%$ with minimal residual tumor, STR was classified as $< 95\%$ but $> 78\%$, and GRD as $< 78\%$ resection), post-operative care (postoperative day [POD] of discharge, radiation, chemotherapy, and follow-up data), and survival data (overall survival [OS] and progression-free survival [PFS]). EOR was estimated based on the operating surgeon's assessment of the postoperative imaging study, as well as the radiologists' report. The survival data were further divided according to EOR and age (> 60 or < 60 years). The EOR and age categories were cross-tabulated to obtain mean and median survival rates for each subgroup. Kaplan–Meier survival curves with log-rank analysis were generated for OS, PFS according to institution, EOR, age, and preoperative KPS. A p-value of less than 0.05 was considered as significant for long-rank test.

The study was approved by the institutional review board/ethical review committee at both the institutions. Patient consent was not required as this was a retrospective chart review, and no patient identifiers were disclosed.

Results

Demographics

At UK, 174 patients with high grade glioma were identified (►Table 1). After applying exclusion parameters, 86 patients with confirmed GBM were studied. Forty-eight (55.8%) were men and 38 (44.2%) were women. Mean age was 58.8 years. Thirty-seven (43%) were less than 60 years old and 49 (57%) were older than 60 years. Comorbidities included hypertension in 43 (50%), diabetes in 16 (18.6%), chronic obstructive pulmonary disease (COPD) in 6 (7%), prior cancer in 12 (13.9%), and smoking in 20 (23.2%). Most common presenting symptoms were headache (56.6%) and confusion (53.4%). Seizures on presentation were noted in 19.8% of patients. KPS of 90 to 100 was noted in 67 patients (77.9%), and 80 to 89 in 19 (22.1%), 17 of whom were above 60 years of age. Forty-four (50.9%) had a right-sided lesion and 42 (50.1%) had left-sided pathology. The tumor was centered in the frontal lobe in 37 patients (43.1%), temporal in 26 (30.2%), parietal in 15 (17.5%), and occipital in 8 (9.3%). On preoperative radiographic analysis, 71 (82.6%) tumors were presumed to be GBM by an attending radiologist, 2 as grade III (2.4%), 1 as grade II (1.2%), and 12 (14%) as metastatic lesions.

At AKUH, 70 patients were identified for chart review. Of these, 38 patients were included who met criteria. This cohort consisted of 26 (68.4%) men and 12 (31.6%) women. Mean age was 49.1 years. Thirty patients (79%) were less than 60 years of age, and 8 (21%) were older than 60 years. Comorbidities included hypertension in 18 (47.4%), diabetes in 10 (26.3%), COPD in 1 (2.6%), prior cancer in 3 (7.9%), and

Table 1 Demographics

	UK	AKUH
Patients	86	38
Gender	M = 48 (55.8%) F = 38 (44.2%)	M = 26 (68.4%) F = 12 (31.6%)
Mean age (y)	58.81 > 60: 49 (57%) < 60: 37 (43%)	49.11 > 60: 8 (21%) < 60: 30 (79%)
Comorbidities	Hypertension: 43 (50%) Diabetes: 16 (18.6%) Smoking: 20 (23.2%)	Hypertension: 18 (47.4%) Diabetes: 10 (26.3%) Smoking: 4 (10.5%)
Common presenting symptoms	Headache (56.6%) Confusion (53.4%) Seizures (19.8%)	Headache (52.6%) Seizures (23.7%)
KPS	90–100 in 67 (77.9%) 80–89 in 19 (22.1%)	90–100 in all patients
Tumor location and side	Right: 44 (50.9%) Left: 42 (50.1%) Frontal: 37 (43.1%) Temporal: 26 (30.2%) Parietal: 15 (17.5%) Occipital: 8 (9.3%)	Right: 13 (34.2%) Left: 25 (65.8%) Frontal: 17 (44%) Temporal: 8 (21.1%) Parietal: 11 (28.9%) Occipital: 1 (5.2%) Insular: 1 (5.2%)
Radiographic assessment	GBM: 71 (82.6%) Metastatic: 12 (14%) Grade III: 2 (2.4%) Grade II: 1 (1.2%)	GBM: 17 (44.7%) Metastatic: 2 (5.2%) Grade III: 15 (39.5%) Grade II: 4 (10.5%)
Lost to follow-up	8 lost to follow up after surgery. 78 included in the survival analysis	None

Abbreviations: AKUH, Aga Khan University Hospital; GBM, glioblastoma; KPS, Karnofsky's performance scale; UK, University of Kentucky.

smoking in 4 (10.5%) patients. Most common presenting symptom was headache (52.6%). Seizures were seen in 23.7% of patients. KPS was 90 to 100 in all patients. Thirteen (34.2%) had a right-sided lesion and 25 were (65.8%) left sided. The tumor was centered in the frontal lobe in 17 (44.7%) patients, temporal in 8 (21.1%), parietal in 11 (28.9%), and one each in the occipital and insular regions (5.2%). Preoperatively on radiographic analysis, 17 (44.7%) tumors were presumed to be GBM, 15 (39.5%) to be grade III, 4 (10.5%) grade II, and 2 (5.2%) as metastatic lesions. At both institutions, all patients underwent craniotomy for maximal safe resection, with the goal always being GTR or NTR.

Extent of Resection and Postoperative Course

At UK, GTR was achieved in 26 (30.2%), NTR in 29 (33.7%), and STR in 17 (19.8%; ►**Table 2**). GRD was seen in 14 (16.3%). In the 37 patients with less than 60 years of age, GTR was achieved in 12 (32.4%), NTR in 14 (37.8%), STR in 4 (10.8%), and GRD remained in 7 (18.9%). In 49 patients older than 60 years, GTR was achieved in 14 (28.5%), NTR in 15 (30.6%), STR in 13 (26.5%), and GRD was present in 7 (14.2%) patients.

Seventy-three (84.9%) patients were discharged in the first 3 days after surgery (55 [64%] on POD 1, 13 [15.1%] on POD 2, and 5 [5.8%] on POD 3). Seven (8.2%) were discharged between POD 4 to 7. Six (7%) were discharged after POD 7 due to rehabilitation needs. Seventy-three (84.9%) patients received standard adjuvant radiation therapy and chemotherapy, whereas five (5.8%) refused further treatment. Eight patients (9.3%) were lost to follow-up after surgery and further treatment and survival data were not available.

Table 2 Rates of EOR and postoperative discharge

	UK n (%)	AKUH n (%)
EOR		
GTR	26 (30.2)	15 (39.5)
NTR (> 95% with minimal residual)	29 (33.7)	6 (15.8)
STR (< 95% but > 78%)	17 (19.8)	11 (28.9)
GRD	14 (16.3)	6 (15.8)
Discharge day		
POD 1	55 (64)	None
POD 2	13 (15.1)	3 (7.9)
POD 3	5 (5.8)	10 (26.3)
POD 4–7	7 (8.2)	23 (60.5)
After POD 7	6 (7)	2 (5.3)

Abbreviations: AKUH, Aga Khan University Hospital; EOR, extent of resection; GRD, gross residual disease; GTR, gross-total resection; NTR, near-total resection; POD, postoperative day; STR, subtotal resection; UK, University of Kentucky.

Table 3 Impact of EOR and age on OS and PFS

Institute	OS and PFS (mo)	OS and PFS according to age (left) and extent of resection (right) in months (Mean/median)							
UK	Mean OS = 13.6 Median OS = 11.5 Mean PFS = 7.4 Median PFS = 5					GTR	NTR	STR	GRD
					OS	17.7/16	13.7/9.5	11.7/9.5	8.5/6
					PFS	11.4/11	5.4/4	6.1/4.2	6.7/4
		Age (y)	OS	PFS		OS and PFS according to age and EOR combined			
		< 60	15.2/16	7.9/6		OS: 22.3/25.6 PFS: 12.5/12	OS:13.3/6 PFS:4.5/4.0	OS:12.7/10 PFS:8/4	OS: 9.3/4.5 PFS:7.2/6
		> 60	12.3/11	6.8/5		OS:13.1/11.5 PFS:8.9/8	OS: 14.2/9.5 PFS: 6.3/5	OS: 11.5/7 PFS: 5.7/4.2	OS: 7.6/6 PFS: 6/4
AKUH	Mean OS = 22.1 Median OS = 18 Mean PFS = 13 Median = 7					GTR	NTR	STR	GRD
					OS	28.1/24	18.5/16	19.2/12	16.3/9
					PFS	19/13	4.6/3	11/5	10.3/4
		Age (y)	OS	PFS		OS and PFS according to both age and EOR combined			
		< 60	24/20	15.1/12		OS: 26.5/24 PFS: 20/15	OS: 18.6/16 PFS:4.8/3	OS: 25.5/16 PFS: 14.5/7	OS: 19.5/8 PFS: 13.7/4
		> 60	15.3/9	5.1/3		OS: 38.5/22 PFS: 12.5/12	OS: 18/18 PFS: 4/4	OS: 2.6/3 PFS: 1.6/2	OS: 10/9 PFS: 3.5/3

Abbreviations: AKUH, Aga Khan University Hospital; EOR, extent of resection; GRD, gross residual disease; GTR, gross-total resection; NTR, near-total resection (> 95%); OS, overall survival; PFS, progression-free survival; STR, subtotal resection (< 95% but > 78%); UK, University of Kentucky.

At AKUH, GTR was achieved in 15 (39.5%), NTR in 6 (15.8%), and STR in 11 (28.9%). GRD was seen in 6 (15.8%). In 30 patients with less than 60 years of age, GTR was achieved in 13 (43.3%), NTR in 5 (16.6%), STR in 8 (26.6%), and GRD remained in 4 (13.3%) patients. In eight patients older than 60 years, GTR was achieved in only 2 (25%), NTR in 1 (12.5%), STR in 3 (37.5%), and GRD was present in 2 (25%) patients.

Thirteen (34.2%) patients were discharged in the first 3 days after surgery (none on POD 1, 3 [7.9%] on POD 2, and 10 [26.3%] on POD 3). Twenty-three (60.5%) were discharged between POD 4 to 7. Two (5.3%) were discharged after POD 7. Majority of the patients received standard postoperative radiation therapy (37 [97.3%]) and chemotherapy (36 [94.7%]). No patients were lost to follow-up.

Survival Data

At UK, in 78 patients with complete survival data available, mean OS was 13.6 (95% confidence interval [CI]: 11.4–15.9) months, and median OS was 11.5 (95% CI: 8.9–14) months (►**Table 3**). At AKUH, mean OS was 22.1 (95% CI: 17.1–27.1) months, and median OS was 18 (95% CI: 13.9–22) months ($p = 0.002$). At UK, mean PFS was 7.2 (95% CI: 5.9–8.9) months and median PFS was 5 (95% CI: 3.3–6.8) months. Mean PFS at AKUH was noted to be 13 (95% CI: 8.6–17.4) months, while median PFS was 7 (95% CI: 0.9–13) months ($p = 0.01$; ►**Fig. 1**).

EOR and its effect on OS and PFS was also compared. With GTR, at UK, mean OS was 17.7 (95% CI: 13.9–16) months, and median OS was 16 (95% CI: 9.5–22.4) months, whereas at AKUH, mean OS was 28.1 (95% CI: 20.4–35.8) months, and median OS was 24 (95% CI: 17.6–30.3) months ($p = 0.011$). Similarly, at UK, mean and median PFS were 11.4 (95% CI: 7.9–14.9) and 11 (95% CI: 7.6–14.3) months, respectively, while at AKUH, mean PFS was 19 (95% CI: 10.9–27) months, and median PFS was 13 (9.2–16.7) months ($p = 0.001$; ►**Fig. 2**).

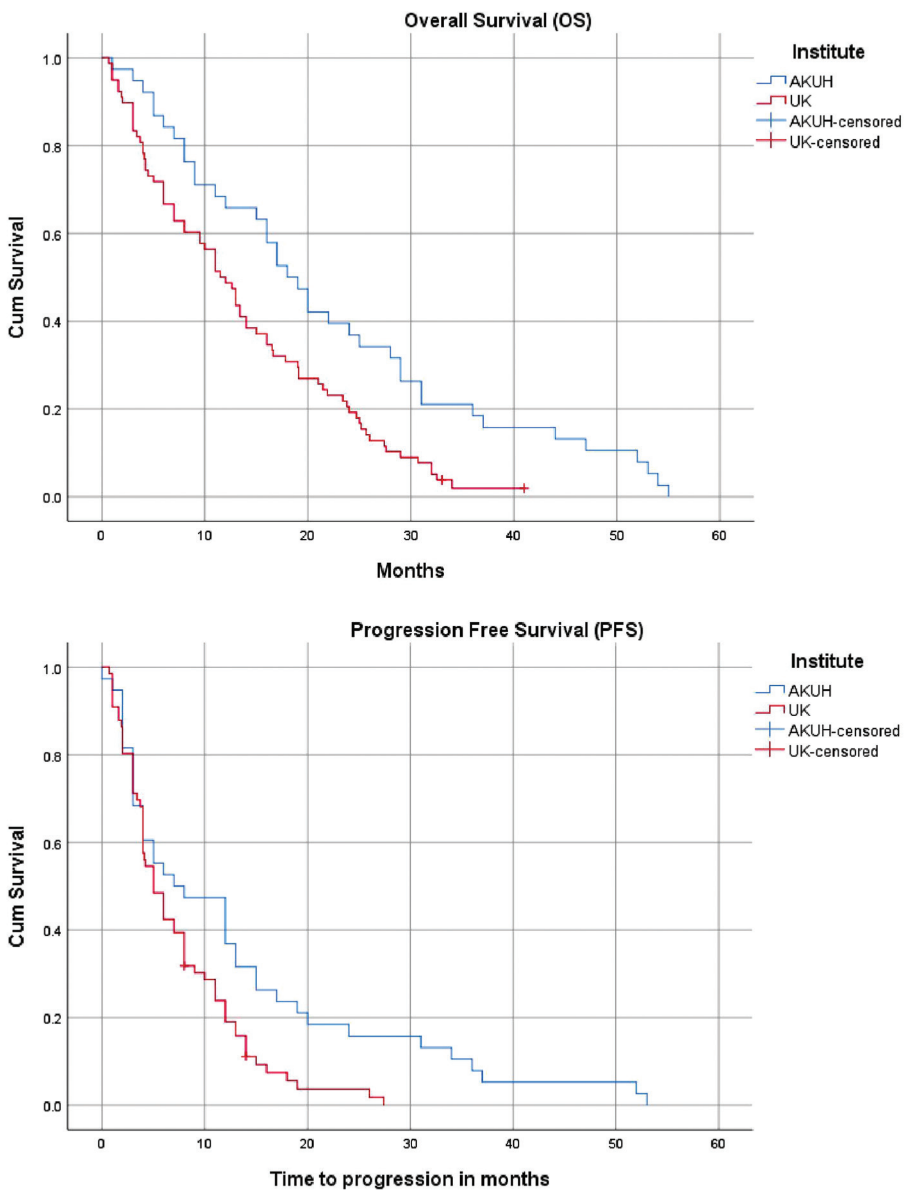

Fig. 1 Overall survival and progression free survival at UK and AKUH. AKUH, Aga Khan University Hospital; UK, University of Kentucky.

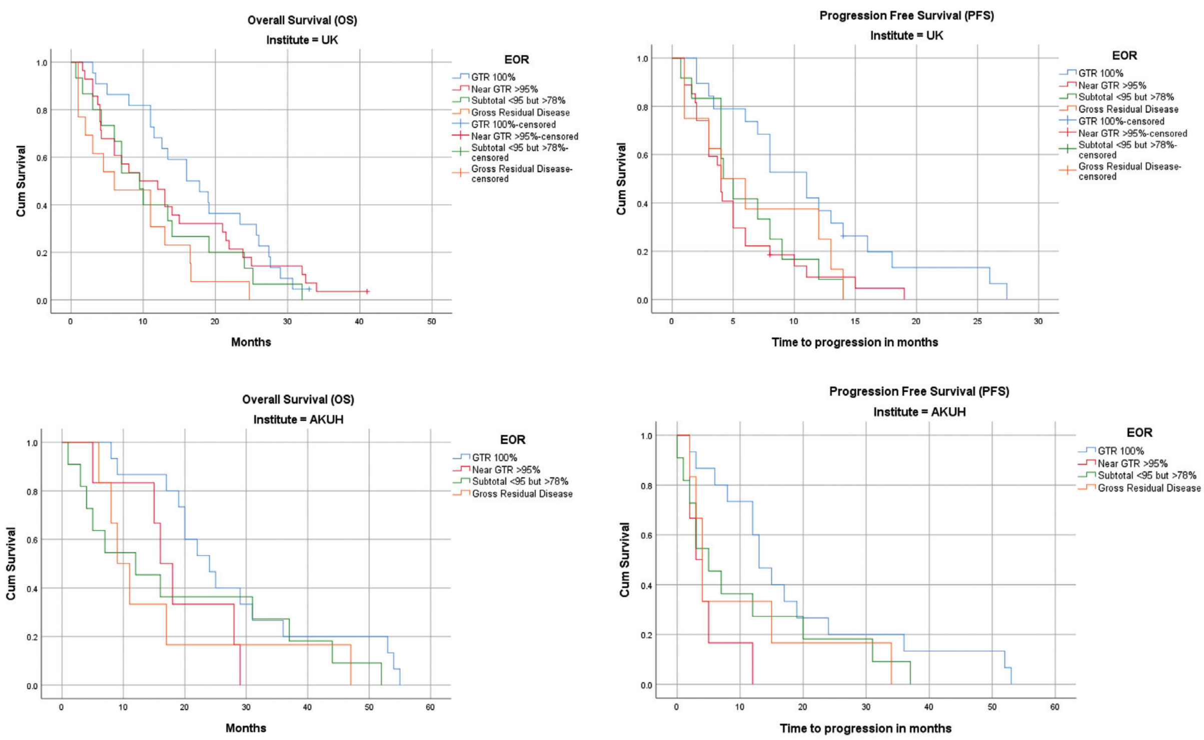

Fig. 2 Impact of extent of resection on overall survival and progression-free survival.

Similarly, effects of age on OS and PFS were compared. At UK, 35 patients (44.9%) and at AKUH, 30 (79%) patients were younger than 60 years of age. In this cohort of less than 60 years, mean OS at UK was 15.2 (95% CI:11.7–18.8) months and median OS was 16 (95% CI: 11.5–20.5) months, while at AKUH mean OS was 24 (95% CI: 18.6–29.3) months, and median OS was 20 (95% CI: 10.6–29.3) months ($p = 0.299$). At UK, mean and median PFS were 8 (95% CI: 5.4–10.3) and 4.1 (95% CI: 2–6.1) months, respectively, while at AKUH, mean and median PFS were 15.1 (95% CI: 9.8–20.4) and 12 (95% CI: 5.3–18.6) months, respectively ($p = 0.099$). At UK, 43 patients (55.1%) and at AKUH, 8 (21%) patients were older than 60 years. In this subgroup, at UK, mean OS was 12.3 (95% CI: 9.4–15.2) and median OS was 11 (95% CI: 7.1–14.8) months, and at AKUH, mean OS was 15.3 (95% CI: 3.1–27.5), and median OS was 9 (95% CI: 0–18) months. At UK, mean and median PFS were 6.8 (95% CI: 5.2–8.5) and 5 (95% CI: 2.9–7) months, respectively, whereas at AKUH, mean PFS was 5.1 (95% CI: 1.8–8.4) months, and median PFS was 3 (95% CI: 1.6–4.3) months (►**Fig. 3**).

Mean and median OS in the 80 to 89 KPS group of patients was particularly low, being 7 (95% CI:4.5–9.5) and 6 (95% CI: 2.1–9.8) months, respectively ($p = < 0.0005$; ►**Fig. 4**).

Discussion

Notable advances have been made in GBM care in the last few decades.[10,18,19] Surgical resection, complemented with multiple operative adjuncts, remains the cornerstone of treatment.[20,21] Several studies primarily in Caucasian populations have evaluated the impact of EOR, age, KPS, and tumor genetics on OS and PFS, both in high- and low-grade gliomas.[3–9,22–26] Of these factors, only the extent of resection can be changed. Our study clearly shows the benefit of maximal resection on OS and PFS across all age groups at both institutions. Both at UK and AKUH, patients who had a GTR and were less than 60 years of age achieved the longest mean/median OS of 22.3/25.6 and 26.5/24 months, respectively. The same held true for mean/median PFS which at UK and at AKUH was 12.5/12 and 19/13 months, respectively (►**Table 3**). Resection rates were comparable at the two institutions (►**Table 2**).

There were some important differences in patient demographics (►**Table 1**). At UK, 57% of patients were older than 60 years compared with 21% of AKUH patients. All patients at AKUH had a KPS greater than 90. At UK, 22.1% of patients had a KPS of 80 to 89, and majority of these were older than 60 years. Expectedly, lower KPS had an independent negative effect on OS in this subset of UK patients. Early discharge from the hospital after surgery was more common at UK where 79.1% patients were discharged on either POD 1 or 2 which is consistent with our previously published results.[27] The pre- and postoperative workflow for all patients with intra-axial brain tumors presenting to UK has been described previously.[27] The workflow at the two institutions was noted to be largely similar with some minor differences (►**Table 4**).

Interestingly, of all the patients at AKUH who underwent surgery for high-grade glioma during the study period, 41.4% were of the World Health Organization (WHO) grade-III gliomas which were eventually excluded from our study. This proportion was much smaller in UK patients (13.7%). It is well established that primary GBMs are more common

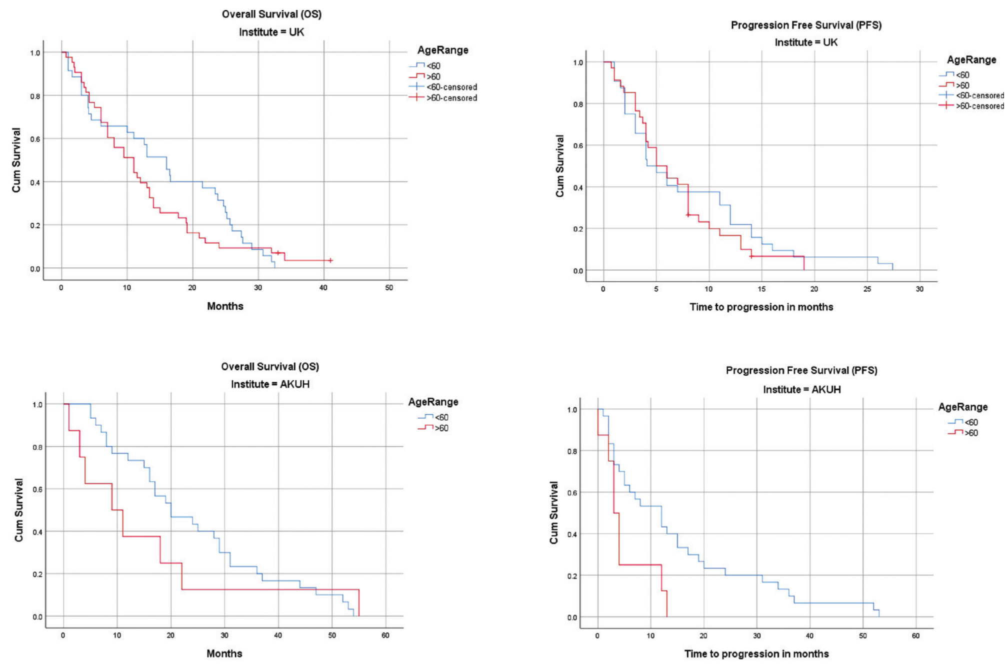

Fig. 3 Impact of age on overall survival and progression-free survival.

overall (80–90% of all GBMs) and occur more commonly in older patients.[10,28,29] It is possible that the younger patient cohort at AKUH had secondary GBMs which arose from lower grade tumors. This, in addition to other unknown factors, such as O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status and tumor molecular markers, may explain the longer OS and PFS noted in the AKUH cohort.[30,31] At the time of this study, these tests were not available at AKUH but recently isocitrate dehydrogenase (IDH1/2) mutation and MGMT status testing has started, albeit sporadically due to limited availability of testing kits.

The 2016 WHO classification of brain tumors incorporated molecular parameters for diagnosis, and since then, methods are being devised to radiographically predict the molecular status of gliomas.[28] IDH mutant GBMs may not always present with the typical "ring-enhancing mass with central necrosis" look of an IDH-wild type GBM. Similarly, tumors or low-grade glioma (LGG) on MRI could be astrocytomas due to lack of 1p/19q codeletion. It is interesting to note that in comparison to UK where 82.6% tumors were read as GBM by the radiologist, at AKUH, only 44.7% tumors were presumed to be GBM on preoperative radiographic images, 39.5% were read as grade III and 10.5% as grade II. This disparity in MRI findings again brings up the possibility that the AKUH cohort harbored secondary GBMs arising from lower grade lesions or IDH mutant tumors, which had an impact on survival. But without molecular testing, this remains unclear.

The population of Pakistan, especially Karachi, is a heterogenous mixture of several different ethnicities.[32–35] The United States is likely more of a melting pot than Pakistan, but the population largely comprises of ethnicities not commonly residing in South Asia and vice versa. Genetic variations are bound to influence mutations in glioma patients and have an effect on survival.[36] Large scale population-based studies and the Surveillance, Epidemiology, and End Results (SEERS) analyses from the United States have shown that as compared with Caucasian patients, African Americans, Asians, and Hispanic have improved OS.[37–40] Since there is no population-based study on gliomas available from Pakistan, we are unable to extrapolate these findings in this population. However, it can be implied that the underlying genetic heterogeneity contributes to some of the longer mean/median OS and PFS seen in the AKUH group, specifically with GTR in younger patients.

Temozolomide (TMZ) crosses the blood brain barrier (BBB); however, in contrast to conventional chemotherapeutics does now no longer set off DNA harm or misalignment of segregating chromosomes directly.[41] Hence, it is concomitant use with radiotherapy postsurgical resection that has gained popularity in both AKUH and the UK as means of increasing both OS and the quality of life. As compared with a recent report,[17] in this study, no patients were lost to follow-up in the AKUH cohort, whereas eight patients were lost to follow-up after surgery at UK. We suspect the main reason for this is the regionalization of comprehensive cancer care in Pakistan, therefore when/if patients do choose to complete their care, they do so within the same hospital as their index operation. At UK, patients often prefer to receive adjuvant treatment at centers closer to their hometowns, and, in the process, are occasionally lost to follow-up. It is also possible that patients who go to inpatient rehabilitation centers after surgery do not make it to their chemotherapy and radiation appointments in time and are subsequently lost to follow-up from there. Postsurgery inpatient rehabilitation is more often sought in the United States, whereas in Pakistan, cost constraints and lack of facilities limit this opportunity for

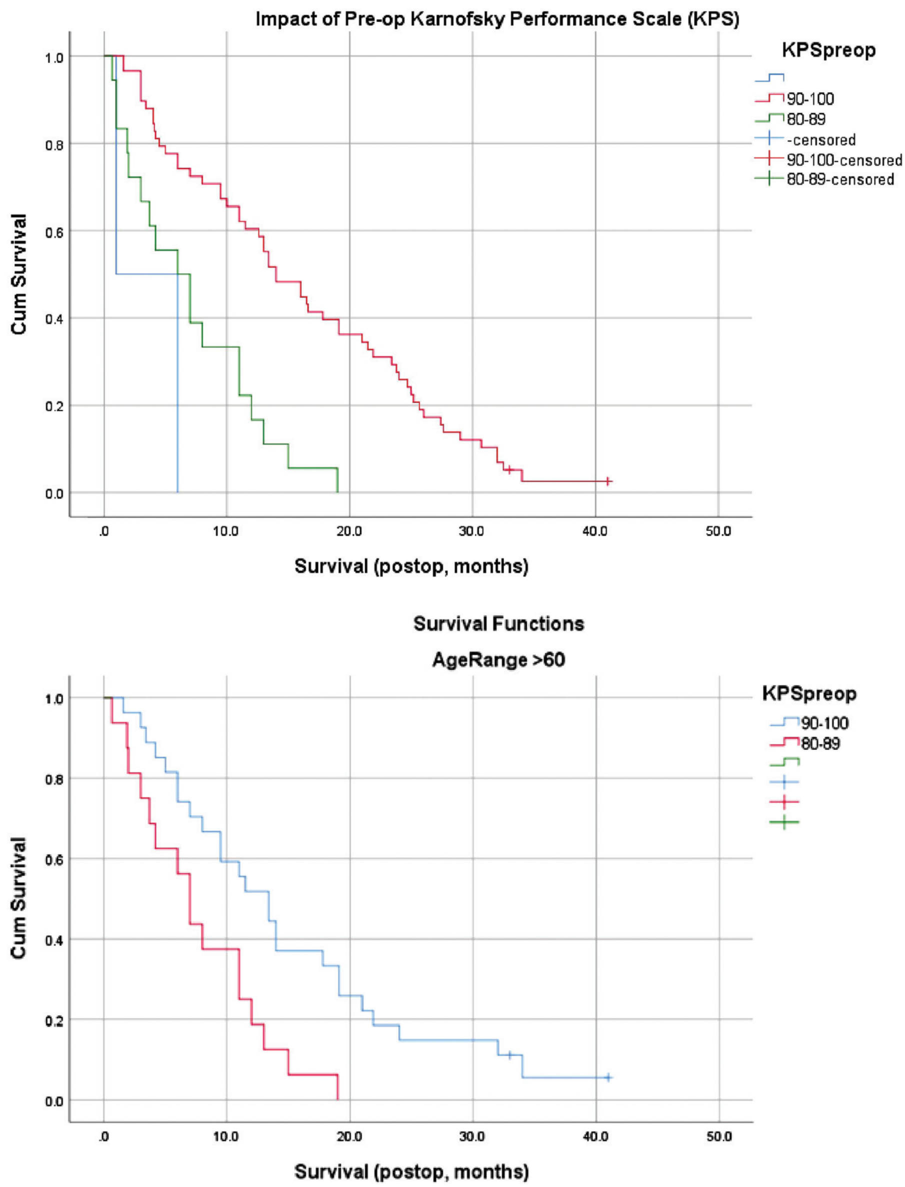

Fig. 4 Impact of preoperative KPS on overall survival. KPS, Karnofsky's performance scale.

most patients. Older age, as seen in the UK cohort, and the social structure may also be a reason behind this.

The social and cultural set up in the two countries is quite different. As opposed to the nuclear family system in the United States, in Pakistan, patients are usually part of an extended family with several layers of support systems available. Studies in the United States have shown that being married has a positive effect on patient outcomes.[42] Not necessarily by virtue of marriage but the fact that there is an extensive support system available, this may be one of the reasons for longer OS in Pakistani patients who are being well taken care of at home and are regularly receiving adjuvant treatment. This, among other plausible factors, was not systematically evaluated in this study but will be the subject of future studies.

The state of Kentucky has the highest all-site cancer incidence rate and the highest rate of cancer deaths in the United States.[43] UK Markey Cancer Center (MCC), is one of the 13 National Cancer Institute (NCI) designated Cancer Centers in the United States. It caters to one of the most economically disadvantaged, disease-burdened, and medically underserved regions in the United States, with a catchment population of nearly 8 million people.[43] Cancer care in Pakistan is developing but high-quality care is limited to a few centers.[17,44–46] The last two decades have seen the emergence of regional cancer registries for all cancer types, but the prevalence of central nervous system tumors remains poorly understood.[32–35,47] AKUH, located in Karachi, is a large private sector university hospital that has personnel, infrastructure, and resources at par with international standards. It treats some of the most complex neurosurgical problems in the country. The same standards are not readily available in most of the public sector facilities in the country. A large majority of patients seek care in public sector hospitals or do not seek care at all, both due to a multitude of factors.[17,44,46] Therefore, despite the Karachi

Table 4 Workflow for brain tumor patients at UK and AKUH

	UK27	AKUH
Admission	Same day as surgery for elective operations	One day before planned surgery
Preoperative steroids	IV or PO dexamethasone 4 mg every 6 hours	Same
Preoperative imaging	Gadolinium enhanced MRI or CT with contrast with fiducial markers	Same
Surgeon	Single surgeon (T.P.)	Multiple surgeons
Postoperative care	Extubated in the operating room (OR) before being transferred to the post anesthesia care unit (PACU) where they remain for 2–4 hours. In the PACU the nurse to patient ratio is 1:2	Same In the PACU the nurse to patient ratio is 1:3
Floor bed or ICU	Patients are subsequently moved to a regular floor bed on a specialized neurosurgical floor where they are cared for by nursing staff trained to perform neurological examinations, NIH stroke scales, etc. Patients with EVDs and those who still require a ventilator after surgery are transferred to ICU beds. The ICU is a dedicated neurosurgical unit and is also staffed by nurses who specialize in the care of neurosurgical patients. Vital signs and neurologic examinations are checked every hour in the ICU. Nurse to patient ratio is usually 1:2 in the ICU; however, depending on the severity of illness, 1:1 care is utilized as needed	Patients are subsequently moved to a special care bed on a combined neurological and neurosurgical floor where they are cared for by nursing staff trained to perform neurological exams, NIH stroke scales, etc. They are shifted out to regular floor bed after 16–24 hours from surgery, i.e., usually the next morning. Patients who still require a ventilator after surgery are transferred to ICU beds. The ICU is staffed by nurses who specialize in the care of neurosurgical patients however it has both medical and surgical patients from different specialties and not a dedicated neurosurgical ICU. Vital signs and neurologic examinations are checked every hour in the ICU. Nurse to patient ratio is usually 1:1 in the ICU
Postoperative imaging	All patients undergo postoperative imaging with contrasted MRI, or contrasted CT if there is any contraindication to MRI	Same
Ambulation	Ambulation is encouraged as early as possible after surgery	Same
Deep venous thrombosis (DVT) prophylaxis	Subcutaneous heparin for DVT prophylaxis is initiated in all patients on the first POD 1, unless they are being discharged the same day	TED stockings are given to all patients in OR until they start ambulating on POD 1. Subcutaneous heparin is given only to those who are unable to ambulate early
Pain control	Achieved with acetaminophen, ice pack or light massage. Narcotics or any sedatives are strictly avoided	Initially achieved with acetaminophen and tramadol is usually kept on PRN basis along with antiemetics (metoclopramide)
Antiepileptic drugs (AEDs)	Only if patient presents with or has new onset seizures in the hospital. Not used as prophylaxis	Loaded with levetiracetam 1-g preoperatively and continued as maintenance dose 500-mg 12 hourly
Discharge	Majority of patients are discharged within first 3 days of surgery	Majority of patients are discharged within first 3 to 5 days of surgery
Postoperative steroids	Dexamethasone is continued at the same dose and tapered to a low dose or to off depending on patient's pathology	Same
Multidisciplinary care	Prior to discharge, the medical oncology and radiation oncology teams are notified of the patient to establish follow-up	After multidisciplinary tumor board has taken place
	Once final histology including molecular markers are available, usually within one to 2 weeks, the case is discussed in a multidisciplinary tumor board and final decision for patient's adjuvant treatment is taken	Same

Abbreviations: AKUH, Aga Khan University Hospital; CT, computed tomography; EVD, external ventricular drain; ICU, intensive care unit; IV, intravenous; MRI, magnetic resonance imaging; NIH, National Institute of Health; PO, per oral; POD, postoperative day; TED, thrombo-embolus deterrent; UK, University of Kentucky population being a true representative sample of the multiethnic Pakistani population, the AKUH cohort of patients in this study and their outcomes may not be entirely representative of the rest of the patient population in Pakistan.

Strengths and Limitations

This is a retrospective analysis of patients with histological diagnosis of GBM who underwent surgery at the two institutions. The numbers are small and only represent a homogenous subset of GBM patients who underwent surgery with the intention of GTR or NTR in line with maximal safe resection, while those with multifocal disease or who underwent biopsy alone were not included. Despite the small sample size, this study provides a unique insight into two considerably different patient populations and their outcomes, as well as two contrasting health care systems and social set ups.

Conclusion

Our study highlights some of the comparative factors in the care of GBM patients from two distinct populations and health care systems. Several facets of glioma care remain unexplored in Pakistan. Despite local limitations, AKUH is providing high quality of care at par with international standards. OS and PFS at UK were consistent with U.S. data but was noted to be longer at AKUH. This is likely due to differences in patient genetics, as well as a younger patient cohort with a higher preoperative KPS. Future studies between the two institutions will focus on understanding and comparing underlying variations in tumor genetics and molecular markers, as well as assessment of supramaximal resection and its impact on survival.

Note

Portions of this manuscript were presented in poster format at the 2019 Congress of Neurological Surgeons (CNS) meeting held in San Francisco, California, United States of America, in October 19-23, 2019.

Authors' Contributions

F.A.M. contributed to the study conceptualization, data collection and analysis, literature review, developing and finalizing themanuscript, approval of the final manuscript M.W.S.B. contributed to data collection and analysis and manuscript development. U.H. contributed to data collection and analysis and manuscript development. M.M.H. contributed to data collection and analysis and manuscript development. M.S.S. contributed to the study supervision and conceptualization, manuscript development, and approval of the final manuscript. S.A.E. contributed to the study supervision and approval of the final manuscript. T.P. contributed to the study supervision and conceptualization, approval of the final manuscript.

Conflict of Interest

None declared.

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