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Initial care and outcome of glioblastoma multiforme patients in 2 diverse health care scenarios in Brazil: does public versus private health care matter?

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Background. The aim of this study was to describe the epidemiological and survival features of patients with glioblastoma multiforme treated in 2 health care scenarios—public and private—in Brazil.

Methods. We retrospectively analyzed clinical, treatment, and outcome characteristics of glioblastoma multiforme patients from 2003 to 2011 at 2 institutions.

Results. The median age of the 171 patients (117 public and 54 private) was 59.3 years (range, 18–84). The median survival for patients treated in private institutions was 17.4 months (95% confidence interval, 11.1–23.7) compared with 7.1 months (95% confidence interval, 3.8–10.4) for patients treated in public institutions ($P < .001$). The time from the first symptom to surgery was longer in the public setting (median of 64 days for the public hospital and 31 days for the private institution; $P = .003$). The patients at the private hospital received radiotherapy concurrent with chemotherapy in 59.3% of cases; at the public hospital, only 21.4% ($P < .001$). Despite these differences, the institution of treatment was not found to be an independent predictor of outcome (hazard ratio, 1.675; 95% confidence interval, 0.951–2.949; $P = .074$). The Karnofsky performance status and any additional treatment after surgery were predictors of survival. A hazard ratio of 0.010 (95% confidence interval, 0.003–0.033; $P < .001$) was observed for gross total tumor resection followed by radiotherapy concurrent with chemotherapy.

Conclusions. Despite obvious disparities between the hospitals, the medical assistance scenario was not an independent predictor of survival. However, survival was directly influenced by additional treatment after surgery. Therefore, increasing access to resources in developing countries like Brazil is critical.

Keywords: clinical practice patterns, developing countries, glioblastoma, insurance, survival.

The management of glioblastoma multiforme (GBM) remains challenging even in highly specialized centers. Since 2005, a maximum safe and feasible surgical resection followed by the combination of radiotherapy (RT) and temozolomide (TMZ) has become the standard of care for GBM patients.[1] Although this regimen has resulted in improved survival, GBM patients still face a dismal prognosis, with a median overall survival (OS) of 14 months and a 2-year survival rate of ~30%.[2,3] The prognostic variables for outcome include age, KPS, extent of resection, molecular biomarkers, RT, and chemotherapy.[3–11]

The implications of socioeconomic factors on the incidence and prognosis of GBM have also been discussed.[12–19] However, whether these aspects substantially affect patient outcome is unclear. A comprehensive therapeutic strategy that overcomes economic barriers and achieves OS rates reached in developed countries is also important.[20–22] In Brazil, a country with major socioeconomic and health access disparities, ~9000 new cases of primary central nervous system tumors were estimated for 2013.[23] The data regarding GBM incidence, patient characteristics, treatment strategies, and survival are scarce.[24–26] Therefore, we performed a retrospective study to evaluate patients with newly diagnosed GBM treated in 2 different health care scenarios—public and private—in Brazil.

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Materials Methods

We retrospectively analyzed patients aged 18 years or older with newly diagnosed GBM according to World Health Organization classification[27] treated between January 2003 and December 2011 at 2 institutions: Hospital Israelita Albert Einstein (HIAE), a private-practice service, and Hospital São Paulo–Universidade Federal de São Paulo (HSP-UNIFESP), a public health care center. In Brazil, the health care system is supported by 2 funding sources: the public system, known as Sistema Único de Saúde (SUS), and the private system, composed of noncompulsory health plans and insurance. HIAE is a private hospital in which only privately insured patients have access to medical assistance. The public institution admits patients from SUS.

The medical records of 186 patients (118 from HSP-UNIFESP and 68 from HIAE) were reviewed to gather information on demographics and clinical variables (gender, age at diagnosis, KPS, first symptom, time from first symptom to surgery, and date of death or last follow-up), neurosurgical intervention (date, number of procedures, and extent of resection), and adjuvant treatment (RT and chemotherapy strategies). The interval from the first symptom to surgery was categorized according to the median, and the interval between surgery and RT was categorized based on median and historical data.[28] We excluded 15 patients because of missing data; 6 patients had no information on the extent of resection, and 9 had no information regarding the adjuvant treatment. The subsequent analysis was restricted to 171 patients (117 patients from HSP-UNIFESP and 54 from HIAE).

Neurosurgery was performed to attain the maximum safe and feasible resection in both institutions. Both institutions have suitably equipped surgical centers. The extent of resection definition was based on immediate (<48 h) postoperative imaging.

Patients underwent 3D localized external beam RT delivered to the contrast-enhancing lesion shown on CT/T1-weighted images or T2/fluid attenuated inversion recovery sequence MRI. The dose was prescribed according to the guidelines of the International Commission of Radiological Units fields once daily at 2 Gy per fraction, 5 days a week, for a total of 60 Gy. The treatment protocols and personnel varied over time and between centers.

Chemotherapy regimens also varied between centers. At HIAE, all patients were treated with concomitant and adjuvant TMZ according to the protocol of the European Organisation for Research and Treatment of Cancer–National Cancer Institute of Canada (EORTC-NCIC).[1] At HSP-UNIFESP until 2008, patients received 200 mg/m^2 carmustine (bis-cloroethylnitrosourea [BCNU]) at 6-week intervals starting 6 weeks after RT. Since 2009, TMZ has been available and patients could be treated with the EORTC-NCIC protocol.[1] The patients who underwent chemotherapy treatment according to the EORTC-NCIC protocol were categorized as "RT concurrent with chemotherapy." The patients who received BCNU were defined as having "RT and sequencing chemotherapy." The patients who received neither RT nor chemotherapy were defined as having "best supportive care."

This study was approved by the ethics review board from both institutions.

Statistical Analysis

The data were described using absolute and relative frequencies for categorical data. Quantitative data were described using median and range because of skewing. Overall survival was calculated from the time of diagnosis until death or last follow-up (cutoff date October 17, 2012).

The data from the public and private institutions were compared using Pearson's chi-square or Fisher's test for categorical data and a Mann–Whitney *U*-test for quantitative variables. $P < .05$ was considered significant.

Survival curves were constructed according to the Kaplan–Meier method and compared between groups using a log-rank test to explore relationships between well-recognized prognostic factors and survival in the univariate analysis. To avoid multicollinearity, we explored the interrelationships between well-recognized prognostic factors and variables that achieved a P value $<.1$ in the univariate analysis before using a stepwise multivariate model. We observed a significant correlation between age and KPS. However, because both are widely known prognostic factors, we chose to maintain them in the model. In addition, because the surgical intervention might influence the complementary treatment after surgery, we combined these 2 aspects for the multivariate analysis. A conditional stepwise proportional hazard analysis (Cox regression model) was used to identify independent predictors of survival.

The statistical analysis was performed using the statistical software R (http://www.R-project.org) and SPSS v17.0.

Results

Patient and Treatment Characteristics

The patient and treatment characteristics are summarized in Table 1. The male:female ratio was 1.6:1. The median age at diagnosis was 59.3 years (range, 18–84). The median follow-up was 9.7 months (range, 0.2–58.0). At the end of the follow-up period (October 17, 2012), 144 patients had died (41 at the private center and 103 at the public center). The most frequent tumor location was the frontal lobe (24.0%), and the tumor was localized in more than one lobe in 38.6%. Most patients presented focal deficits (48.4%) as the first symptom.

A single surgical intervention (including therapeutic and nontherapeutic) was performed in 137 patients (80.1%), whereas 34 patients (19.9%) had a subsequent operation. In 5 patients, a third resection was performed and only 1 patient underwent a fourth procedure. One hundred twenty patients (70.2%) received postoperative RT with a median total radiation dose of 60 Gy (range, 56–66). The median time from surgical intervention to RT was 6.0 weeks (range, 3.9–8.3). Additional irradiation was performed in 7 patients (4.1%) with a median dose of 25 Gy (range, 8–25). At least one regimen of chemotherapy was administered in 91 patients (53.8%), which consisted of TMZ given concurrently with RT in the most common regimen (67.9%). Only 9 (5.3%) patients received more than one regimen of chemotherapy.

Univariate Analysis

Table 1 shows the median survival for patients based on treatment characteristics.

An important factor was the survival of first-line treatment after surgery ($P < .001$; Fig. 1). The difference between the survival of patients who underwent RT and chemotherapy (concurrent or sequential) and those who received best supportive care is substantial.

Median OS for the entire cohort was 10.2 months (95% confidence interval, 7.9–12.4). The median survival for patients from the private hospital was 17.4 months (95% confidence interval, 11.1–23.7), whereas median survival was 7.1 months (95% confidence interval, 3.8–10.4) for patients at the public hospital ($P < .001$; Fig. 2).

Differences Between Institutions

A comparison of the data from the private (HIAE) and public (HSP-UNIFESP) institutions is summarized in Table 2.

The median time from the first symptom to surgery was longer in the public hospital (31 days for the private institution vs 64 days for the public hospital; $P = .003$). No differences were observed either for the number of surgical interventions or for the extent of

Table 1. Patient characteristics and overall survival

Characteristics	*n* (%)	Median OS, mo (95% CI)	*P*
Gender			
Male	106 (62.0)	9.2 (6.3–12.1)	.042
Female	65 (38.0)	11.9 (9.5–14.2)	
	171 (100.0)		
Age, y			
<50	38 (22.2)	17.7 (13.6–21.8)	.002
≥50	133 (77.8)	7.1 (4.3–9.8)	
	171 (100.0)		
KPS, %			
<70	49 (33.8)	4.0 (2.2–5.9)	<.001
≥70	96 (66.2)	15.2 (12.2–18.3)	
	145 (100.0)		
Time from first symptoms to surgery, days			
≤55	75 (50.3)	12.1 (8.7–15.5)	.109
>55	74 (49.7)	8.1 (4.2–11.9)	
	149 (100.0)		
Number of surgical interventions			
1	137 (80.1)	8.1 (5.2–10.9)	.030
≥2	34 (19.9)	16.6 (11.9–21.4)	
	171 (100.0)		
Extent of the first surgical intervention			
Biopsy	33 (19.3)	3.3 (1.7–4.8)	<.001
Partial resection	75 (43.9)	7.1 (3.8–10.3)	
Gross total resection	63 (36.8)	14.1 (11.4–16.8)	
	171 (100.0)		
Postoperative RT			
Yes	120 (70.2)	14.2 (11.9–16.6)	<.001
No	51 (29.8)	2.0 (1.5–2.5)	
	171 (100.0)		
Number of RT lines			
1	113 (94.2)	13.5 (11.7–15.3)	.035
≥2	7 (5.8)	27.1 (21.9–32.4)	
	120 (100.0)		
Time from surgery to RT, wk			
<6	48 (41.7)	13.5 (7.7–19.3)	.421
≥6	67 (58.3)	14.2 (11.8–16.6)	
	115 (100.0)		
Final dose of first RT treatment			
<60 Gy	38 (34.5)	11.0 (8.2–13.7)	.038
≥60 Gy	72 (65.5)	16.3 (13.1–19.5)	
	110 (100.0)		
Chemotherapy			
Yes	91 (53.8)	16.6 (14.3–19.0)	<.001
No	80 (46.2)	3.3 (2.4–4.1)	
	171 (100.0)		
Chemotherapy regimens			
1	82 (90.1)	16.6 (12.7–20.6)	.852
≥2	9 (9.9)	17.8 (13.4–22.1)	
	91 (100.0)		
First-line treatment after surgery			
Best supportive care	51 (29.8)	2.0 (1.5–2.5)	<.001
RT only	29 (17.0)	7.1 (4.3–9.9)	
RT and sequencing chemotherapy	34 (19.9)	15.8 (13.4–18.2)	
RT concurrent with chemotherapy	57 (33.3)	17.8 (14.7–20.9)	
	171 (100.0)		

*Fisher's test.
#Pearson's chi-square test.

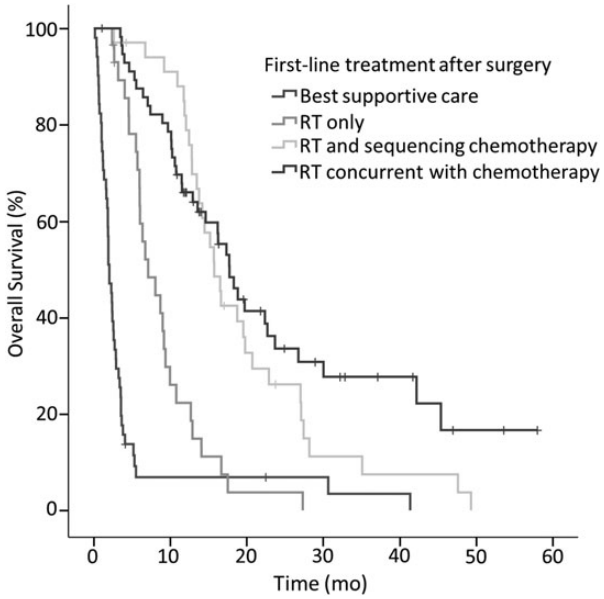

Fig. 1. Overall survival according to first-line treatment after surgery ($P < .001$).

resection of the first surgery. Of note, only patients from the private center underwent additional irradiation once they experienced disease progression ($P < .001$). Furthermore, RT in patients at the private hospital started earlier (<6 wk; $P < .001$). We noted that chemotherapy was administered more often in the private setting (70.4% vs 45.3%; $P = .002$) and that the number of regimens available was higher ($P < .001$).

The first-line treatment after surgery differed between the centers. At the private hospital, patients were more likely to receive the standard treatment of RT concurrent with chemotherapy. At the public hospital only 21.4% of patients were able to receive the same approach because of assessment limitations ($P < .001$).

Multivariate Analysis

We could not detect differences regarding age and institution using a Cox regression model (Table 3). However, the hazard ratio (HR) for KPS ≥70% was 0.592 (95% confidence interval [CI], 0.356–0.984; $P = .043$). There is a remarkable benefit from the addition of any

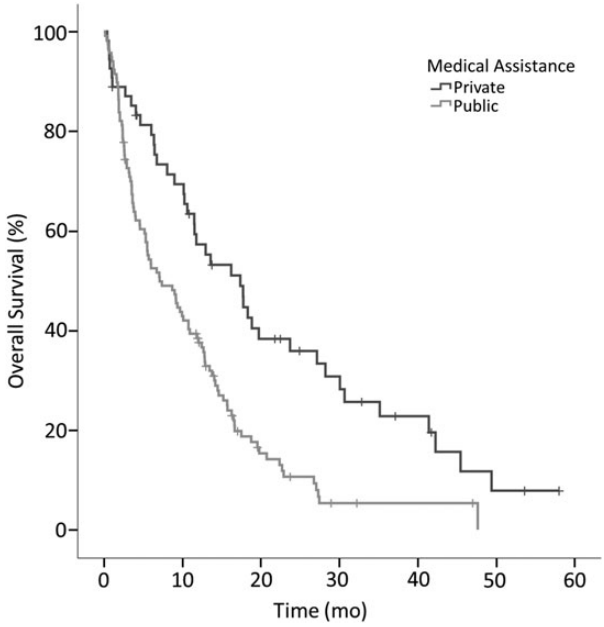

Fig. 2. Overall survival according to patients' medical assistance scenario ($P < .001$).

treatment after surgery regardless of the resection extent compared with best supportive care. The HR was 0.010 (95% CI, 0.003–0.033; $P < .001$) for gross total tumor resection followed by RT concurrent with chemotherapy, which is currently the standard of care for GBM.

Discussion

To date, this study is the largest and most comprehensive series examining the survival of Brazilian patients with GBM. Median OS for the entire cohort was 10.2 months (95% confidence interval, 7.9–12.4), consistent with that of other developing countries.[11,20–22,29–31]

The outcome of GBM patients is dependent on well-known factors such as age, KPS, and extent of surgical resection, which was confirmed by our results (Table 1). The median age in this study was 59.3 years (range, 18–84), comparable to that in other Brazilian GBM patient series.[24–26] The benefit of gross total resection is highlighted by median survival of 14.1 months (95% confidence interval, 11.4–16.8). This survival is significantly longer than 7.1 months (95% confidence interval, 3.8–10.3) for partial resection and 3.3 months for biopsy only (95% confidence interval, 1.7–4.8 mo, $P < .001$; Table 1). Despite the wide variability, previous reports suggest that the extent of surgical resection is a predictor of longer survival regardless of the use of chemotherapy or RT.[6,8] In contrast, our results show that the impact of the extent of resection was directly influenced by additional treatment (chemotherapy and/or RT). Partial and gross total resections are not predictors of survival compared with biopsy only if no additional treatment is administered (Table 3).

Median OS for private hospital patients was 17.4 months (95% confidence interval, 11.1–23.7), which is slightly better than the established values in the literature[1–3] and clearly longer than 7.1 months (95% confidence interval, 3.8–10.4) for the public hospital patients ($P < .001$). The difference in OS highlights the heterogeneity of health care in Brazil, because when it is economically feasible to treat patients with the best care, it is possible to achieve results comparable to those in developed countries.[4,32–35] There is increasing evidence that socioeconomic status may affect the survival rate of GBM,[15,19,36–38] and the data available for Brazilian

Table 2. Comparison of private and public institutions

	Institution				*P*
	Private (HIAE)		Public (HSP-UNIFESP)		
	n	%	*n*	%	
Gender					
Male	28	51.9	78	66.7	.064[b]
Female	26	48.1	39	33.3	
Age, y					
<50	10	18.5	28	23.9	.429[b]
≥50	44	81.5	89	76.1	
KPS, %					
<70	7	25.0	42	35.9	.273[b]
≥70	21	75.0	75	64.1	
Number of surgical interventions					
1	46	85.2	91	77.8	.259[b]
≥2	8	14.8	26	22.2	
Extent of the first surgical intervention					
Biopsy	13	24.1	20	17.1	.395[b]
Partial Resection	20	37.0	55	47.0	
Gross total Resection	21	38.9	42	35.9	
Time from first symptom to surgery, days					
≤55	23	69.7	52	44.8	.012[b]
>55	10	30.3	64	55.2	
Postoperative RT					
Yes	42	77.8	78	66.7	.140[b]
No	12	22.2	39	33.3	
Number of RT lines					
1	35	83.3	78	100	<.001[a]
≥2	7	16.7	0	0.0	
Time from surgery to RT, wk					
<6	35	89.7	13	17.1	<.001[b]
≥6	4	10.3	63	82.9	
Chemotherapy					
Yes	38	70.4	53	45.3	.002[b]
No	16	29.6	64	54.7	
Chemotherapy regimens					
1	30	78.9	52	98.1	<.001[a]
≥2	8	21.1	1	1.9	
First-line treatment after surgery					
Best supportive care	12	22.2	39	33.3	<.001[b]
RT only	4	7.4	25	21.4	
RT and sequencing chemotherapy	6	11.1	28	23.9	
RT concurrent with chemotherapy	32	59.3	25	21.4	

[a]Fisher's test.
[b]Pearson's chi-square test.

Table 3. Multivariate analysis

Variable	HR	95% CI	*P*
Age <50 y	0.680	0.406–1.140	.144
KPS ≥70%	0.592	0.356–0.984	.043
Private institution (HIAE)	0.597	0.339–1.051	.074
Combined treatment strategies:			
Biopsy + best supportive care			
Biopsy + RT only	0.133	0.034–0.520	.004
Biopsy + RT and sequencing chemotherapy	0.023	0.005–0.115	<.001
Biopsy + RT concurrent with chemotherapy	0.051	0.010–0.268	<.001
PR + best supportive care	0.665	0.334–1.323	.245
PR + RT only	0.055	0.020–0.153	<.001
PR + RT and sequencing chemotherapy	0.018	0.006–0.052	<.001
PR + RT concurrent with chemotherapy	0.028	0.010–0.080	<.001
GTR + best supportive care	0.494	0.139–1.760	.277
GTR + RT only	0.056	0.021–0.151	<.001
GTR + RT and sequencing chemotherapy	0.030	0.010–0.089	<.001
GTR + RT concurrent with chemotherapy	0.010	0.003–0.033	<.001

Abbreviations: PR, partial resection; GTR, gross total resection.

patients, albeit limited, suggest that low levels of education and family income are factors influencing survival.[25] Therefore, it is possible that privately insured patients might enjoy a higher socioeconomic status, and this result partially explains a better OS. However, our study did not assess socioeconomic variables.

Despite the survival differences between the analyzed centers, the medical assistance scenario itself was not found to be an independent predictor of survival (HR, 0.597; 95% CI, 0.339–1.051; $P = .074$; Table 3). Substantial data support differing quality of care depending on insurance status (public vs private) for brain tumor patients.[15,39–42] Curry et al.[15] observed in the United States that private insurance patients had decreased mortality (odds ratio, 0.81; 95% CI, 0.68–0.97; $P = .02$) compared with patients in the public health system (Medicare). Yabroff et al.[42] found that the type of health insurance was significantly associated with receiving standard-of-care therapy for GBM. In addition, El-Sayed et al.[40] reported more postoperative complications among nonprivately insured patients. In Brazil, previous reports of other tumors (prostate, kidney, and breast cancers) suggest the same trend of disparities between medical assistance scenarios.[43–46] Data regarding the outcome of GBM patients with respect to the health care setting are scarce in Brazil. Lynch et al.[25] analyzed patients from 2 diverse hospitals (a private and a public institution) and observed a higher mortality for public patients in a nonadjusted analysis (HR, 2.59; 95% CI, 1.29–5.18; $P = .007$). However, when adjusted for age, KPS, and RT status, there was no difference between institutions (HR, 1.54; 95% CI, 0.67–3.56; $P = .313$).[25] Our findings consistently show a significantly higher median survival for private patients in univariate analysis (Fig. 2). However, we could not detect differences between the private and public hospitals when adjusting for other relevant prognostic factors, such as KPS and age (HR, 1.675; 95% CI, 0.951–2.949; $P = .074$; Table 3). Access to treatment after surgery probably explains the survival disparity among the analyzed centers. At the private center, most patients (59.3%) received the standard-of-care strategy,[1] whereas at the public institution, only a small proportion (21.4%) were treated equivalently. Historical data have demonstrated the impact of RT concurrent with TMZ for GBM treatment.[1–3] Nevertheless, TMZ was available only after 2009 in our public hospital. This difference may have reduced the survival of those patients. Our findings highlight the need for consistent management to improve survival. The HR is 0.010 (95% CI, 0.003–0.033; $P < .001$) for the maximum feasible tumor resection followed by RT concurrent with chemotherapy compared with best supportive care. This result is similar to that obtained by Yabroff et al.,[42] who observed an HR of 0.26 (95% CI, 0.19–0.36) for American patients receiving RT concurrent with TMZ compared with no adjuvant treatment. Unfortunately, this is not a practical approach worldwide because of its high cost and technical complexity.[20,21,29,47,48]

Another explanation for the difference between the 2 hospitals is admission to the health care system, which may be assessed by the interval between diagnosis and treatment. Most patients from the public hospital (55.2%) had a significantly longer interval from first symptom to surgery (>55 days). However, this difference was not associated with survival. These results agree with previous data from Lynch et al.[25] that reported a longer duration of symptoms for public health care patients (average of 2.76 ± 2.26 mo), although the difference is not statistically significant. Although it is not currently a reliable prognostic factor, failing to obtain adequate care when symptoms first occur may be related to poor outcome.[39] Furthermore, patients who are referred later may present with more advanced disease and may require urgent admission. Lynch et al.[25] found that uninsured individuals had more advanced disease at presentation. Furthermore, Curry et al.[15] demonstrated that patients with private insurance were more likely to have non-urgent admissions. Additional determinants may play a role in delayed presentation. Idowu and Apemiye[49] studied Nigerian patients with brain tumors and observed that factors associated with treatment delay were primarily patient related (62%) or a result of the inability of the physician to recognize disease severity (21%).

The interval between surgery and RT is not well established as a reliable prognostic variable.[28] The controversy is illustrated by the

most recent studies enrolling patients treated in the TMZ era. Noel et al.[32] investigated patients specifically treated according to the EORTC-NCIC protocol[1] and found no effect of time until initiation of RT. Similarly, Graus et al.[35] found no effect on OS, although early initiation of RT ($\leq$6 wk) was associated with longer progression-free survival. Conversely, Valduvieco et al.[50] showed a detrimental effect on OS if the initiation of RT was delayed >6 weeks. In our study, privately insured patients commonly underwent postoperative RT in <6 weeks (89.7%). Only 17.1% of patients in the public system underwent RT in <6 weeks ($P < .001$). However, this difference was not associated with survival. This contrast might be explained by the imbalance between supply and demand for RT, which results in waiting lists in publicly funded health systems around the world.[51] There remains a shortage of RT resources in Brazil, although the number of radiation units (0.93/million population) is comparable to the global median in Latin American countries (0.45–2.73/million).[52]

Our study has some limitations. We did not assess data regarding the patient's' family income or racial/ethnic distribution. These are recently identified socioeconomic predictors of survival[15,16,38,39] and could have an impact on the outcomes of the analyzed patients. With respect to racial impact, we must emphasize that the miscegenation of our population could mitigate the importance of such a predictive factor. This is a retrospective study with a relatively small cohort and is subjected to limitations. Our findings are derived from a sample bounded by time and space, and they may not be generalizable to other studies. However, by selecting patients from 2 diverse health care settings, we were able to evaluate the likely spectrum of care available in Brazil. Last, in Brazil the vast majority of the population has access to health care only through SUS, whereas privately insured patients benefit from both public and private systems. This interchangeable condition did not appear to influence our results, but in what degree it happens is speculative.

In this retrospective subset of Brazilian GBM patients, we observed obvious disparities between the analyzed hospitals. However, the medical assistance scenario was not found to be an independent predictor of survival. Increasing patient access to the best resources is still a challenging task in developing countries. Brazil is an extraordinary example of this limitation given its extreme financial and medical disparities. Because medical insurance is not available to most Brazilian patients, a carefully planned strategy by the public health care system is necessary to provide quality standard-of-care treatment and address the disparities reported here to attain outcomes comparable to those obtained in developed countries.

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