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Patterns and disparities of care in glioblastoma

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Abstract

Background. Glioblastoma is an aggressive disease with a defined standard of care offering crucial survival benefits. Disparities in care may influence treatment decisions. This study seeks to evaluate potential patterns in care delivery using the National Cancer Database (NCDB).

Methods. We evaluated the NCDB from 1998 to 2011 for patients diagnosed with glioblastoma older than 20 years of age in order to describe current hospital-based demographics, rates of treatment modality by age, race, gender, likelihood of receiving treatment, and survival probabilities.

Results. From 1998 to 2011, 100 672 patients were diagnosed with glioblastoma in the United States. Of these, 54% were younger than 65 years of age, while 20% were 75 years of age or older. The most common type of treatment was surgery (73%), followed by radiation (69%) and chemotherapy (50%). Eleven percent of patients did not receive any form of therapy. Patients receiving no form of treatment were more likely to be older, female, black, or Hispanic. Tumors that did not involve brainstem, ventricles, or the cerebellum were associated with more aggressive treatment and better overall survival. The median survival was 7.5 months. The use of concomitant surgical resection, chemotherapy, and radiation demonstrated greater survival benefit.

Conclusions. Median survival for glioblastoma is significantly less than reported in clinical trials. Sociodemographic factors such as age, gender, race, and socioeconomic status affect treatment decisions for glioblastoma. The elderly are greatly undertreated, as many elderly patients receive no treatment or significantly less than standard of care.

Key words

Glioblastoma | treatment | survival | patterns of care

Glioblastoma is the most common malignant primary brain tumor and affects over 12 000 cases projected annually in the United States.[1] It is an infiltrative tumor known to spread along axonal pathways, and cannot be effectively treated by surgery alone.[2] Improvements in survival have been demonstrated with receipt of surgery, concurrent chemoradiation, and adjuvant temozolomide; as demonstrated by the European Organization for Research and Treatment of Cancer (EORTC) 22981/26981 and National Cancer Institute of Canada Clinical Trials group (NCIC) CE.3 randomized trial.[3] This approach achieved a 14.6-month survival, setting the standard of care.[3] Survival is now reported to be greater than 20 months in clinical trials.[3–7]

Inequalities in treatment delivery have been described in different types of cancer,[8–10] due to disparities in receiving optimal and timely medical care. Optimal treatment may not be widely accessible and factors such as race, gender, education level, insurance, and median income may have

a higher role than expected in treatment decision making. Evidence from single center experiences have reported inequalities in access to established neuro-oncology centers based on sociodemographic factors.[11–13] Our study offers an analysis of the largest clinical cancer registry, the American College of Surgeons National Cancer Database (NCDB), to describe current patterns of care and their influence in survival in patients with glioblastoma.

Methods

We queried the NCDB, from the American College of Surgeons and the American Cancer Society.[14] NCDB gathers extensive and retrospective data of newly diagnosed cancer cases in the U.S. from over 1500 accredited hospitals. A total of 100672 glioblastoma patients who were 20 years or older were identified from 1998 to 2011. Glioblastoma was defined with the International Classification of Diseases for Oncology (ICD-O-3) histology/behavior codes 9440/3, 9441/3, and 9442/3. Primary tumor site was limited to C70.0-C72.9, C75.1-C75.3, and was reported as: cerebrum (C71.0) and brain lobes (C71.1, C71.2, C71.3, C71.4), brain stem (C71.7), cerebellum (C71.6) and ventricles (C71.5), and others (71.8–71.9). Data were abstracted according to the Facility Oncology Registry Data Standards (FORDS) manual. Descriptive statistics were reported overall, and stratified arbitrarily by age groups (20–49, 50–64, 65–74, ≥75) using frequencies for categorical variables. Patients were classified in a particular treatment modality group if they received that therapy during their first course of treatment.

The insurance variable was determined at the time of diagnosis and/or treatment. Median household income and education status were derived from the 2000 U.S. Census data based on the patient's residential zip code at the time of diagnosis.[15]The education variable refers to the number of adults who did not graduate from high school and was divided in ≥ 29%, 20–28.9%, 14–19.9%, and ≤14%. Region was defined by comparing the patient's residential state and county Federal Information Processing Standard (FIPS) code at diagnosis to the 2003 files Rural-Urban Continuum Codes as developed by the U.S. Department of Agriculture Economic Research Service. Counties with a population size larger than 250000 were defined as metropolitan, population size from 2500 to 250000 was designated as urban region, and less than 2500 as rural region.

Logistic regression was performed for factors that influence treatment receipt. Statistically significant variables in univariate models were included in the regression models. Backward model selection was performed to identify critical variables with lower values of Akaike Information Criterion (AIC). Due to missing covariates, 9463 cases were excluded from the treatment combination logistic regression model.Tumor size was removed from the analysis due to the great number of missing values.

Over 10% of data were missing in the covariates of race, Hispanic heritage, and dwelling region, as well as treatment outcomes of radiation, chemotherapy, and surgery status. We employed 2 methods for handling missing data, including all covariates, and made comparison between both methods to reduce potential bias when fitting the logistic regression and proportional hazard regression models. The methods included: the conventional approach, which is based on treating missing information as an unknown group for each covariate and the multiple imputation approach with fully conditional specification. There was no statistically significant difference in values of the parameter estimates between models and the decision was made to report the results from the conventional approach.

The definition of survival was the interval of time from diagnosis until death due to all causes. Data for survival analysis in this article were available from 1998 to 2006 due to the 5-year NCDB lag in collecting and reporting survival and follow-up data (n = 61346). We analyzed treatment delivery and survival in 2 time periods, from 1998 to 2004 and after 2005, due to the acknowledgment of the standard of care in 2005 by Stupp et al,[3] who demonstrated the benefits of temozolomide as concomitant and adjuvant treatment to radiotherapy. Kaplan-Meier estimates of overall survival were calculated. Cox proportional hazards models were employed to assess the risk of mortality according to receiving treatment while adjusting for other potential risk factors. All analyses were performed with SAS software package version 9.4 for Microsoft Windows on x64 (SAS Statistical Institute, Cary, NC).

Results

From 1998 through 2011, a total of 100672 subjects aged 20 years and older diagnosed with glioblastoma were included in the NCDB (Table 1). Almost 54% of patients (n = 54142) were younger than 65 years of age, while 20% were 75 years of age or older (n = 20414). As expected, males were more prevalent than females (57% vs. 43%), and the vast majority of patients were white. Only 5% of cases were noted to be patients of Hispanic heritage. Forty-five percent of patients had private insurance at the time of diagnosis, while 42% of patients had Medicare. Seventy-three percent of patients younger than 65 years of age had private insurance, while 81% of those aged 65 years and older were insured under Medicare. Those with no insurance tended to be younger (6.8% in those under 65 years versus 0.9% in those aged 65 years and older). The majority of patients lived in a county with a median income of $46000 or more and with a low percentage of people who did not graduate from high school. Three-quarters lived in a metropolitan area.

Diagnoses of giant cell glioblastoma and gliosarcoma were both rare (0.7% and 2%, respectively) compared to a diagnosis of glioblastoma, not otherwise specified (NOS). Diagnosis was confirmed by pathology in 91.75% of the patients, was based on imaging modalities in 4.81%, and was diagnosed by direct visualization without microscopic confirmation in 0.35% of the patients. Of patients who did not receive treatment, 61.82% underwent biopsy and the rest were diagnosed by clinical and imaging suspicion.

The primary site was mostly cerebrum/brain lobes (74.6%), followed by others (24.1%), and ventricle/cerebellum/brain stem (1.4%). As first course of treatment,

Table 1 Demographic characteristics of adults diagnosed with glioblastoma in the National Cancer Database, 1998–2011

		20–49 y/o N = 16336		50–64 y/o N = 37806		65–74 y/o N = 26116		≥ 75 y/o N = 20414		Total N = 100672	
		N	%	N	%	N	%	N	%	N	%
Sex	Male	10268	62.9	22634	59.9	14594	55.9	9779	47.9	57275	56.9
	Female	6068	37.1	15172	40.1	11522	44.1	10635	52.1	43397	43.1
Race	White	14282	87.4	34328	90.8	24061	92.1	19132	93.7	91803	91.2
	Black	1259	7.7	2167	5.7	1194	4.6	715	3.5	5335	5.3
	Others	591	3.6	879	2.3	563	2.2	342	1.7	2375	2.4
	Unknown	204	1.3	432	1.1	298	1.1	225	1.1	1159	1.2
Hispanic	Yes	1209	7.4	1866	4.9	1122	4.3	665	3.3	4862	4.8
	No	13996	85.7	33019	87.3	22909	87.7	18022	88.3	87946	87.4
	Unknown	1131	6.9	2921	7.7	2085	8.0	1727	8.5	7864	7.8
Insurance	None	1343	8.2	2347	6.2	288	1.1	137	0.7	4115	4.1
	Private	11455	70.1	27863	73.7	4241	16.2	2167	10.6	45726	45.4
	Medicaid	1946	11.9	2660	7.0	376	1.4	193	0.	5175	5.1
	Medicare	726	4.4	3457	9.1	20399	78.1	17365	85.1	41947	41.7
	Unknown	566	5.3	1479	3.9	812	3.1	552	2.7	3709	3.7
Income	<$30 000	1808	11.1	4328	11.5	3156	12.1	2456	12.0	11748	11.7
	$30 000–$34 999	2597	15.9	6433	17.0	4831	18.5	3855	18.9	17716	17.6
	$35 000–$45 999	4227	25.9	9807	25.9	7021	26.9	5589	27.4	26644	26.5
	≥ $46 000	6591	40.4	14973	39.6	9610	36.8	7421	36.4	38595	38.3
	Unknown	1113	6.8	2265	6.0	1498	5.7	1093	5.4	5969	5.9
Education[a]	≥29%	2545	15.6	5516	14.6	3844	14.7	2833	13.9	14738	14.6
	20–28.9%	3339	20.4	8023	21.2	5722	21.9	4521	22.2	21605	21.5
	14–19.9%	3539	21.7	8381	22.2	6140	23.5	4903	24.0	22963	22.8
	≤14%	5798	35.5	13618	36.0	8906	34.1	7064	34.6	35386	35.2
	Unknown	1115	6.8	2268	6.0	1504	5.8	1093	5.4	5980	5.9
Region	Metropolitan	12574	77.0	28413	75.2	19105	73.2	15275	74.8	75367	74.9
	Urban/rural	2623	16.1	7024	18.6	5347	20.5	3851	18.9	18845	18.7
	Unknown	1139	7.0	2369	6.3	1664	6.4	1288	6.3	6460	6.4
Primary site	Cerebrum/Brain lobes	12265	75.1	28381	75.1	19487	74.6	14896	73	75029	74.6
	Ventricle/cerebellum/ brainstem	435	2.7	471	1.3	252	1.0	218	1.1	1376	1.4
	Others	3636	22.3	8954	23.7	6377	24.4	5300	26.0	24267	24.1
Histology	GBM, NOS	15716	96.2	36724	97.1	25447	97.4	20025	98.1	97912	97.3
	Giant Cell GBM	233	1.4	254	0.7	156	0.6	76	0.4	719	0.7
	Gliosarcoma	387	2.4	828	2.2	513	2.0	313	1.5	2041	2.0
CT	Yes	10577	64.8	22698	60.0	12111	46.4	5174	25.4	50560	50.2
	No	5277	32.3	13910	36.8	13208	50.6	14721	72.1	47116	46.8
	Unknown	482	3.0	1198	3.2	797	3.1	519	2.5	2996	3.0
RT	Yes	12844	78.6	28935	76.5	17892	68.5	9936	48.7	69607	69.1
	No	3214	19.7	7878	20.8	7180	27.5	8954	43.9	27226	27.0
	Refused	175	1.1	743	2.0	903	3.5	1431	7.0	3252	3.2
	Unknown	103	0.63	250	0.66	141	0.54	93	0.46	587	0.6
Combination	RT+CT+S	8607	52.7	17879	47.3	9096	34.8	3447	16.9	39029	38.8
	RT+CT	1407	8.6	3615	9.6	2267	8.7	1209	5.9	8498	8.4
	RT+S	2114	12.9	5264	13.9	4299	16.5	2884	14.1	14561	14.5
	Surgery only	1867	11.4	458	12.1	4219	16.2	4208	20.6	14882	14.8

Table 1 *Continued*

		20–49 y/o N = 16336		50–64 y/o N = 37806		65–74 y/o N = 26116		≥ 75 y/o N = 20414		Total N = 100672	
		N	%	N	%	N	%	N	%	N	%
	None	754	4.6	2280	6.0	2685	10.3	5344	26.2	11063	11.0
	Others	1587	9.7	4180	11.1	3550	13.6	3322	16.3	12639	12.6
Surgery	Total/Gross/Partial	13481	82.5	29742	78.7	18854	72.2	11333	55.5	73410	72.9
	Biopsy only	1465	9.0	4442	11.8	3537	13.5	3296	16.2	12740	12.7
	None	1379	8.4	3601	9.5	3698	14.2	5759	28.2	14437	14.3
	Unknown	11	0.1	21	0.1	27	0.1	26	0.1	85	0.1

CT, chemotherapy; GBM, glioblastoma; NOS, not otherwise specified; RT, radiotherapy; S, Surgery; y/o: years old
[a]Education refers to the percentage of non-High school graduates in the patient's residential zip code.

only 50% of cases received chemotherapy, 69% received radiation therapy, and 73% underwent surgery. Eleven percent of all patients did not receive any form of therapy. Major differences were found across age groups in treatment frequencies; this was notable among elderly patients. In those aged 75 years and older, only 17% received standard therapy, while 44% did not receive radiation, 72% did not receive chemotherapy, 44% did not receive surgery or biopsy, and 26% did not receive any form of treatment. In those aged 20 to 49 years, 53% received standard care and only 5% received no treatment. The rest of the demographics are summarized in Table 1.

We compared the frequency of combination treatment from 1998 to 2004 and from 2005 to 2011. Before 2005, 12 485 patients (26.67%) received radiation, chemotherapy, and surgery and 5506 (11.76%) received no treatment. After 2005, 26 544 (49.29%) received radiation, chemotherapy, and surgery, but the no treatment group remained similar at 5557 (10.32%).

Logistic regression was used to determine predictors of treatment by receiving radiation therapy, chemotherapy, and surgery (standard therapy) (Table 2). This analysis was performed overall and in patients diagnosed before 2004 and after 2005; the determinants of standard of care receipt were the same between both time periods. An inverse association was found between age of diagnosis and receiving standard therapy, with increasing receipt of all 3 treatments in progressively younger age groups. After controlling all the other factors in the model, females were about 10% less likely to receive standard therapy than males with glioblastoma. Patients identified as non-white racial groups and those of Hispanic heritage were more than 10% less likely to receive chemotherapy, radiation, and surgery than white and non-Hispanic patients. Patients with any type of insurance were significantly more likely to have received standard of care than those without insurance. Those living in counties with progressively lower median incomes and counties with a progressively lower percentage of patients that graduated high school were increasingly less likely to have received radiation therapy, chemotherapy, and surgery. Compared to patients diagnosed from 1998 to 2004, those diagnosed from 2005 to 2011 were 3 times more likely to have received all 3 treatments in the first course of therapy. Patients with giant cell glioblastoma or gliosarcoma were more likely to have received standard therapy than those with glioblastoma, NOS. Patients receiving standard therapy were almost 3 times more likely to have tumors that did not involve brainstem, ventricles, cerebellum, or the cerebrum compared to primary location in the cerebrum (OR = 2.95, $P < .0001$).

Overall, median survival for glioblastoma patients was 7.5 months, with 2.5% (1560/61346) surviving to 2 years and 2.0% (1234/61346) surviving up to 5 years. Patients diagnosed after 2004 had higher survival estimates compared to patients diagnosed before 2004 (median survival 8.4 months versus 7.2 months, respectively) (Figure 1). The log-rank test comparing survival for these 2 periods was significant ($P < .0001$)(Figure 1).

Based on our analysis (Table 1), the majority of patients received some form of treatment. It is important to note, however, that a higher percentage of elderly patients (65 years and older) did not receive (34.67% versus 20.48%) or refused (5.01% versus 1.69%) initial radiation therapy as compared with younger patients (20 to 64 years). Patients who did not receive radiation had lower survival compared to patients who did receive radiation ($P < .0001$) (Figure 2). The 1-, 3-, and 5-year survival estimates in patients that did not receive radiation were 14%, 3%, and 2% compared with 39%, 7%, and 4% in patients who did receive radiation.

Chemotherapy was associated with an increase in survival. The 1-, 3-, and 5-year survival estimates in patients who did not receive chemotherapy was 19%, 3%, and 2% compared with 49%, 10%, and 5% in patients who did receive chemotherapy. Surgery was also related to an increase in survival ($P < .0001$). The 1-, 3-, and 5-year survival estimates in patients who did not receive surgery as initial treatment was 12%, 25%, and 1% compared with 39%, 8%, and 4% in patients who did receive surgery as initial treatment.

Using Cox proportional hazards modeling, average effects of predictors on survival were examined (Table 3). As expected, improved survival was inversely associated with age at diagnosis, with those aged 20 to 49 years having 65% longer survival than those aged 75 years or more. Glioblastoma patients who were of non-white race and/or that were of Hispanic heritage had better survival than those who reported white race and non-Hispanic heritage. Females had 5% better survival than male patients.

Table 2 Multivariate logistic regression of risk factors for receiving standard of care (surgery, chemotherapy, and radiation) of adults diagnosed with glioblastoma in the National Cancer Database, 1998–2011

		Odds ratio	95% CI	*P* value
Age group (years)	20–49	6.15	5.77–6.56	<.0001
	50–64	4.36	4.12–4.62	<.0001
	65–74	2.78	2.65–2.92	<.0001
	≥75	ref	-	-
Race	Black	0.78	0.73–0.83	<.0001
	Other	0.87	0.79–0.96	.004
	Unknown	0.65	0.56–0.75	<.0001
	White	ref	-	-
Sex	Female	0.90	0.88–0.94	<.0001
	Male	ref	-	-
Hispanic	Yes	0.87	0.81–0.94	.0002
	Unknown	1.05	0.99–1.11	.098
	No	ref	-	-
Insurance	Medicaid	1.36	1.24–1.49	<.0001
	Medicare	1.65	1.51–1.79	<.0001
	Private	1.97	1.84–2.12	<.0001
	Not insured	ref	-	-
Income	≤$30 000	0.81	0.76–0.86	<.0001
	$30 000–$34 999	0.86	0.82–0.91	<.0001
	$35 000–$45 999	0.94	0.91–0.98	.005
	> $46 000	ref	-	-
Education[a]	≥29%	0.79	0.74–0.83	<.0001
	20–28.9%	0.87	0.83–0.91	<.0001
	14–19.9%	0.94	0.90–0.98	.002
	≤14%	ref	-	-
Region	Metro	0.96	0.93–1.00	.077
	Unknown	0.85	0.76–0.95	.005
	Urban/Rural	ref	-	-
Primary tumor site	Others	1.93	1.67–2.22	<.0001
	Cerebrum and brain lobes	2.95	2.56–3.39	<.0001
	Ventricle/cerebellum/brainstem	ref	-	-
Histology	Gliosarcoma	1.46	1.32–1.61	<.0001
	Giant Cell GBM	1.33	1.12–1.56	.001
	GBM, NOS	ref	-	-
Years of Diagnosis	2005–2011	3.03	2.95–3.13	<.0001
	1994–2004	ref	-	-

GBM, glioblastoma; NOS, not otherwise specified; ref, reference
[a]Education refers to the percentage of non-High school graduates in the patient's residential zip code.

Patients on Medicaid and Medicare had an increased risk of mortality compared to those with no insurance (11% and 12%, respectively). Those with private insurance had similar survival outcomes to those with no insurance. Income levels below $46 000 were associated with a 7% to 10% increased risk of mortality. A diagnosis of giant cell glioblastoma was associated with 25% better survival than a diagnosis of glioblastoma, NOS, while those with a glioblastoma in the cerebrum had the poorest survival. Those receiving any treatment had statistically significantly better survival than those receiving no treatment. However, comparing the various treatment combinations revealed that patients receiving radiation, chemotherapy, and surgery had significantly better survival than any other treatment combination (Figure 2).

Discussion

Using the NCDB we found 100 672 patients with a diagnosis of glioblastoma. This group had a median survival of

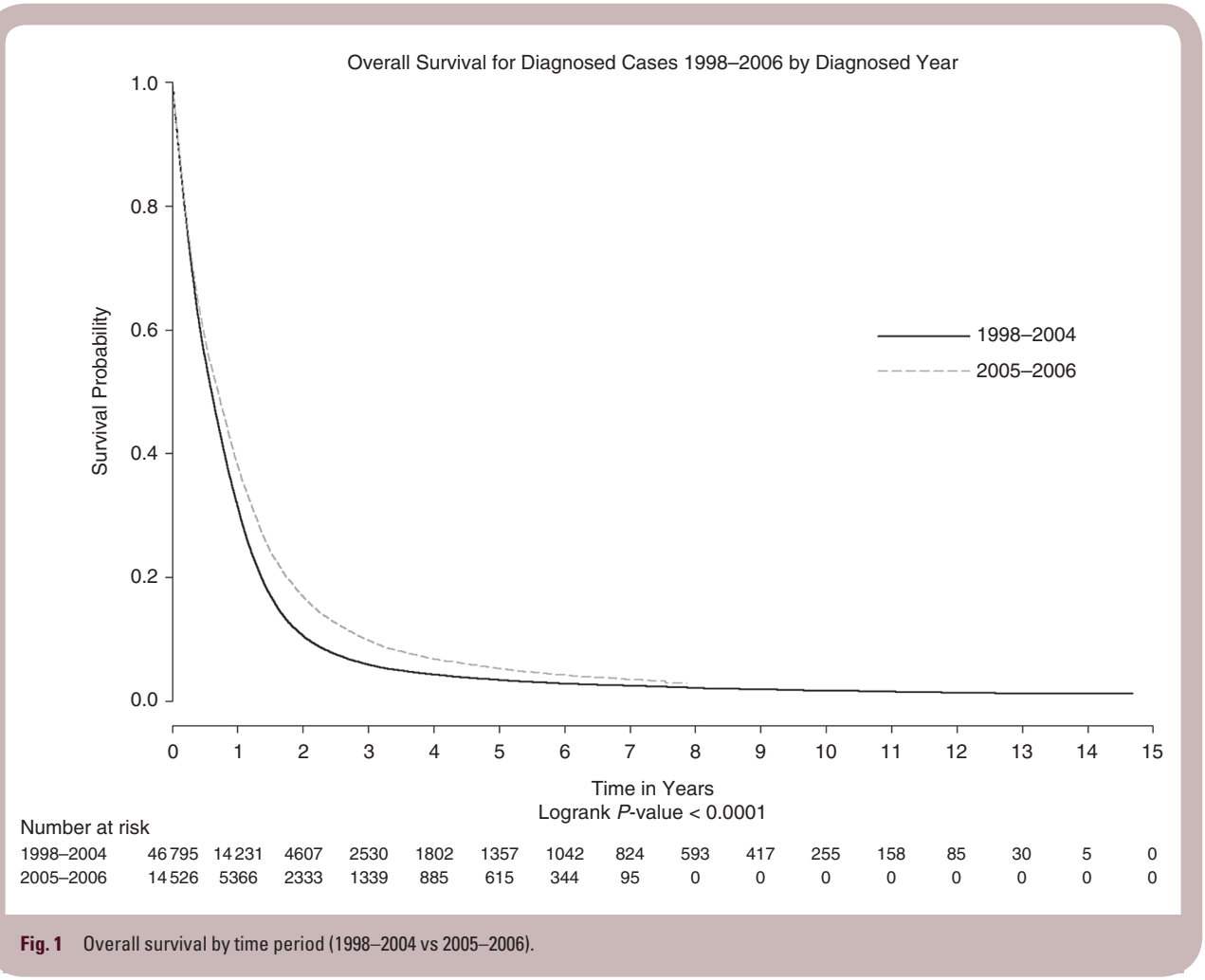


Fig. 1 Overall survival by time period (1998–2004 vs 2005–2006).

7.5 months, which is significantly less than in published clinical trials, but similar to population based analysis[16]; this likely reflects a real-world survival estimation of this disease. Our study includes an overview of current hospital-based patterns of care in glioblastoma, representing over 70% of the population.

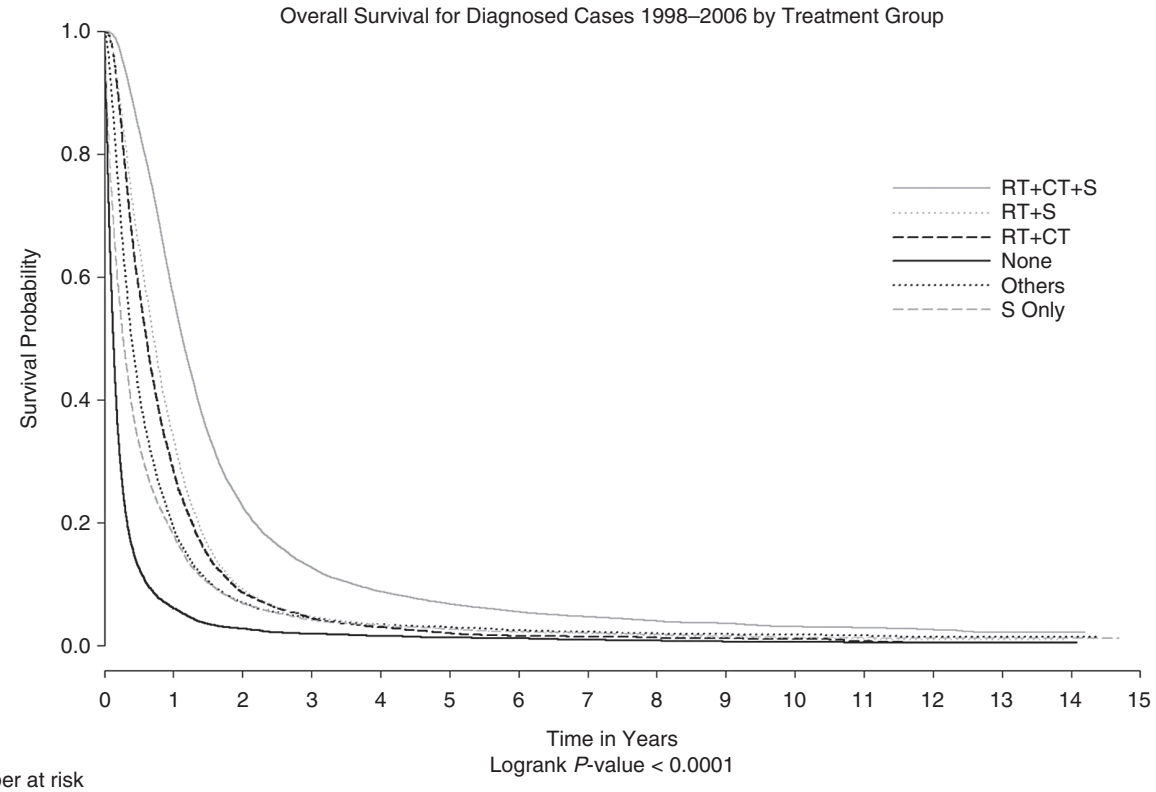
The frequency of glioblastoma was higher in males, whites, and non-Hispanics. These findings match the demographics described in other U.S. population studies.[1,11] The strongest determinant of treatment was age; however, other factors such as race, gender, histology, primary site location, education, and insurance status also influenced the likelihood and modality of treatment receipt. We found females and Hispanics were 10% less likely to receive standard therapy, but female gender was found to be a protective factor for mortality compared to males. The survival benefits of the female gender have also been reported in smaller cohorts.[17] This may be associated with less comorbidities compared to males,[18] and the overall younger age of females in our cohort; over 75% of women were less than 65 years of age. Females are also reported to be more likely to have IDH-mutant glioblastoma,[19] which is associated with a better prognosis.

We found the use of standard combination therapy—tumor resective surgery, radiation, and chemotherapy—was low and was more common in younger patients, among patients with higher socioeconomic status, and among those living in a region with higher educational level. Only 53% of patients from 20 to 49 years old received standard therapy. These findings demonstrate the uneven distribution of care even in younger patients.

Overall, the most commonly used method of treatment was surgery (73%), followed by radiotherapy and chemotherapy (69% and 50%, respectively). Elderly patients were commonly undertreated, presenting lower frequencies for any form of treatment. We found a 2-fold decrease in treatment delivery with increasing age group. The cause of the large variation in treatment receipt could be related to both difficulties in access to neuro-oncology services and physicians' beliefs on the usefulness of surgery and radiation therapy in nonoptimal patients.[12,13,20–22]

Following the EORTC/NCIC trial published in 2005, there has been a significant change in the overall survival of glioblastoma patients.[23] Our analysis demonstrated an increased frequency of the standard treatment of radiation, chemotherapy, and surgery receipt after 2005, and also a decreased frequency of receiving surgery only or no treatment. Population-based analysis has also demonstrated a significant improved survival after temozolomide adoption irrespective of age.[16]

Treatment delivery regardless of modality was associated with better survival. Similar effects are found in other



Number at risk

RT+CT+S	7047	400	167	111	86	65	51	32	25	15	10	7	7	3	1	0
RT+S	9173	1707	597	371	275	221	164	109	71	54	37	23	11	4	1	0
RT+CT	4122	1147	340	173	112	71	45	30	20	16	9	5	2	0	0	0
None	19 163	10 655	4186	2328	1578	1153	800	508	316	225	131	77	42	15	2	0
Others	12 531	4081	1076	543	380	278	203	156	109	77	49	33	17	6	0	0
S Only	9285	1607	574	343	256	184	123	84	52	30	19	13	6	2	1	0

Fig. 2 Overall survival by combination therapy from 1998–2006.

cohorts, including in elderly patients, particularly for gross total resection and adjuvant therapies[20,24]; even if higher complication rates are expected.[12,24] No large study has shown significant side effects or decreased quality of life in elderly patients that receive chemotherapy or radiation alone,[25,26] and the survival benefits were comparable to younger adults.[27,28] However, elderly patients are more likely to have greater comorbidities and are at higher risk of mortality. Standard treatment, short course radiotherapy schemes, and temozolomide monotherapy are alternative therapies in elderly patients that have demonstrated survival benefits.[29–32] Nevertheless, even after adjusting for comorbidities and treatment type, elderly patients tend to have the worst outcomes. This observation may be partially explained by a more aggressive tumor biology, driven by the higher number of mutations and a less favorable molecular profiling.[33]

The majority of glioblastoma patients in our analysis lived in metropolitan areas and had a high socioeconomic status. The median survival of 7.5 months demonstrates the working state of care for glioblastoma in the U.S. and lack of optimal receipt of standard treatment. Patients with private insurance were more likely to be treated; still, survival was similar when comparing patients with private and no insurance. Similar results regarding socioeconomic factors have been previously described in the literature.[34]

Survival analysis of patients on Medicaid and Medicare demonstrated an increased risk of mortality (11% and 12%, respectively), compared to patients without insurance. Other studies have also highlighted the increased mortality risk of patients in Medicaid.[35] Several factors related to patients' age and lifestyle differences between payer groups maybe more important than insurance status. Previous investigation of the NCDB in patients with glioblastoma demonstrated over 80% of elderly patients had either Medicare or Medicaid.[36]This large elderly population could result in a higher number of Medicare and Medicaid patients being frail and having increased risk of mortality. Other possible explanations could be related to longer care wait-time, economic difficulties in treatment distribution, and a higher likelihood of receiving palliative care due to its coverage under Medicare. Health care provider bias and institutional type may also play a role impacting outcomes

Table 3 Factors associated with mortality in adults diagnosed with GBM from the National Cancer Data Base, 1998–2006 from a multivariate Cox proportional hazards model

		Hazard ratio	95% CI	*P* value
Age group (years)	20–49	0.35	0.34–0.37	<.0001
	50–64	0.54	0.52–0.56	<.0001
	65–74	0.73	0.71–0.75	<.0001
	≥75	ref	-	-
Race	Black	0.88	0.85–0.92	<.0001
	Other	0.72	0.67–0.76	.007
	Unknown	0.82	0.75–0.89	<.0001
	White	ref	-	-
Sex	Female	0.95	0.94–0.97	<.0001
	Male	ref	-	-
Hispanic	Yes	0.80	0.77–0.84	.0002
	Unknown	1.05	1.01–1.08	.005
	No	ref	-	-
Insurance	Medicaid	1.11	1.05–1.18	<.0001
	Medicare	1.12	1.07–1.18	<.0001
	Private	0.98	0.94–1.03	<.0001
	Not insured	ref	-	-
Income	≤$30 000	1.08	1.04–1.12	<.0001
	$30 000–$34 999	1.10	1.07–1.14	<.0001
	$35 000–$45 999	1.07	1.05–1.10	<.0001
	> $46 000	ref	-	-
Education[a]	≥29%	0.96	0.93–0.99	.002
	20–28.9%	0.98	0.95–1.01	<.0001
	14–19.9%	1.01	0.99–1.04	<.0001
	≤14%	ref	-	-
Primary site	Others	1.03	0.96–1.11	.443
	Cerebrum and brain lobes	0.89	0.82–0.96	.002
	Ventricle/cerebellum/brainstem	ref	-	-
Histology	Gliosarcoma	1.03	0.97–1.10	.32
	Giant Cell GBM	0.74	0.66–0.82	<.0001
	GBM, NOS	ref	-	-
Years of Diagnosis	2005–2006	0.90	0.88–0.92	<.0001
	1998–2004	ref	-	-
Treatment	Radiation + Chemotherapy+Surgery	0.25	0.25–0.26	<.0001
	Radiation+Surgery	0.34	0.33–0.36	<.0001
	Radiation+Chemotherapy	0.40	0.38–0.41	<.0001
	Surgery	0.57	0.55–0.59	<.0001
	Other Combinations	0.47	0.46–0.49	<.0001
	None	ref	-	-

GBM, glioblastoma; NOS, not otherwise specified
[a]Education refers to the percentage of non-High school graduates in the patient's residential zip code.

for Medicaid and Medicare patients; private insurance may result in more specialized care.

The main limitations of our analysis are based on its retrospective nature; we performed multivariate analysis and Akaike Information Criterion to mitigate bias and ensure a correct interpretation of the variables. Due to a great number of missing values and the inherent limitations of our model we were unable to adjust for secondary glioblastoma subtype, which are well-known prognostic factors (eg, *IDH1/2* mutations and *MGMT* promoter methylation status). In addition, the lack of specific chemotherapy received, single vs multiple chemotherapy agent, radiation dosing, disease progression, and treatment failure information may pose limitations in

analyzing our findings. As NCDB only gathers cancer-accredited centers, it is possible that patients with fewer options for treatment were not captured. Our data, however, show important differences in treatment distribution related to age, race, gender, and socioeconomic status, even in settings where clinical trial enrollment and maximal therapy is expected.

In summary, despite the acknowledged benefits of the EORTC regimen, age, race, gender, and socioeconomic status are important determinants that influence treatment delivery in glioblastoma. Moreover, overall survival in patients with glioblastoma is dramatically less than the survival reported in published clinical trials.

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