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Demographic, Clinical and Area-based Socioeconomic Factors Associated with Glioblastoma Multiforme Prognosis: An Analysis of Surveillance Epidemiology and End Results Data

Abstract

Glioblastoma multiforme (GBM) is the most common and most lethal primary brain tumor, with a five-year relative survival probability of 5.7 percent. This study was conducted to confirm known GBM prognostic factors and to examine prognostic capacity of additional demographic, clinical, and area-based socioeconomic factors. Cases were diagnosed with GBM from 2010 through 2013 in one of 18 Surveillance, Epidemiology and End Results (SEER) registries. Cox proportional hazards regressions, univariate and multivariate, were used to determine hazard ratios (HR) reflecting associations with GBM survival probability. Analyses confirmed that age, treatments, and tumor size and extension were independently and significantly associated with GBM prognosis. There were weak, yet statistically significant and independent, associations between GBM survival probability and race, insurance, marital status, and two county-level socioeconomic factors. GBM survival probability was significantly lower among those who were older (HR per year: 1.032, 95% CI: 1.031-1.034), those with Medicaid (compared to those insured through other means, HR: 1.197, 95% CI: 1.113-1.288), those who were single and separated or divorced (compared to those who were married, HR: 1.129, 95% CI: 1.056-1.207; HR: 1.184, 95% CI: 1.096-1.278, respectively), those who did not have surgery (HR: 1.733, 95% CI: 1.643-1.828) and radiation (HR: 2.714, 95% CI: 2.579-2.855), those with larger tumors (HR: 1.335, 95% CI: 1.158-1.535), and those with some tumor extension (HR: 1.389, 95% CI: 1.323-1.458). GBM survival probability was significantly higher among females (HR: 0.941, 95% CI: 0.899-0.985), Asian/Pacific Islanders (compared to Whites, HR: 0.802, 95% CI: 0.721-0.893), those in counties with higher incomes (HR: 0.819, 95% CI: 0.770-0.871, and, unexpectedly, those in counties with higher percentages of less than high school education (HR: 0.879, 95% CI: 0.824-0.938). Associations between GBM prognosis and both contextual area-based and individual-level socioeconomic factors should be studied to better understand these complex relationships.

Keywords: Glioblastoma multiforme; Glioma; Socioeconomic status; Surveillance epidemiology and end results; Poverty

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Abbreviations: GBM: Glioblastoma Multiforme; TMZ: Temozolomide; KPS: Karnofsky Performance Status; SEER: Surveillance, Epidemiology and End Results; ICD: International Classification of Disease; HR: Hazard Ratios; MGMT: Methylguanine-DNA-Methyltransferase

Introduction

Glioblastoma multiforme (GBM), a WHO grade IV tumor of astrocytic lineage, is the most common primary malignant brain tumor and the most common malignant central nervous system tumor [1,2]. Despite advances in treatment over the past several decades, prognosis for patients diagnosed the GBM remains very poor, as GBM is largely fatal. Two and five-year relative survival probabilities, based on patients diagnosed in 2006-2012 and followed into 2013 are 18.8 percent and 5.7 percent, respectively [2]. Surgical resection followed by radiation was the standard first-line treatment of GBM patients until the results of Stupp et al. [3] provided evidence of an increase in median survival time from 12.1 months to 14.6 months associated with the addition of concurrent temozolomide (TMZ). A modest increase in GBM survival time has resulted since this standard has changed [4].

Little is known about factors affecting GBM prognosis. Only younger age at diagnosis, favorable preoperative Karnofsky Performance Status (KPS, a measure of patient well-being and quality of life), advantageous tumor location, smaller tumor, and complete or maximal tumor resection are widely-accepted GBM prognostic factors [1,5,6]. Results from studies examining race, marital status, insurance type, and factors related to

socioeconomic status (e.g. family income, educational attainment) have not produced consistent results. This study was conducted to confirm, using Surveillance, Epidemiology and End Results (SEER) Program data, the previously-identified prognostic factors of age at diagnosis, and surgery and radiation, and to determine which, if any, additional demographic/social (e.g. race, marital status, insurance), clinical, and area-based socioeconomic factors ascertained by SEER is associated with GBM survival probability.

Methods

Data were obtained from the SEER Program of the National Cancer Institute. The SEER Program collects data concerning cancers diagnosed in 18 registries [2]. These 18 population-based, central cancer registries cover approximately 28 percent of the United States.

GBM diagnoses were classified by SEER using the International Classification of Disease – Oncology – Version 3 (ICD-O-3) [7] code '9440'. The following factors were collected about all GBM diagnoses included in SEER and diagnosed from 2010 through 2013 9the most recent four-year period for which SEER data is available): age, sex, race, ethnicity, insurance, marital status, tumor size, and tumor extension (which characterizes contiguous growth or extension of GBM within the brain or direct extension into neighboring organs). In addition, the following county-level socioeconomic information was obtained from SEER: percent with less than high school education, percent of families below poverty, percent unemployed, and median family income. SEER also provided information about residence in a metropolitan county, which was ascertained from rural-urban continuum code. Tertiles were used as cutpoints to create categories for county-level socioeconomic factors.

Medians and percentages were used to describe demographic, clinical and area-based socioeconomic factors potentially related to GBM survival probability. Cox proportional hazards regressions, both univariate and multivariate, were used to determine hazard ratios (HR), which were evaluated based on direction (greater or lesser than 1.0) and magnitude to determine association with GBM survival probability. An HR greater than 1.0 indicates an increased risk of GBM death or worse prognosis. For example, an HR of 2.0 for the association between male sex and GBM survival probability indicates that males died at twice the rate of females per month. A multivariate model was created by initially including all factors with at least one significant category and, one by one, removing factors without at least one statistically significant category. The final model included only factors with at least one statistically significant category. Assumptions of Cox proportional hazards regression, including the assumption that hazards were proportional, were examined. No considerable violations of assumptions were observed.

SEER*Stat software was used to obtain the above-mentioned data through a case listing session. SAS was used to conduct statistical analyses. Alpha was set at 0.05 for hypothesis testing concerning whether or not factors, individually and after control for confounding by one another, were associated with GBM survival probability.

Results

There were 11,812 GBM cases diagnosed in one of 18 SEER registries from 2010 through 2013. Of these, 69.7 percent (8,234) were dead as of the study cutoff date (December, 2013). The maximum amount of time a patient may have survived was 47 months, if diagnosed in January, 2010. Of those alive at study cutoff (3,578), the median months survived was nine. Of those dead at study cutoff, the median months survived was five. Median survival time for all cases, both deal and alive, was six months at study cutoff.

Table 1 shows demographic and clinical characteristics of these cases. More cases were male, White, not Hispanic/Latino, insured, and married. There were reports of surgery and radiation for approximately three-fourths of cases (76.7 percent and 71.0 percent, respectively). Median tumor size was 45 millimeters (not shown in Table 1) and, for the majority (67.1 percent) of GBM cases, no tumor extension was reported.

Table 1: Demographic and Clinical Factors and Associations with Glioblastoma Survival Probability from Univariate Proportional Hazards Regressions among 11,812 Cases Reported to Surveillance, Epidemiology and End Results Program Registries, 2010-2013.

Demographic and Clinical Factors	Percent	Hazard Ratio (95% CI)
Age (per year)	**64.0 (Median)**	**1.038 (1.036-1.040)**
Sex		
Male	69.7	Referent
Female	30.3	1.033 (0.988-1.079)
Race		
White	88	Referent
Black/African American	6.1	0.960 (0.875-1.053)
American Indian/Alaska Native	0.4	1.150 (0.817-1.619)
Asian/Pacific Islander	5	0.788 (0.709-0.876)
Unknown	0.5	0.652 (0.444-0.958)
Hispanic/Latino Ethnicity		
Not Hispanic/Latino	89.8	Referent
Hispanic/Latino	10.2	0.936 (0.869-1.007)
Insurance		
Insured/Insured (no specifics)	82.6	Referent
Any Medicaid	10.9	1.080 (1.008-1.158)
Uninsured	3.8	0.852 (0.756-0.961)
Unknown	2.8	1.228 (1.072-1.408)

Marital Status		
Married	60.9	Referent
Single	15.7	0.953 (0.895-1.016)
Separated/Divorced	9	1.195 (1.107-1.289)
Widowed	9.8	1.976 (1.843-2.118)
Unknown	4.6	1.058 (0.949-1.178)
Surgery		
Performed	76.7	Referent
Not Performed	23.3	2.434 (2.318-2.557)
Radiation		
Performed	71	Referent
Not Performed	29	3.284 (3.135-3.440)
Tumor Size (mm.)		
0-40	34.7	Referent
41-79	46.2	1.108 (1.055-1.164)
80+	2.4	1.335 (1.159-1.538)
Unknown	16.7	1.198 (1.123-1.277)
Tumor Extension		
None	67.1	Referent
Some	29.6	1.382 (1.318-1.448)
Unknown	3.3	1.366 (1.210-1.542)

In univariate regressions shown in Table 1, age, race, insurance, marital status, surgery, radiation and tumor size and extension were significantly associated with GBM survival probability. Groups with significantly greater risk of death were those who were older (risk increased three percent with each increase in age in years), those with insurance type of any type of Medicaid and unknown insurance (compared to those who were insured through other means), those with marital statuses of separated or divorced and widowed (compared to those who were married), those who did not have surgery or radiation, those with greater than 41 millimeter and unknown tumor size, and those with some and unknown tumor extension. GBM survival probability was significantly lower among those with unknown race (compared to whites) and, unexpectedly, among those who were uninsured (compared to those who were insured). In univariate regressions, the greatest magnitudes of association (HR magnitude of approximately 2.0 or greater) occurred among those who were widowed (HR=1.976) and among those who did not receive surgery (HR=2.434) and radiation (HR=3.284).

Table 2 shows area-based socioeconomic characteristics. (Note that percentages shown for area-based socioeconomic factors in Table 2 are contrived because tertiles were used to create categories.) The median value for percent with less than high school education was 13.26 percent, 10.36 percent for percent of families under poverty level, 9.59 for percent unemployed, and $69,340 for median family income. In univariate regressions, each of the area-based socioeconomic was significantly associated with GBM survival probability, although the magnitudes of associations were small. In univariate analyses, groups with significantly lower GBM survival probability were those residing in counties with higher percentages of individuals with less than high school education, those in counties with higher percentages of families below the poverty level and higher percentages of unemployment, and those residing in non-metropolitan areas. Those residing in areas with higher median family incomes had a significantly higher GBM survival probability.

Table 2: Area-based Socioeconomic Factors and Associations with Glioblastoma Survival Probability from Univariate Proportional Hazards Regressions among 11,812 Cases Reported to Surveillance, Epidemiology and End Results Program Registries, 2010-2013.

Area-based Socioeconomic Status Factors	**Percent**	**Hazard Ratio (95% CI)**
Percent with < High School Education*		
<11.15%	32.3	Referent
11.15%-15.87%	32.9	1.023 (0.969-1.080)
15.88%+	34.9	1.105 (1.048-1.165)
Percent of Families Below Poverty Level*		
<8.75%	33.0	Referent
8.76%-13.23%	33.2	1.104 (1.047-1.165)
13.24%+	33.8	1.132 (1.073-1.194)
Percent Unemployed*		
<8.79%	29.9	Referent
8.79%-10.84%	36.7	1.031 (0.977-1.088)
10.85%+	33.4	1.063 (1.007-1.122)
Median Family Income*		
< $62,370	36.8	Referent
$62,370-$77,950	30.2	0.924 (0.877-0.974)
$77,960+	33.1	0.824 (0.782-0.868)
Metropolitan Residence Status		
Metropolitan	88.8	Referent
Non-metropolitan	11.2	1.191 (1.115-1.274)

*Categories for socioeconomic factors were created by selecting values nearest the tertiles.

To determine which, if any, of the factors shown in Tables 1 & 2 is associated with GBM survival probability after adjustment for confounding by one another, a final model was constructed by initially including all factors that contained at least one category that was statistically significant category. In addition, sex was included in the final model because it was likely that sex confounded associations between other factors and GBM survival probability. After removing factors that were not statistically significant one by one, the final model shown in Table 3 resulted.

GBM survival probability was significantly lower among those who were older, those with any Medicaid (compared to those insured through other means), those who were single and separated or divorced (compared to those who were married), those for whom surgery and radiation were not performed, those with larger and unknown tumor sizes, and those with some tumor extension. GBM survival probability was significantly higher among females, those who were Asian/Pacific Islander and those with unknown race (compared to Whites), those with unknown insurance and unknown tumor extension, those residing in counties with higher percentages of less than high school education, and those residing in counties with higher median family income. Figures 1-9 show survival curves, after adjustment for confounding by factors shown in Table 3, for race, insurance type, marital status, surgery status, radiation status, tumor size, tumor extension, percent with less than high school education in county of residence, and median family income in county of residence.

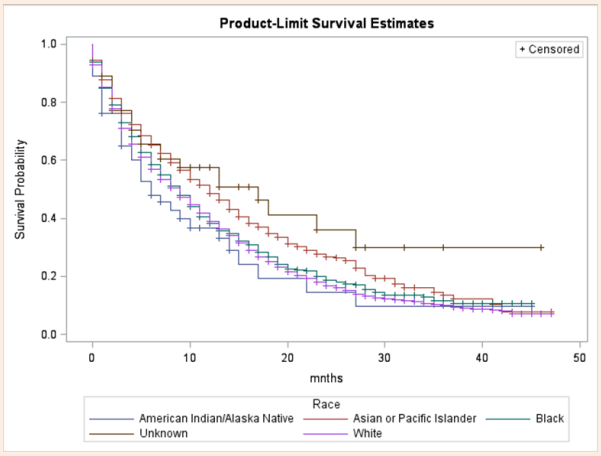

Figure 1: Adjusted Survival Curves for Glioblastoma Cases by Race from the SEER Data, 2010-2013.

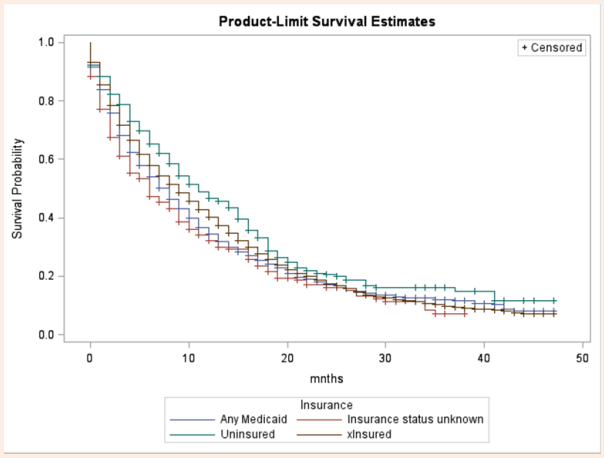

Figure 2: Adjusted Survival Curves for Glioblastoma Cases by Insurance from the SEER Data, 2010-2013.

Results from the multivariate model were similar to those found in univariate results (Tables 1 & 2) for age, race, tumor size, and median family income; however, adjustment for confounding by other factors in the model resulted in substantial changes in direction and statistical significance of HRs for female sex, uninsured and unknown insurance types, single and widowed marital statuses, unknown tumor extension, and higher percent with less than high school education. For example, the lower GBM survival probability observed in a univariate model for those who were widowed was largely attenuated after adjustment for confounding by other factors.

Table 3: Final Model of Demographic, Clinical and Area-based Socioeconomic Factors Associated with Glioblastoma Survival Probability among 11,812 Cases Reported to Surveillance, Epidemiology and End Results Program Registries, 2010-2013.

Factors	Hazard Ratio (95% CI)
Demographic Factors	
Age (per year)	1.032 (1.031-1.034)
Sex: Female (referent: male)	0.941 (0.899-0.985)
Race: Black/African American (referent: white)	0.990 (0.902-1.088)
Race: American Indian/Alaska Native	1.050 (0.745-1.480)
Race: Asian/Pacific Islander	0.802 (0.721-0.893)
Race: Unknown	0.672 (0.457-0.989)
Insurance: Any Medicaid (referent: insured/ insured (no specifics))	1.197 (1.113-1.288)
Insurance: Uninsured	1.048 (0.927-1.184)
Insurance: Unknown	0.860 (0.743-0.996)
Marital Status: Single (referent: married)	1.129 (1.056-1.207)
Marital Status: Separated/Divorced	1.184 (1.096-1.278)
Marital Status: Widowed	1.067 (0.988-1.151)
Marital Status: Unknown	1.032 (0.925-1.152)
Clinical Factors	
Surgery: Not Performed (referent: performed)	1.733 (1.643-1.828)
Radiation: Not Performed (referent: performed)	2.714 (2.579-2.855)
Tumor Size: 41-79 (referent: 0-40)	1.131 (1.076-1.188)
Tumor Size: 80+	1.335 (1.158-1.535)
Tumor Size: Unknown	1.155 (1.080-1.236)
Tumor Extension: Some (referent: none)	1.389 (1.323-1.458)
Tumor Extension: Unknown	0.717 (0.622-0.821)
Area-based Socioeconomic Factors	
% < High School Education: 11.15%-15.87% (referent: <11.15%)	0.936 (0.885-0.990)
% < High School Education: 15.88%+	0.879 (0.824-0.938)
Median Family Income: $62,370-$77,950 (referent: < $62,370)	0.954 (0.898-1.013)
Median Family Income: $77,960+	0.819 (0.770-0.871)

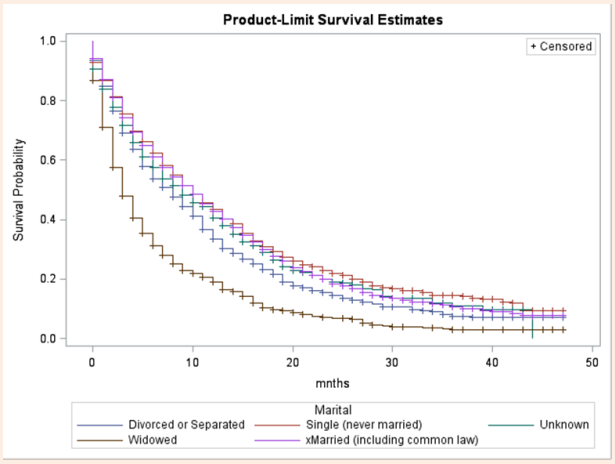

Figure 3: Adjusted Survival Curves for Glioblastoma Cases by Marital Status from the SEER Data, 2010-2013.

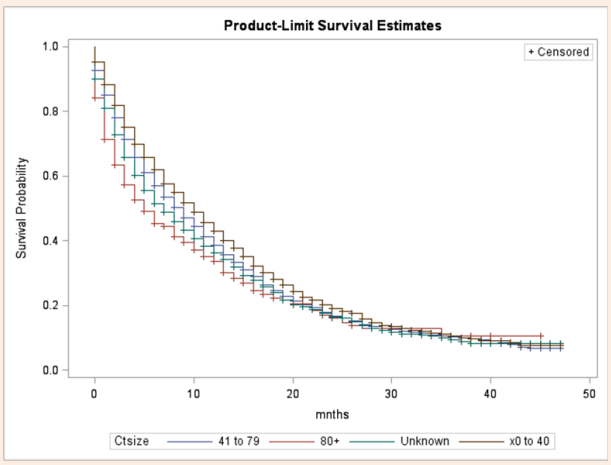

Figure 6: Adjusted Survival Curves for Glioblastoma Cases by Tumor Size from the SEER Data, 2010-2013.

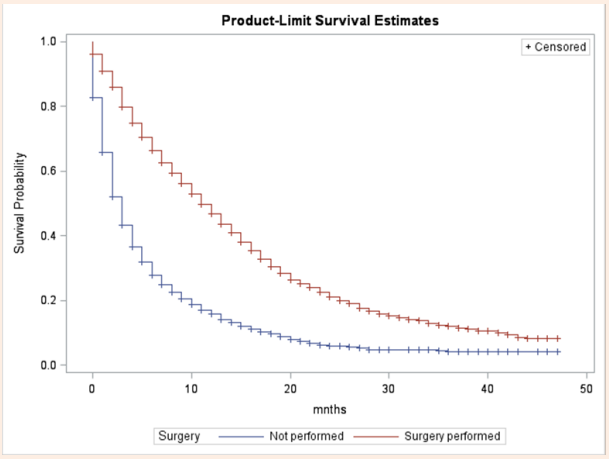

Figure 4: Adjusted Survival Curves for Glioblastoma Cases by Surgery Status from the SEER Data, 2010-2013.

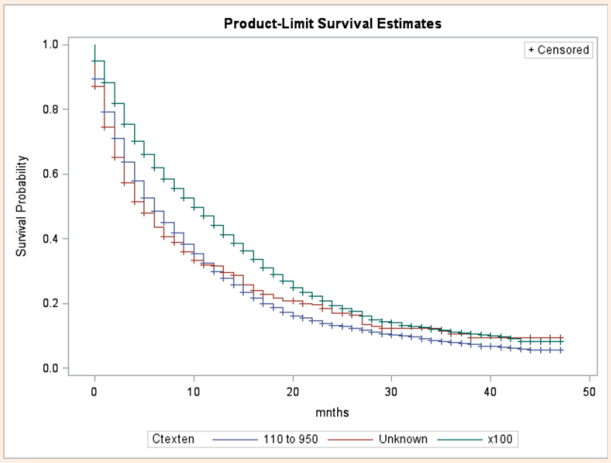

Figure 7: Adjusted Survival Curves for Glioblastoma Cases by Tumor Extension from the SEER Data, 2010-2013.

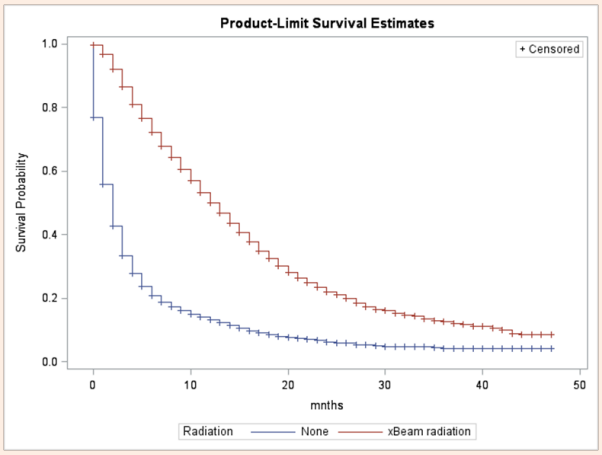

Figure 5: Adjusted Survival Curves for Glioblastoma Cases by Radiation Status from the SEER Data, 2010-2013.

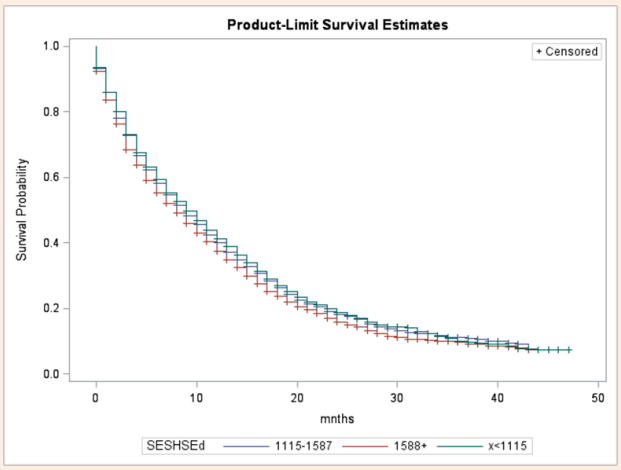

Figure 8: Adjusted Survival Curves for Glioblastoma Cases by Percent with Less than High School Education in County of Residence from the SEER Data, 2010-2013

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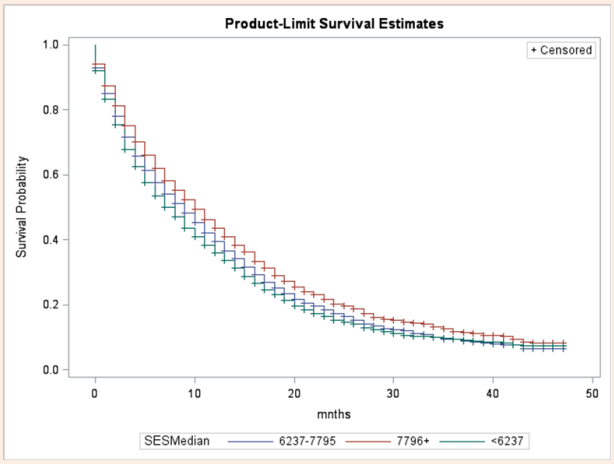

Figure 9: Adjusted Survival Curves for Glioblastoma Cases by Median Family Income in County of Residence from the SEER Data, 2010-2013.

Discussion

GBM survival probability is extremely low with the latest years of SEER data suggesting a relative five-year survival probability of less than six percent. Analyses reported here confirmed the importance of age at diagnosis, surgery and radiation treatments, and tumor size and extension, to GBM prognosis. In addition, there were weak, yet statistically significant, associations between GBM survival probability and race, insurance type, marital status, and two area-based socioeconomic factors (percent with less than high school education and median family income, both in the county of residence). These factors were significantly associated with GBM survival probability, even after adjustment for confounding by other factors.

Age at diagnosis is a well-known prognostic factor for GBM [1,5,6]. Further, men have a known survival advantage and this has been shown in numerous studies, in addition to SEER survival probabilities. Clinical factors of treatments and tumor size and extension are also relatively well-described. The results presented here pertaining to age at diagnosis, sex, and the clinical characteristics of treatment and tumor size and extension are in-line with these known prognostic factors.

Results pertaining to other demographic/social factors are conflicting. In the present study, compared to Whites, adjusted GBM survival probability among Asian/Pacific Islanders was approximately 20 percent higher, and adjusted GBM survival probability among those with unknown race was approximately 33 percent higher. It is difficult to interpret these results, especially the latter. Similar results were reported by Thumma et al. [8] who also examined SEER data. It is possible that there are biologic or molecular differences between Whites and Asian/Pacific Islanders and/or that survival differences are attributable to differences in treatment or income [8-10]; although, impacts from treatments of surgery and radiation were adjusted. Blacks/African Americans are diagnosed, on average, at younger ages, compared to Whites; therefore, adjustment for age at diagnosis is important. In the present study, the non-significant elevated HR for Blacks/African-Americans was attenuated after adjustment. Race differences in GBM prognosis have not been reported in most studies; for example, Wrensch et al. [11] found no significant difference between Whites and non-Whites in a multivariate model assessing GBM prognosis; further, Barnholtz-Sloan et al. [9], in a study of GBM cases contained in the SEER-Medicare linked dataset, found no overall difference in prognosis between Blacks and non-Hispanic Whites after adjustment for factors such as treatment, but found a more favorable prognosis among Asians in the west geographic region (similar to that reported in the present study).

After adjustment for other factors, there was a modest association between each marital status (as compared to married) and GBM survival probability, with single and separated/divorced cases having approximately 13 percent and 18 percent worse survival. These results are similar to those reported by others [11-13]. Chang and Barker found that unmarried supratentorial GBM patients had larger tumors, were less likely to undergo treatments, and survived shorter periods of time [12]. The survival benefit afforded by marriage may result from social support or earlier diagnosis. It is unlikely that the benefit is the result of access to treatments because analyses reported here were adjusted by both insurance type and treatments. Wrensch et al. [11] found that marital status was related to GBM radiation treatment but not to chemotherapy or extent of surgery, and that an association between GBM survival and marital status persists even after adjustment for radiation treatment; further, in a subset of cases, the marital status-prognosis association was either confounded by KPS or KPS worked as an intermediate, suggesting earlier diagnosis as a result of higher KPS or that higher social support from marriage increased KPS. The relationship between marital status and GBM prognosis should be explored further.

There were also modest associations between GBM prognosis and several categories of insurance type. Similar to the results presented here, Rong et al. [13] reported that insurance types of Medicaid and uninsured were independently and significantly associated with shorter GBM survival, after adjustment for other factors. Alternatively, Kasl et al. [14], in a study of 218 GBM cases, reported that longer survival time was associated, after adjustment for other factors, with an insurance type of Veteran's Affairs/TriCare/Medicaid, as compared to private insurance. Reasons for these differences and for the mechanisms governing these associations are unclear but do not seem to be directly related to treatments.

There is conflicting research about the impact of socioeconomic factors on GBM prognosis. For example, Field et al. [15] found no impact of the socioeconomic factors of regional versus city residence or public versus private hospital on GBM prognosis in Australia. Alternatively, Tseng et al. found, using the Carstairs Index (an index of material deprivation based on postcodes), that prognosis worsened with increasing level of socioeconomic deprivation among glioma patients in the United Kingdom [16]. These associations may vary by country as socioeconomic factors have different impacts based on sociopolitical environments. In

the U.S., using zip code tabulation areas, Kasl et al. [14] found no association between an estimate of socioeconomic status and GBM survival time. Further, examining patients in the San Francisco Bay area, Wrensch et al. found no association, after adjustment for other factors, between being a college graduate and GBM prognosis [11]. Socioeconomic status is associated with many factors, including sex, race, marital status, insurance type, and GBM treatments. It is difficult to disentangle these conflated factors. In the present study, the effects of factors were statistically adjusted for one another. However, there was no individual-level socioeconomic information available from SEER; instead, the county-level factors examined in the present study (e.g. median family income) are contextual and represent a socioeconomic environment in which other potential prognostic factors, such as insurance type, race, marital status and individual socioeconomic status, may operate. In the present study, prognosis was significantly better among those residing in counties with higher median family incomes, and this is consistent with the notion that higher income equates to improved outcomes in the U.S.; however, the finding of significantly higher GBM survival probability among those residing in counties with higher percentages of less than high school education is counter-intuitive. Socioeconomic and related factors should be examined in large studies in which complex interactions with multiple levels of variation (individual-level, census tract-level, etc.) can be examined.

There are several limitations with this study. First, there was no available information on individual-level socioeconomic status; as a result, results presented here were those area-based measures included in SEER and pertaining to counties, which are relatively large areas likely encompassing many disparate geographic regions. As estimates of individual-level phenomena, counties are likely too large to provide useful information; however, as estimates of contextual regions demonstrating U.S. socioeconomic variation, the level of county may suffice. Indeed, there were statistically significant differences in GBM survival probability based on these geographic units; counties probably capture some degree of large-scale differences in factors such as educational attainment and median family income. Second, it was not possible to conduct a thorough evaluation of GBM prognosis because SEER data do not include information about the confirmed prognostic factor of KPS or a similar scale, such as the Charlson Index. Similarly, SEER data only include information about the first course of treatment (surgery, radiation), while chemotherapy is not captured. It was also not possible to examine potential prognostic molecular markers, such as the hypermethylation of the O6-methylguanine-DNA-methyltransferase (MGMT) gene. Third, both clinically and pathologically diagnosed GBM cases were included in this analysis because exclusion of clinically diagnosed cases would have resulted in excluding a large portion of cases. The strengths of this analysis lie in the high quality and case completeness of SEER registry data and the large, heterogeneous group of the 18 SEER cancer registries. There is little opportunity for ascertainment bias.

Conclusion

Analyses reported here confirmed the importance of age at diagnosis, surgery and radiation treatments, and tumor size and extension, in predicting GBM prognosis. There were independent and statistically significant associations between GBM survival probability and race, insurance type, marital status, and two area-based socioeconomic factors (percent with less than high school education and median family income, both in the county of residence). These factors were significantly associated with GBM survival probability, even after adjustment for confounding by other factors. Continued research is needed to elucidate important differences between those who survive this largely fatal disease for longer periods of time.

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