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*Original Article*

# Socioeconomic status and survival in glioblastoma

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**Abstract:** Background: Glioblastoma (WHO Grade IV glioma) patients have a dismal prognosis, with a median life expectancy of under two years. The influence of patient socioeconomic status on survival has not been clearly established. Methods: We retrospectively reviewed glioblastoma patients seen and treated at our institution from 2001-2012, correlating survival with socioeconomic status, as estimated by the census tract poverty levels, defined by the Surveillance, Epidemiology and End Results Program of the NCI. Results: A total of 131 patients were evaluable. Median overall survival (OS) was 12 months (95% confidence interval (CI): 10.51-14.89 months). No association between OS and socioeconomic status was identified. Conclusions: Socioeconomic status does not seem to have an effect on overall survival in glioblastoma. This suggests that the dismal prognosis of this disease reflects the intrinsic biology of this tumor type, as patients had access to all currently available treatments including surgery, radiation therapy, and since 2005, standard chemotherapy with temozolomide.

**Keywords:** Glioblastoma, prognostic factors, socioeconomic status, survival

## Introduction

Primary central nervous system (CNS) malignancies are uncommon with an estimated 23000 new cases and 14000 deaths in the US in 2013 [http://www.cancer.gov/cancertopics/types/brain]. High grade brain gliomas, especially glioblastoma (GBM) are the most common and also the most lethal forms of this disease, with the majority of patients not surviving beyond 2 years [1]. Standard treatment for GBM includes surgical resection and chemoradiation with temozolomide followed by adjuvant temozolomide for up to 6-12 cycles [1]. This has been shown to improve median survival by about 2.5 months compared to radiation treatment only, with 5-year survival of less than 10%. Methylation of the MGMT promoter has been shown to predict benefit from temozolomide [2]; Additionally, prognostic significance has recently been argued for the IDH1/IDH2 mutations [3]. Bevacizumab, an anti-VEGF monoclonal antibody has been approved in the second line setting [4], but no overall survival benefit was shown when combined with the standard upfront chemoradiation regimen in two recent studies [5, 6], although a positive effect on progression free survival was demonstrated in one.

There has been recent interest in defining differences in socioeconomic status (SES) that may be associated with differences in health outcomes. Evidence supporting this proposition has been presented for many medical conditions such as coronary artery disease [7] screening practices [8] and treatment of several cancers including liver, breast among others [9, 10]. Socioeconomic factors, when in play, are presumptively associated with different risk factor exposures, variable accesses to high quality health care, diverse attitudes to screening, treatment and follow-up, and other unspecified factors, which all ultimately translate to differences in survival. This effect, however, has not been consistent and it is remains true that cultural, geographic and disease-specific variables may lead to different conclusions in different studies [11].

Our institution is one of the two major tertiary hospitals in the upper Maryland area and, quite uniquely, serves some very diverse ethnic and racial groups such as several minorities (predominantly African Americans, who account for about 20-30% of the patient mix in some cases). This is not a random phenomenon and has more to do with acceptance of a wide vari-

**Table 1.** Patient characteristics

| | N | % |
|---|---|---|
| Poverty level | | |
| 0-10 | 98 | 74.8 |
| 10-20 | 24 | 18.3 |
| 20+ | 9 | 6.9 |
| Gender | | |
| Male | 75 | 57.3 |
| Female | 56 | 42.7 |
| Race | | |
| White | 107 | 81.6 |
| Black | 20 | 15.2 |
| Other | 4 | 3.2 |
| Initial treatment | | |
| Standard chemoradiation | 70 | 53.4 |
| Standard radiation only | 15 | 11.4 |
| No treatment given | 2 | 1.5 |
| Clinical trial/other chemoradiation | 15 | 11.4 |
| No data | 29 | 22.3 |

ety of insured and uninsured patients. This reality has allowed us to evaluate an inhomogeneous and more representative sample of the total population. We, therefore, sought to see if differences in SES in general and over time translate to differences in survival of patients with glioblastoma.

## Materials and methods

After IRB approval, the electronic records of all patients with the diagnosis of glioblastoma (pathologic diagnosis of WHO grade IV glioma or GBM) referred to and treated partially or fully at our institution between 2001 and 2012 were examined. Information is current as of 05/15/2014, based on file review; no patients or families were contacted as part of this research.

The following data was extracted: age, race, gender, census tract information, date of diagnosis and presentation, death date and apparent cause of death (when available). The dates of death were retrieved from the social security death index. Census tract data was collected from the registered addresses of the patients. We identified census tracts and corresponding poverty levels from the Federal Financial Institutions Examination Council's (FFIEC) web site [http://www.ffiec.gov/default.htm.] and adjusted them to the diagnosis dates.

Socioeconomic status (SES) has been approached in many different ways with little consensus among different authors. In this paper we used the census tract poverty level as an indicator of the area SES as per methods described in the SEER publication "Area Socioeconomic Variations in U.S. Cancer Incidence, Mortality, Stage, Treatment, and Survival, 1975-1999" [http://seer.cancer.gov/publications/ses/methods.pdf.]. This option has been considered in other publications as well [11, 13], and seems to represent a simple and useful means of initial stratification.

We ran survival analyses using as plausible risk factors the following patient characteristics: the census tract poverty percentage, year of diagnosis, and age at diagnosis. We also focused on patients of different SES treated before and after 2005 and in predetermined subgroups (no surgery, radiation only, lost to follow-up).

### *Statistical analysis*

Overall survival (OS) functions were estimated using the Kaplan-Meier approach. OS was defined from the date of diagnosis to the date of death from any cause or censored at the date last known alive. Patients were grouped according to three area poverty categories (<10%, 10-20% and >20%). The percentages denote the population fraction in a specific census tract that lies below the poverty level. Overall survival was compared between the three groups using the log rank test. A multivariable Cox regression model was used to examine the effect of the defined plausible risk factors on overall survival. For the survival curves, OS in years was truncated to 4 due to insufficient number of cases. A Fischer's exact test was used for examining the distribution of poverty levels across racial groups. Univariable and multivariable Cox analyses were used to examine differences in survival in the before 2005 and after 2005 groups, as well as between different treatment groups. Analyses were conducted in S-plus (TIBCO, v.8.2), all tests were done at the 0.05 level of significance, and were two-sided.

## Results

Over the 12 years examined, 131 patients treated for GBM were ultimately available for

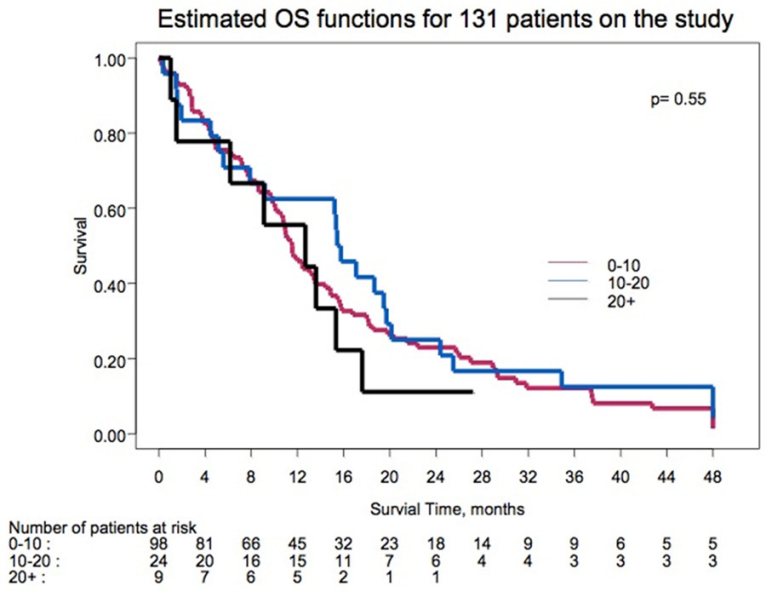


**Figure 1.** OS estimated by the Kaplan-Meier method for patients grouped according to their census tract poverty level. OS times in months were truncated at 4 years of follow-up due to insufficient number of cases.

this analysis (some CPT codes initially eligible referred erroneously to grade III astrocytomas and oligodendrogliomas). Nine of the patients were alive as of last follow-up. Patient characteristics are summarized in **Table 1**. Fifty-seven percent were men and 43% were women. Whites amounted to 81.6% of the population with 18.4% nonwhites. Median age at diagnosis was 61 years (range: 22-88) and median overall survival was 12 months (95% CI: 10.51-14.89). Median census tract poverty level was 5.1 percent with an impressive variation (range: 0.0-42.4). The distribution of the poverty level was very different across three racial groups (Caucasian, African American, other, Fischer's exact test P=0.0001, data not shown).

Fifty-three percent of the patients received standard chemoradiation and 11% received radiation only; another 11% received a non-standard regimen or entered a clinical trial while follow-up data other than date of death was missing on 22% (lost to follow-up or were seen as a one-time consultation).

*Socioeconomic status and survival*

All patients were categorized according to their poverty levels in three categories, <10, 10-20, and >20 (**Figure 1**). There was no difference in survival across these three groups (*P*-value =0.6).

*Other analyses*

The Cox regression model was also used with year of diagnosis, age at diagnosis and poverty level. Consistent with earlier studies, age at diagnosis was a significant predictive factor of survival with age >70 having a higher hazard of death than age <52, (HR: 3, 95% CI: 1.8-5.0). Patients who were aged between 60-69 years carried more risk of dying in comparison to the youngest group (<60 years; HR=2.0).

There was no association between race, year of diagnosis or absolute poverty category and overall survival (Cox regression model, data not shown). When we excluded patients lost to follow-up, patients who received radiation treatment only and patients receiving surgery only and re-run the analyses, there was no difference in survival between SES categories. This lack of survival differences between poverty levels held true also when patients were evaluated in the before Temozolomide (before 2005) and after Temozolomide era.

## Discussion

Glioblastoma is almost invariably lethal with a life expectancy that has been increasing but usually does not extend beyond 2 years. In this study we were able to demonstrate that this phenomenon does not seem to correlate with the patient's socioeconomic status, as assessed by census tract poverty levels.

There are no comprehensive studies examining socioeconomic status and survival in glioblastoma patients that we are aware of. Porter et al [13] analyzed SEER data and showed a strong association between SES and glioblastoma risk but did not include survival data. Shaw et al [14] attempted to quantify the impact of race on survival in patients with GBM and examined data from 8688 GBM patients in the 2002 Central Brain Tumor Registry of the United States. Breakdown by race was 93.6% whites, 4.1% blacks, and 2.2% other non-whites. The

RTOG reexamined its database of GBM patients included in the revised recursive partitioning analysis [15], specifically evaluating the impact of race on survival for 1652 GBM patients (90% white, 4.8% black, and 5.3% other), showing that age and Karnofsky performance status (KPS) were significantly different by race. More non-whites were <50 years old compared to whites and had a significantly lower risk of death (HR 0.84, 95% CI 0.71 to 0.99, P=0.040), whereas more whites had a KPS of 70 or more compared to non-whites. The difference in survival by race was limited to Recursive Partitioning Analysis (RPA) class IV patients (RTOG 1997), in whom the hazard ratio for death was 0.68 for blacks (95% CI 0.47 to 0.99, P=0.046) and 0.89 for other (95% CI 0.63 to 1.26, P=0.51). The authors concluded that the data showed better survival for non-white patients, (driven primarily by better long-term survival among RPA class IV black patients) and raised questions as to whether there may be environmental and/or genetic differences in susceptibility to the disease and response to treatment. They did not, however, address SES as a variable.

The strengths of our study include the considerable variation in poverty levels, which reflects the diverse population being served at this facility and the long timeframe over which data was available (pre and post Temozolomide use). As mentioned before, this is a tertiary center that serves a unique mix of minorities with various insurances and socioeconomic statuses (our dataset includes poverty levels of both 0% for affluent areas and 40% for poorer census tracts). We agree that, ideally, one would have evaluated more than 131 patients over a shorter period of time, and that could have yielded stronger statistical associations. We had the option of using post 2005 data (94 patients) but chose to stretch out our search strategy to evaluate the effect of standardization of chemoradiation with Temozolomide on our results; there was none. We also ran analyses of SES excluding missing to follow-up patients and patients receiving specific treatments, and our data remained the same.

There are several explanations for our findings. Most are relevant to the aggressive nature of the disease, and limited efficacy of standard treatment. In several other diseases, access to care and insurance status often determines whether routine screening for early detection occurs or not, and this often affects the subsequent outcome; for GBM there is no established screening test and, therefore, access to care for screening will usually not make a difference. In sharp contrast to diseases such as vascular or renal dysfunction as well as other cancers like melanoma or breast cancer, the initial presentation of GBM often includes acute events such as severe headache, seizures and neurologic findings, all of which will usually warranty immediate medical attention, minimizing detection lag bias between different populations. In terms of treatment, resection is usually performed at tertiary centers with large, specialized neurosurgical departments and the initial chemoradiation regimen generally follows within a few weeks. Therefore, there is not much variability in how patients are treated by socioeconomic status. Last but not the least, even though one can assume variation in follow up (imaging, adjuvant cycles of chemotherapy) between patients of different socioeconomic statuses, GBM is usually rapidly lethal and the short average life expectancy can easily mask any differences in the follow-up care, something that may not happen in malignancies with much longer survival.

In our study we were unable to stratify patients by MGMT/IDH1 status, as these biomarkers were not available for the majority of patients. Molecular testing during the period covered was not a routine, insurance-approved process in GBM, and remains an open question as to the frequency of MGMT methylation status or IDH mutational status in different ethnic groups presenting with high grade gliomas.

The limitations of this study also include its retrospective nature with the associated risk of significant bias. The limited amount of data over a long period of time may very well have had an impact on the results-an update of this study is being planned in a few years. However, a considerable difference in survival could have been detected with this dataset, if there were one.

One should also note that census tract data reflects a snapshot of the US population at a specific period of time, which may or may not correspond correctly to the SES at the time the patients were actually treated-it seems to be

the current way to approach this issue, however. The median survival for glioblastoma in our cohort is shorter than in many current reports; but one must note that this includes the pre and post temozolomide era and could reflect changes in imaging, treatment and supportive care. It is worth noting that in recent reports, the median survival rates reported for GBM vary significantly. For example, while analysis of SEER data in the pre and post temozolomide era has confirmed the EORTC results [16]. A randomized study from Poland also showed pronounced effects from the introduction of the radiation-temozolomide regimen with a median survival of close to 16 months compared to 12.5 months in the radiotherapy group [17].

Our study suggests that socioeconomic differences may continue to have little impact on overall survival, and this is possibly inherent to the malignant nature of the disease, leading to rapid mortality. One can hope that this may change in the future if new, effective treatments are active in GBM, and all patients regardless of SES have the opportunity to benefit from their use.

## Disclosure of conflict of interest

MPM is on the BOD of Pharmacyclics, with stock options; and has served in a consulting role with Celldex, Elekta, Genentech, Novocure; and has research funding from Novocure and Novellos; also serves on the BOD of Pharmacyclics, with stock options.

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