**Article**

**Title: Survival trends of grade I, II, and III astrocytoma patients and associated clinical practice patterns between 1999 and 2010: A SEER-based analysis.**

Xuezhi Dong, Abraham Noorbakhsh, Brian R. Hirshman, Tianzan Zhou, Jessica A. Tang, David C. Chang, Bob S. Carter, and Clark C. Chen.

School of Medicine

University of California, San Diego

9500 Gilman Drive

La Jolla, CA 92093

(X.D., A.N., B.R.H., T.Z., J.A.T.)

Division of Neurological Surgery

University of California, San Diego

200 West Arbor Drive #8893

San Diego, CA 92103

(B.S.C., C.C.C.)

Department of Surgery

University of California, San Diego

200 West Arbor Drive #8220

San Diego, CA 92103

(D.C.C.)

**Running Title:** Survival of WHO grade I-III astrocytoma 1999-2010

**Corresponding Author:**

Clark Chen, M.D., Ph.D.,

Division of Neurosurgery

University of California, San Diego

3855 Health Science Drive #0987

La Jolla 92093-0987

Phone: 619-246-0674

Fax: 858-822-4715

e-mail: clarkchen@ucsd.edu

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**ABSTRACT**

**Background**

The survival trends and the patterns of clinical practice pertaining to radiation therapy and surgical resection for WHO grade I, II, and III astrocytoma patients remain poorly characterized.

**Methods**

Using the Surveillance, Epidemiology and End Results (SEER) database, we identified 2497 grade I, 4113 grade II and 2755 grade III astrocytomas during the period of 1999-2010. Time-trend analyses were performed for overall survival (OS), radiation treatment (RT), and the extent of surgical resection (EOR).

**Results**

While overall survival of grade I astrocytomas remain unchanged during the study period, we observed improved overall survival for grade II and III astrocytoma patients (Tarone-Ware $p<0.05$). The median survival increased from 44 to 57 months and from 15 to 24 months for grade II and III astrocytoma patients, respectively. The differences in survival remained significant after adjusting for pertinent variables including age, ethnicity, marital status, sex, tumor size, tumor location, EOR, and RT status. The pattern of clinical practice in terms of EOR for grade II and III astrocytoma patients did not change significantly during this study period. However, there was decreased RT utilization as treatment for grade II astrocytoma patients after 2005.

**Conclusion**

Results from the SEER database indicate that there were improvements in the overall survival of grade II and III astrocytoma patients over the past decade. Analysis of the clinical practice patterns identified potential opportunities for impacting the clinical course of these patients.

**Keywords:** WHO grade I, II, III astrocytomas, survival, population-based SEER database, practice pattern.

## INTRODUCTION

Glioma refers to tumors derived from neoplastic transformation of glial cells and constitutes the most common form of primary brain cancer [1-3]. "Glia" is a Greek word meaning "glue". The word is meant to describe the non-neuronal cells in the nervous system that are found interspersed among neurons, "gluing" the distinct neurons into a cohesive system. Central nervous system (CNS) glial cells consist of distinct histologic cellular subtypes. In the adult CNS, the three types of glial cells that give rise to tumors include astrocytes, oligodendrocytes, and ependymal cells. The tumors derived from these glial cells differ in terms of the mechanism of pathogenesis as well as clinical behavior. Of these glioma types, tumors derived from astrocytes or their precursors are called astrocytomas and are most common.

Astrocytic tumors are classified histologically based on World Health Organization (WHO) criteria [4]. Grade I tumors are biologically benign and complete surgical excision is typically curative. Grade II astrocytomas are characterized by hyper-cellularity with diffuse infiltration into the surrounding cerebral parenchyma. Complete surgical excision of grade II tumors cannot generally be achieved. The median survival for patients afflicted with grade II astrocytomas ranges from 5 to 8 years [5]. Grade III or IV astrocytomas are considered malignant. In addition to hyper-cellularity, grade III astrocytomas, also known as anaplastic astrocytomas, exhibit nuclear atypia and increased mitotic figures. The median survival for grade III tumor is approximately 3 years [6]. Grade IV astrocytomas, or glioblastomas, are characterized by histologic findings of angiogenesis and necrosis. Grade IV tumors are extremely aggressive and are associated with a median survival of 12-18 months [7].

Radiation, chemotherapy, and surgical resection play critical roles in the management of grade I, II, and III astrocytoma patients. Surgery remains a primary treatment modality for all

three cancer types. Because gross total resection is typically curative for grade I astrocytoma, these patients are rarely treated with radiation and chemotherapy [8]. For grade II and III astrocytomas, there is accumulating evidence based on institutional experiences that the extent of resection influences overall survival [6,9-11]. However, controversy remains in this matter as the thesis has not been definitively demonstrated through randomized control studies [12]. In terms of chemotherapy and radiation therapy, oncologists typically stratify the risk profile of grade II astrocytoma patients based on clinical variables as to determine whether chemotherapy and radiation therapy would be appropriate. Of note, there is no formal consensus in terms of standard of treatment for grade II astrocytoma patients [13,14]. Similarly, there is relatively little data specifically addressing the standard of care for grade III astrocytoma patients. However, these patients are routinely treated with radiation and chemotherapy [15].

Analysis of the historical trends of patient survival represents a valuable means of assessing progress in clinical outcome [16]. Correlating these trends to the changing patterns of clinical practices further identifies needs for future improvement. While a great deal of effort has been focused on glioblastoma in this regard [17-20], few studies have been devoted to lower grade astrocytomas. The goal of this study is to assess changes in overall survival pattern of patients afflicted with grade I, II, and III astrocytomas using the Survival Epidemiology, and End Results (SEER) registry [21]. We used the SEER registry because the data set is broadly representative of the oncology care provided to the US population, including patients treated at both academic and non-academic centers [22]. Furthermore, the registry offers access to data related to surgical resection and radiation treatment. Finally, given the rarity of low grade gliomas, the SEER registry affords analysis on a scale that cannot be matched by any single institutional experience.

## MATERIALS AND METHODS

*Data and Study Population*

The Surveillance, Epidemiology, and End Results (SEER) Program was established by the National Cancer Institute (NCI) to collect cancer incidence and survival data from 18 population-based cancer registries that cover approximately 28% of total U.S. population (SEER Research Data 1973-2010). We utilized the dataset released in April 2013 that was based on November 2012 submissions downloaded as ASCII text file [23].

This study included patients who were diagnosed between 1999 and 2010 with WHO grade I-IV intracranial astrocytomas as the only cancer diagnosis. The following International Classification of Disease for Oncology-third edition (ICD-O-3) histology codes were used: 9421 (pilocytic astrocytoma, WHO grade I), 9400, 9410, 9411, 9420 (Diffuse astrocytoma, WHO grade II), 9401 (Anaplastic astrocytoma, WHO grade III), 9440-9442 (Glioblastoma, WHO grade IV) and ICD-O-3 topologic site codes C71.0-C71.9. These codes were described in Table 1 of Central Brain Tumor Registry of the United States (CBTRUS) Statistical Report [24]. Patients were excluded from the study if the surgical status was coded as unknown (n = 626, 1.8% of our study population) or if the histology was coded as unconfirmed (n = 2,075, 6% of our study population). Notably, the excluded patients were older than patients remained in the analysis ($p < 0.05$), suggesting that presumptive diagnosis without tissue biopsy is more likely in the elderly population[16]. After these exclusions, we identified a total of 2497 grade I, 4113 grade II, 2755 grade III, and 21962 grade IV glioma cases.

*Covariates and Extent of Resection*

Using published methodology [17,20], patients were grouped into four equal time periods for comparison: 1999-2001, 2002-2004, 2005-2007 and 2008-2010. Survival time was defined as the number of months from diagnosis to the date of death due to any cause or the date of last known follow-up. Demographic variables in the statistical analysis included age (<18, 18-44, 45-59, 60-74, or >75 years), race/ethnicity (White, Black, Asian/Pacific Islander, Hispanic, American Indian/Alaskan Native, or Other/Unknown), marital status (single, married, or [separated, divorced or windowed]), and sex (male or female). Clinical variables included tumor size (<5cm, 5-7cm or >7cm), tumor location (based on ICD-O-3 topologic site codes C71.0-C71.9), radiotherapy status (treatment or no treatment) and surgical treatment received (no surgery, sub-total resection or gross total resection).

With regards to surgical treatment, we utilized the following surgery codes from the SEER registry: no surgery (code 00), local excision/biopsy (code 20), partial resection (code 21, 40), or gross total resection (GTR) (code 30, 55). It is important to note that the exact definition of surgical codes has been slightly modified with each edition of SEER Program Coding and Staging Manual (1998-2003, 2004-2006, 2007-2009, 2010-present) but remained roughly consistent. The current definition for surgical codes can be found in the SEER Program Coding and Staging Manual 2013 released on February 28, 2013 under Appendix C: Surgical Codes for Brain [25]. Historical definitions can also be found on the SEER website [26].We combined local excision/biopsy (code 20) with partial resection (code 21, 40) into one category of sub-total resection in the extended multivariate Cox proportional hazards analysis because the extent of resection achieved between the two categories is ambiguous. Furthermore, a separate analysis

showed that the two categories exhibited similar survival curves that were distinct from those of no surgery and GTR.

Information regarding the use of chemotherapy, performance status, local control, and specific radiotherapy technique (such as fractionation, dose, and beam energy) is not provided in the SEER database and therefore cannot be included in this study.

*Statistical Analysis*

All analyses were conducted using Stata version 11.2 [27], and the level of statistical significance was set at $p < 0.05$. Kaplan-Meier method was used to generate 2-year and 10-year survival curves for grade I-IV gliomas across four equal time periods between 1999 and 2010. Statistical significance was determined using Tarone-Ware test across survival functions [16]. We also calculated percentage of subjects alive at 2 years with 95% confidence interval (CI) and median survival with 95% CI. Next, we conducted an extended multivariate Cox proportional hazard analysis adjusting for demographic and clinical covariates mentioned above to obtain hazard ratios (HR) and 95% CI for death. Lastly, we used multivariate logistic regression analysis adjusting for the same demographic and clinical covariates to obtain odds ratios (OR) of receiving gross total resection (GTR) and receiving radiotherapy in four time periods for grade II and III astrocytoma.

## RESULTS

*Patient and Clinical Characteristics*

Patient characteristics are summarized in **Table 1**. Out of a total of 31,327 patients, there were 2,497 (7.97%) grade I pilocytic astrocytoma, 4,113 (13.13%) grade II diffuse astrocytoma,

2,755 (29.89%) grade III anaplastic astrocytoma, and 21,962 (70.11%) grade IV glioblastoma cases. The median age of diagnosis (interquartile range) was 12 (5-20) for grade I, 44 (29-59) for grade II, 50 (35-64) for grade III, and 61 (52-71) for grade IV gliomas. Overall mortality due to all causes increases with increasing histologic grade with 5.86% mortality for grade I, 51.18% for grade II, 67.4% for grade III and 85.85% for grade IV astrocytoma. The most common sites for grade I tumors were the cerebellum and brainstem whereas for grade II-IV tumors were the frontal lobe and temporal lobe. The epidemiology exhibited by this study sample is consistent with existing literature [5,24].

*Time Trend Analysis of Survival*

To examined the survival trends, we had adapted the published convention [17,20] of dividing the study period into four equal intervals (1999-2001, 2002-2004, 2005-2007, and 2008-2010). Kaplan-Meier plot of these time periods are shown in **Figure 1A**. Consistent with prior studies [17-20], the median survival for grade IV glioblastoma showed a modest increase over the past decade. Importantly, we observed similar improvements for grade II and grade III astrocytomas with Tarone-Ware test (all $p < 0.05$, **Table 2**). Median survival for grade II astrocytoma increased from 44 months in 1999-2001 to 57 months in 2005-2007. For the 2008-2010 period, grade II astrocytoma did not reach the 50% survivor function. Median survival for grade III astrocytoma increased from 15 months in 1999-2001 to 24 months in 2008-2010 period. Because the 10-year survival for grade I pilocytic astrocytoma is 89.69% in our analysis, 50% survivor function was not reached in any of the time periods.

Patients diagnosed in the different time periods had different lengths of follow up. To correct for this, we examined the 2-year survival for all four time periods as this is the length of

follow-up for the most recent time period 2008-2010. Kaplan-Meier plot of survival two years after diagnosis is shown in **Figure 1B**. Over the study period, 2-year survival [95% CI] increased from 9.48% [8.58%-10.42%] (1999-2001) to 19.36% [7.93%-20.83%] (2008-2010) for grade IV glioblastoma. The 2-year survival for grade III astrocytoma increased from 35% [30.99%-39.03%] (1999-2001) to 49.96% [44.80%-54.9%] (2008-2010), and the 2-year survival for grade II astrocytoma increased from 60.54% [57.14%-63.76%] (1999-2001) to 65.62% [61.87%-69.1%] (2008-2010). In contrast, the 2-year survival for grade I astrocytoma remained fairly constant during the study period at 96.15% [94.1%-97.5%] (1999-2001), 97.68% [96.17%-98.59%] (2002-2004), 97.47% [95.84%-98.47%] (2005-2007) and 98.73% [97.02%-99.46%] (2008-2010).

*Multivariate Adjusted HR of Death Analysis*

To determine whether the improvements in survival persist after adjusting for demographic (age, race/ethnicity, marital status, sex) and clinical (tumor size, tumor site, radiotherapy and surgical treatment) variables, we derived adjusted hazard ratios (HRs) for death using an extended multivariate Cox proportional hazards model (**Table 3**). The HR demonstrated downward trend for grade II, III, and IV gliomas, reflecting improved survival throughout the decade after adjusting for the above described variables. Compared to the HR for patients diagnosed during 1999-2001, there were statistically significant decreases in the subsequent three periods. For grade IV glioblastoma, the HR [95% CI] successively decreased from 1.00 (1999-2001) to 0.84 [0.8-0.89] (2002-2004) to 0.75 [0.71-0.97] (2005-2007) to 0.67 [0.63-0.71] (2008-10) during the study period. For grade III anaplastic astrocytomas, there was a significant drop in HR around 2005, with HR decreased from 1.00 and 0.95 [0.8-1.13] (1999-2001 and 2002-2004, respectively) to 0.69 [0.58-0.83] and 0.65 [0.53-0.8] (2005-2007 and 2008-2010,

respectively). Similarly, for grade II astrocytomas, there was a drop in HR around 2005, with HR decreasing from 1.00 and 0.99 [0.84-1.18] (1999-2001 and 2002-2004, respectively) to 0.85 [0.71-1.01] and 0.75 [0.62-0.93] (2005-2007 and 2008-2010, respectively). In contrast, no significant change in the HR of grade I pilocytic astrocytoma was observed during the study period. However, the interpretation of this finding should be caveated with the extremely low number of patients who died from this disease.

*Multivariate Adjusted OR of Radiotherapy and Surgical Treatment Analysis*

To determine whether the improved survival in grade II and III astrocytoma patients can be attributed to increased extent of resection (EOR) or utilization of radiotherapy (RT), we calculated the OR of patients who underwent gross total resection (GTR) or RT during the study period using a multivariate logistic regression model adjusting for demographic and clinical variables described above (**Table 4** and **Table 5**). For grade II astrocytomas, there were no consistent changes in the OR of patients undergoing GTRs. In contrast, there was a statistically significant decline in RT utilization in 2005-2007 and 2008-2010 periods (OR of 0.68 and 0.76, respectively) relative to the 1999-2001 and 2002-2004 periods (1.00 and 1.14, respectively). For grade III astrocytoma patients, there were no significant changes in OR of receiving GTR or RT during the study period.

*Survival analysis in the pre- and post-TMZ era*

Temozolomide (TMZ) treatment of grade II and III astrocytomas was frequently adopted after the landmark study in 2005 by Stupp et al. published in the New England Journal of Medicine [28]. In **Table 6**, we performed an analysis to examine whether the HRs for death in the

post-TMZ era (2005-2010) were lower than those observed in the pre-TMZ era (1999-2004) after accounting for all pertinent demographic and clinical variables described above. No significant change in HR was observed for patients with grade I astrocytoma when comparing pre- and post-TMZ era. In contrast, we observed statistically significant decrease in the HR of death in the post-TMZ era for grade II, III and IV astrocytomas. This correlative data supports the efficacy of TMZ in the treatment of grade II and III astrocytoma patients. However, we cannot exclude the possibility that other advances in the care of neuro-oncology patients contributed to this effect (see discussion).

**DISCUSSION**

Our study is the first to analyze changes in the survival patterns of patients afflicted with grade I, II, and III astrocytomas as well as the prevailing clinical practice patterns in terms of treatment preference using the SEER registry. To date, this is the largest population-based study dedicated to the study of these histologically delineated glioma subtypes. Previous studies suggest improved survival for grade IV astrocytoma patients (a.k.a. glioblastoma) over time [17-20]. We recapitulated this result in our study. On the other hand, the survival patterns for the lower grade astrocytomas remain poorly characterized. Our results indicate that over the past decade, there has been an increase in the overall survival of patients afflicted with grade II and III astrocytomas. Importantly, this increase persisted after adjusting for pertinent demographic and clinical variables including age, race/ethnicity, marital status, sex, tumor size, tumor location, extent of surgical resection, and radiotherapy status. Relative to patients diagnosed with grade II and III astrocytomas in the 1999-2001 period, the adjusted hazard ratio of death for patients diagnosed in 2008-2010 has decreased by 24% and 35%, respectively.

It is important to interpret these findings in the context of the shifting diagnostic landscape of glioma patients. During the study period, there was growing recognition that a diagnosis of oligodendroglioma conferred a more favorable prognosis compared to a diagnosis of purely astrocytic tumor of the same WHO grade [29]. Moreover, oligodendrogliomas exhibit favorable response to select chemotherapy regimen [30-34], and the diagnosis qualify the patient for treatment with these regimens. Consequently, there is an overall increase in the number of patients diagnosed with oligodendroglioma during the period of our study [35]. One interpretation of this increase is that many patients who would have been diagnosed with astrocytoma were instead diagnosed with oligodendrogliomas [36]. If so, the diagnostic shift would deplete a population with favorable natural history from the diagnostic category of grade II astrocytomas. The increased median overall survival may be particularly notable in this context.

The pattern of clinical practice pertaining to RT utilization for the treatment of astrocytoma patients during the study period is of interest. Most grade III astrocytoma patients undergo RT [15]. Our results indicate that the proportion of patients receiving RT has not changed significantly over the past decade. In contrast, there is a notable decrease in the use of RT for grade II astrocytomas after 2005. This change in clinical practice is temporally associated with the publication of two major landmark studies. First, long-term outcome from EORTC 22845, a randomized clinical trial comparing up-front RT with RT at the time of progression for patients with low grade glioma, revealed that up-front RT does not affect overall survival [37]. Second, the efficacy of TMZ against high grade gliomas was reported in another landmark study [28]. Since this report, there has been ongoing studies to explore TMZ only treatment for grade II gliomas [38-42]. It is likely that the combined effects of these studies influenced the decreased utilization of

RT for patients afflicted with grade II astrocytomas. Validation of this thesis can facilitate our understanding of the influence of published literature on clinical practice patterns.

On the other hand, there is no clear trend in terms of the clinical practice pattern pertaining to EOR of grade II or III astrotycomas**.** Over the study period, there is mounting evidence from carefully designed and executed studies that suggest clinical benefit of a maximal surgical resection for grade II and III astrocytomas [43]. The largest surgical series on the matter emerged from the French Glioma Network (FGN) involving 1097 low grade glioma patients. In this series, EOR and post-surgical residual volume remain independent prognostic factors in a multivariate model that accounted for pertinent clinical variables [44]. This association has been reproducibly validated by multiple, independent clinical studies [10,45,46]. Similar results have been reported for anaplastic astrocytomas [6,11]. Our results indicate that these published studies have not significantly affected the overall surgical practice for treatment of grade II and III astrocytomas patients in the U.S. As such, meaningful gains in clinical outcome may be achieved by improving the EOR for grade II and III astrocytoma patients.

Our results indicate that EOR and RT are unlikely to have contributed to the improved overall survival for grade II and III astrocytoma patients. Instead, we suggest the following contributing factors. First, our stratified survival analysis of grade II and III astrocytoma patients in the pre- and post-TMZ era suggest that TMZ may be efficacious for these patient populations. However, this thesis awaits formal validation. Second, there is a general improvement in neuro-oncologic standard of care over the past decade [47], including the recognition of the need for dedicated training of neuro-oncologists, the adaptation of multi-disciplinary tumor boards, and dedicated brain cancer centers. Third, advances in neuro-imaging tools, a better understanding of the natural history and prognostic factors for these diseases [48], and elucidation of the efficacy of

RT [37] afford opportunities for rational decisions in terms of therapeutic intervention. Finally, we cannot exclude the possibility of lead time bias associated with increased utilization of MR imaging as work-up for neurologic complaint [49]. Such practice may afford early disease detection, thereby artificially inflating the overall survival estimate. It is likely that each of these factors contribute to the improved survival of grade II and III astrocytoma patients.

Our study design is subject to several limitations, including the veracity of the data contained in the SEER registry, the absence of key variables (such as the chemotherapy that the patients received, quality of life measures, and location of the tumor in relation to eloquent cortex). Despite these limitations, we have utilized the registry dataset to the fullest extent by adjustment of all pertinent clinical variables available. Additionally, the study result is subject to distortion related to the shifting landscape in terms of the diagnosis of astrocytomas and oligodendrogliomas that took place during the study period [35]. The observation of improved survival for astrocytoma patients despite an increasing number of patients diagnosed with oligodendroglioma, however, suggest that our findings are robust. Finally, we were unable to tease out the relative contribution of TMZ or lead time bias to the overall increase in survival. Despite these limitations, the observed improvement in survival represents valuable information to clinical practitioners, patients, and patient advocacy groups. Moreover, analysis of the clinical practice pattern further identified potential opportunities for impacting the clinical course of patients afflicted with grade II and III astrocytomas.

In conclusion, results from the SEER database indicate improvements in the overall survival of grade II and III astrocytoma patients over the past decade. Analysis of corresponding changes in clinical practice patterns suggests opportunities for improvement in the surgical management of these patients as it pertains to EOR.

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**FIGURE CAPTIONS**

**Figure 1**

**A.** Kaplan-Meier plot of 10-year survival by time period for WHO grade I-IV astrocytomas. Note the survival rate (y-axis) ranges from 0.85 to 1 for grade I pilocytic astrocytoma, from 0.25 to 1 for grade II diffuse astrocytoma and from 0 to 1 for grade III anaplastic astrocytoma and grade IV glioblastoma.

**B.** Kaplan-Meier plot of 2-year survival by time period for WHO grade I-IV astrocytomas. Note the survival rate (y-axis) ranges from 0.9 to 1 for grade I pilocytic astrocytoma, from 0.5 to 1 for grade II diffuse astrocytoma and from 0.25 to 1 for grade III anaplastic astrocytoma and from 0 to 1 for grade IV glioblastoma.

## TABLES

**Table 1** Demographic and clinical characteristic of WHO grade I-IV astrocytoma cases, SEER 1999-2010

| | Grade I Pilocytic | Grade II Diffuse | Grade III Anaplastic | Grade IV Glioblastoma | Total |
|---|---|---|---|---|---|
| **Number of Patients, No. (% of Total)** | 2,497 (7.97) | 4,113 (13.13) | 2,755 (29.89) | 21,962 (70.11) | 31,327 (100) |
| **Age, median (IQR)** | 12 (5-20) | 44(29-59) | 50 (35-64) | 61 (52-71) | 58 (44-69) |
| **Age Category, No. (%)** | n = 2,497 | n = 4,113 | n = 2,775 | n = 21,962 | n = 31,327 |
| Age < 18 | 1,739 (69.64) | 528 (12.84) | 177 (6.42) | 255 (1.16) | 2,699 (8.62) |
| Age 18-44 | 596 (23.87) | 1,591 (38.68) | 929 (33.72) | 2,256 (10.27) | 5,372 (17.15) |
| Age 45-59 | 113 (<5) | 974 (23.68) | 745 (27.04) | 7,179 (32.69) | 9,011 (28.76) |
| Age 60-74 | 41 (<2) | 673 (16.36) | 593 (21.52) | 8,520 (38.79) | 9,827 (31.37) |
| Age ≥ 75 | <10 (<1) | 347 (8.44) | 311 (11.29) | 3,752 (17.08) | 4,418 (14.1) |
| **Race, No. (%)** | n = 2,497 | n = 4,113 | n = 2,775 | n = 21,962 | n = 31,327 |
| White | 1,623 (65) | 3,008 (73.13) | 2,097 (76.12) | 17,665 (80.43) | 24,393 (77.87) |
| Black | 207 (8.29) | 287 (6.98) | 180 (6.53) | 1,213 (5.52) | 1,887 (6.02) |
| Asian/Pacific Islander | 118 (4.73) | 189 (4.6) | 138 (5.01) | 845 (3.85) | 1,290 (4.12) |
| Hispanic | 493 (19.74) | 576 (14) | 325 (11.8) | 2,137 (9.73) | 3,531 (11.27) |
| American Indian/Alaskan Native | 18 (0.72) | 28 (0.68) | 7 (0.25) | 66 (0.3) | 119 (0.38) |
| Other/Unknown, Non-Hispanic | 38 (1.52) | 25 (0.61) | 8 (0.29) | 36 (0.16) | 107 (0.34) |
| **Marital Status, No. (%)** | n = 2,460 | n = 4,000 | n = 2,669 | n = 21,311 | n = 30,440 |
| Single | 2,125 (86.38) | 1,379 (34.48) | 697 (26.11) | 3,008 (14.11) | 7,209 (23.68) |
| Married | 288 (11.71) | 2,094 (52.35) | 1,581 (59.24) | 14,165 (66.47) | 18,128 (59.55) |
| Separated, Divorced, Widowed | 47 (1.91) | 527 (13.18) | 391 (14.65) | 4,138 (19.42) | 5,103 (16.76) |

| **Sex, No. (%)** | n = 2,497 | n = 4,113 | n = 2,775 | n = 21,962 | n = 31,327 |
|---|---|---|---|---|---|
| Male | 1,263 (50.58) | 2,354 (57.23) | 1,533 (55.64) | 12,905 (58.76) | 18,055 (57.63) |
| Female | 1,234 (49.42) | 1,759 (42.77) | 1,222 (44.36) | 9,057 (41.24) | 13,272 (42.37) |
| **Tumor Size, No. (%)** | n = 1,725 | n = 2,436 | n = 1,744 | n = 16,847 | n = 22,752 |
| <5cm | 1,158 (67.13) | 1,568 (64.37) | 1,107 (63.47) | 9,630 (57.16) | 13,463 (59.17) |
| 5-7cm | 471 (27.3) | 620 (25.45) | 429 (24.6) | 5,728 (34) | 7,248 (31.86) |
| >7cm | 96 (5.57) | 248 (10.18) | 208 (11.93) | 1,489 (8.84) | 2,041 (8.97) |
| **Tumor Site, No. (%)** | n = 2,497 | n = 4,113 | n = 2,775 | n = 21,962 | n = 31,327 |
| Frontal Lobe | 117 (4.69) | 1,179 (28.67) | 861 (31.25) | 5,840 (26.59) | 7,997 (25.53) |
| Temporal Lobe | 134 (5.37) | 821 (19.96) | 531 (19.27) | 5,377 (24.48) | 6,863 (21.91) |
| Parietal Lobe | 65 (2.6) | 450 (10.94) | 323 (11.72) | 3,691 (16.81) | 4,529 (14.46) |
| Occipital Lobe | 38 (1.52) | 79 (1.92) | 61 (2.21) | 952 (4.33) | 1,130 (3.61) |
| Brain Stem | 305 (12.21) | 197 (4.79) | 88 (3.19) | 133 (0.61) | 723 (2.31) |
| Overlapping Lesion of Brain | 76 (3.04) | 579 (14.08) | 405 (14.7) | 3713 (16.91) | 4,773 (15.24) |
| Cerebrum | 217 (8.69) | 330 (8.02) | 272 (9.87) | 851 (3.87) | 1,670 (5.33) |
| Brain, NOS | 397 (15.9) | 262 (6.37) | 136 (4.94) | 1,154 (5.25) | 1,949 (6.22) |
| Ventricle, NOS | 181 (7.25) | 74 (1.8) | 32 (1.16) | 95 (0.43) | 382 (1.22) |
| Cerebellum, NOS | 967 (38.73) | 142 (3.45) | 46 (1.67) | 156 (0.71) | 1,311 (4.18) |
| **Year of Diagnosis, No. (%)** | n = 2,497 | n = 4,113 | n = 2,775 | n = 21,962 | n = 31,327 |
| 1999 | 96 (3.84) | 163 (3.96) | 103 (3.74) | 873 (3.98) | 1235 (3.94) |
| 2000 | 218 (8.73) | 391 (9.51) | 254 (9.22) | 1728 (7.87) | 2591 (8.27) |
| 2001 | 221 (8.85) | 341 (8.29) | 227 (8.24) | 1708 (7.78) | 2497 (7.97) |
| 2002 | 224 (8.97) | 366 (8.9) | 240 (8.71) | 1776 (8.09) | 2606 (8.32) |
| 2003 | 225 (9.01) | 361 (8.78) | 250 (9.07) | 1861 (8.47) | 2697 (8.61) |
| 2004 | 207 (8.29) | 367 (8.92) | 241 (8.75) | 1967 (8.96) | 2782 (8.88) |
| 2005 | 193 (7.73) | 343 (8.34) | 246 (8.93) | 1934 (8.81) | 2716 (8.67) |
| 2006 | 208 (8.33) | 355 (8.63) | 242 (8.78) | 1877 (8.55) | 2682 (8.56) |
| 2007 | 217 (8.69) | 359 (8.73) | 225 (8.17) | 2026 (9.23) | 2827 (9.02) |

| | | | | | |
|---|---|---|---|---|---|
| 2008 | 228 (9.13) | 384 (9.34) | 229 (8.31) | 2063 (9.39) | 2904 (9.27) |
| 2009 | 219 (8.77) | 355 (8.63) | 245 (8.89) | 2041 (9.29) | 2860 (9.13) |
| 2010 | 241 (9.65) | 328 (7.97) | 253 (9.18) | 2108 (9.6) | 2930 (9.35) |
| **Radiotherapy, No. (%)** | n = 2,462 | n = 4,003 | n = 2,698 | n = 21,483 | n = 30,646 |
| No | 2,266 (92.04) | 1,894 (47.31) | 611 (22.65) | 5,353 (24.92) | 10,124 (33.04) |
| Yes | 196 (7.96) | 2,109 (52.69) | 2,087 (77.35) | 16,130 (75.08) | 20,522 (66.96) |
| **Surgery, No. (%)** | n = 2,497 | n = 4,113 | n = 2,775 | n = 21,962 | n = 31,327 |
| Gross Total Resection | 1,161 (46.5) | 916 (22.27) | 537 (19.49) | 6,615 (30.12) | 9,229 (29.46) |
| Partial Resection | 553 (22.15) | 904 (21.98) | 624 (22.65) | 6,170 (28.09) | 8,251 (26.34) |
| Local Excision/Biopsy | 589 (23.59) | 806 (19.6) | 503 (18.26) | 4,459 (20.3) | 6,357 (20.29) |
| No Surgery | 194 (7.77) | 1,487 (36.15) | 1,091 (39.6) | 4,718 (21.48) | 7,490 (23.91) |
| **Overall Mortality, No. (%)** | n = 2,497 | n = 4,113 | n = 2,775 | n = 21,962 | n = 31,327 |
| Living | 2,351 (94.15) | 2,008 (48.82) | 898 (32.6) | 3,108 (14.15) | 8,365 (26.7) |
| Deceased | 146 (5.85) | 2,105 (51.18) | 1,857 (67.4) | 18,854 (85.85) | 22,962 (73.3) |

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; IQR, Interquartile range.

**Table 2** Log-rank and Tarone-Ware tests for survivor functions by time period for WHO grade I-IV astrocytoma

| | Grade I<br>Pilocytic Astrocytoma | Grade II<br>Diffuse Astrocytoma | Grade III<br>Anaplastic Astrocytoma | Grade IV<br>Glioblastoma |
|---|---|---|---|---|
| **Tarone-Ware P-value** | 0.0369 | 0.0205 | <0.0001 | <0.0001 |

**Table 3** Multivariate-adjusted Hazard Ratio* (HR) and 95% CI for death derived from extended Cox proportional hazard model by time period for WHO grade I-IV astrocytomas

| | Grade I<br>Pilocytic Astrocytoma | | Grade II<br>Diffuse Astrocytoma | | Grade III<br>Anaplastic Astrocytoma | | Grade IV<br>Glioblastoma | |
|---|---|---|---|---|---|---|---|---|
| | **Adjusted HR** | **P value** | **Adjusted HR** | **P value** | **Adjusted HR** | **P value** | **Adjusted HR** | **P value** |
| **1999-2001** | 1.00 | *Reference* | 1.00 | *Reference* | 1.00 | *Reference* | 1.00 | *Reference* |
| **2002-2004** | 0.71 (0.38 - 1.34) | 0.29 | 0.99 (0.84 - 1.18) | 0.95 | 0.95 (0.8 - 1.13) | 0.55 | 0.84 (0.8 - 0.89) | <0.0001 |
| **2005-2007** | 0.88 (0.47 - 1.67) | 0.70 | 0.85 (0.71 - 1.01) | 0.07 | 0.69 (0.58 - 0.83) | <0.0001 | 0.75 (0.71 - 0.79) | <0.0001 |
| **2008-2010** | 0.57 (0.22 - 1.47) | 0.25 | 0.76 (0.62 - 0.93) | 0.01 | 0.65 (0.53 - 0.8) | <0.0001 | 0.67 (0.63 - 0.71) | <0.0001 |

*Adjusted for age, race/ethnicity, marital status, sex, tumor size, tumor site, radiotherapy and surgical treatment.

Abbreviations: HR, hazard ratio; CI, confidence interval.

**Table 4** Multivariate-adjusted Odds Ratio* (OR) and 95% CI for gross total resection (GTR) derived from logistic regression model by time period for WHO grade II and III astrocytomas

| | Grade II Diffuse Astrocytoma | | Grade III Anaplastic Astrocytoma | |
|---|---|---|---|---|
| | **Adjusted OR** | **P value** | **Adjusted OR** | **P value** |
| **1999-2001** | 1.00 | *Reference* | 1.00 | *Reference* |
| **2002-2004** | 1.32 (0.98 - 1.78) | 0.073 | 1.27 (0.87 - 1.84) | 0.214 |
| **2005-2007** | 1.11 (0.83 - 1.5) | 0.475 | 1.15 (0.79 - 1.66) | 0.461 |
| **2008-2010** | 0.71 (0.52 - 0.96) | 0.028 | 0.83 (0.57 - 1.21) | 0.323 |

*Adjusted for age, race/ethnicity, marital status, sex, tumor size, tumor site, and radiotherapy.

**Table 5** Multivariate-adjusted Odds Ratio** (OR) and 95% CI for radiotherapy (RT) derived from logistic regression model by time period for WHO grade II and III astrocytomas

| | Grade II Diffuse Astrocytoma | | Grade III Anaplastic Astrocytoma | |
|---|---|---|---|---|
| | **Adjusted OR** | **P value** | **Adjusted OR** | **P value** |
| **1999-2001** | 1.00 | *Reference* | 1.00 | *Reference* |
| **2002-2004** | 1.14 (0.86 - 1.5) | 0.365 | 0.87 (0.59 - 1.28) | 0.465 |
| **2005-2007** | 0.68 (0.52 - 0.89) | 0.005 | 0.92 (0.63 - 1.35) | 0.669 |
| **2008-2010** | 0.76 (0.58 - 0.99) | 0.042 | 0.86 (0.59 - 1.25) | 0.428 |

**Adjusted for age, race/ethnicity, marital status, sex, tumor size, tumor site and surgical treatment.

Abbreviations: OR, odds ratio; CI, confidence interval.

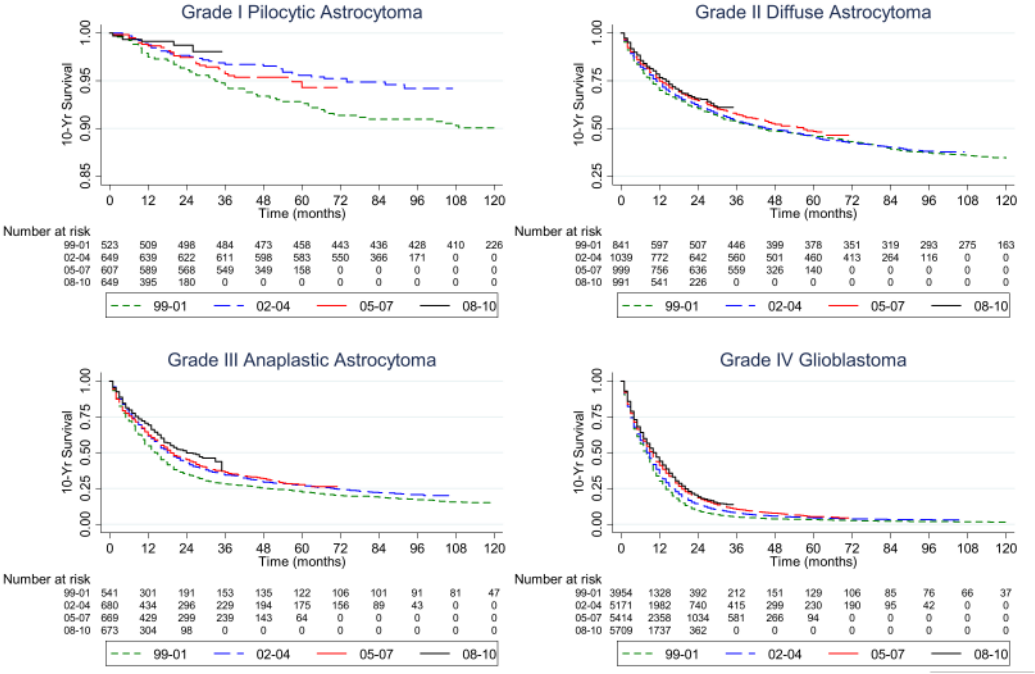
**Table 6** Multivariate-adjusted Hazard Ratio* (HR) and 95% CI for death derived from extended Cox proportional hazard model for pre- and post-TMZ era for WHO grade I-IV astrocytomas

| | Grade I Pilocytic Astrocytoma | | Grade II Diffuse Astrocytoma | | Grade III Anaplastic Astrocytoma | | Grade IV Glioblastoma | |
|---|---|---|---|---|---|---|---|---|
| | **Adjusted HR** | **P value** | **Adjusted HR** | **P value** | **Adjusted HR** | **P value** | **Adjusted HR** | **P value** |
| **Pre-TMZ (1999-2004)** | 1.00 | *Reference* | 1.00 | *Reference* | 1.00 | *Reference* | 1.00 | *Reference* |
| **Post-TMZ (2005-2010)** | 0.92 (0.53-1.57) | 0.748 | 0.82 (0.72-0.93) | 0.002 | 0.70 (0.61-0.79) | <0.0001 | 0.79 (0.76-0.82) | <0.0001 |

*Adjusted for age, race/ethnicity, marital status, sex, tumor size, tumor site, radiotherapy and surgical treatment.

Abbreviations: HR, hazard ratio; CI, confidence interval.

# 10-year survival by time period for WHO grade I-IV astrocytomas



# 2-year survival by time period for WHO grade I-IV astrocytomas