Superior Efficacy of Gross Total Resection in Anaplastic Astrocytoma Patients Relative to Glioblastoma Patients

Jennifer A. Padwal[1], Xuezhi Dong[1,2], Brian R. Hirshman[3], U. Hoi-Sang[3], Bob S. Carter[3], Clark C. Chen[3]

■ INTRODUCTION: **Because of their relative rarity, anaplastic astrocytomas (AAs) often are grouped with glioblastomas in clinical treatment paradigms. There are reasons, however, to expect that the therapeutic response of AAs may differ from those of glioblastoma. Here, we examined the clinical benefit of gross total resection (GTR) in AA relative to glioblastoma patients.**

■ METHODS: **Using the Surveillance, Epidemiology and End Results database, we identified 2755 patients with AA and patients with 21,962 glioblastoma between 1999 and 2010. Surgical resection was defined as GTR, subtotal resection (STR), biopsy only, or no resection. Kaplan-Meier curves and multivariate Cox regression were used to assess the association between GTR and survival.**

■ RESULTS: **The hazard of dying from the AA was reduced in GTR patients by 40% relative to STR patients. This reduction is 59% greater than that observed in glioblastoma where GTR was associated only with a 24% reduction relative to STR (P < 0.0001). The median survival for patients with AA who underwent GTR and subtotal resection were 64 and 24 months, respectively. For glioblastoma patients, the corresponding numbers for median survival were 13 and 9 months, respectively. The survival benefit of GTR in patients with AA was particularly notable in patient age < 50, where the median survival was not reached during the study period.**

■ CONCLUSIONS: **The Surveillance, Epidemiology and End Results data suggest that survival benefit associated with GTR was greater for patients with AA relative to glioblastoma patients, particularly for patients < age 50.**

INTRODUCTION

Anaplastic astrocytoma (AA) is a rare form of brain cancer, accounting for 5.9% of primary central nervous system gliomas[1] and with an incidence rate of 0.25 cases per 100,000 persons per year.[2] Because of its rarity, clinical studies often group together AA and a related but more aggressive form of brain cancer, glioblastoma. Together, these brain cancers are referred to as high-grade gliomas.[3,4] The main rationale for this grouping is that AAs inevitably progress to glioblastomas.[5] As such, proponents of the nomenclature argue that the 2 diseases share a common pathophysiology[6] and should exhibit comparable responses to therapeutics.[7]

Recent molecular characterization of AAs, however, suggests fundamental histopathologic differences between AAs and glioblastomas. For instance, the available evidence suggests that brain tumors harboring isocitrate dehydrogenase (IDH) mutations exhibit a distinct epigenetic landscape,[8,9] molecular physiology,[10,11] and differential response to surgical resection[12,13] and temozolomide (TMZ).[14,15] It is estimated that <10% of glioblastomas harbor the IDH mutations[16] whereas 30%–68% of AAs

Key words
- Anaplastic astrocytoma
- Brain tumor
- Extent of resection
- Glioblastoma
- Glioma
- SEER

Abbreviations and Acronyms
AA: Anaplastic astrocytoma
CI: Confidence interval
GTR: Gross total resection
HR: Hazard ratio
ICD-O-3: *International Classification of Disease for Oncology*, third edition
IDH: Isocitrate dehydrogenase
SEER: Surveillance, Epidemiology, and End Results
STR: Subtotal resection
TMZ: Temozolomide
WHO: World Health Organization

From the [1]School of Medicine, University of California, San Diego, La Jolla, California; [2]Codman Center for Clinical Effectiveness in Surgery, Massachusetts General Hospital (MGH), Boston, Massachusetts; and [3]Division of Neurological Surgery, University of California, San Diego, San Diego, California, USA

To whom correspondence should be addressed: Clark C. Chen, M.D., Ph.D. [E-mail: clarkchen@ucsd.edu]

Citation: World Neurosurg. (2016) 90:186-193.
http://dx.doi.org/10.1016/j.wneu.2016.02.078

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

harbor IDH mutations.[13,17-19] The assumption that therapeutic interventions would produce similar results in glioblastoma and AA, thus, warrant careful scrutiny.

Although there is a large body literature providing class II/III data demonstrating the clinical benefit of gross total resection (GTR) for glioblastomas, the literature supporting such benefit for AAs is more limited.[20,21] A previous study that used the Surveillance, Epidemiology, and End Results (SEER) database demonstrated a reduced hazard ratio (HR) for death in patients with AA who underwent GTR relative to those who underwent surgical biopsy.[22] The efficacy of GTR relative to subtotal resection (STR) in this population, however, was not studied carefully.[23] Moreover, whether these effects differ between patients with glioblastoma and those with AA remains unknown. It is generally accepted that AA, like glioblastoma, is an intrinsically infiltrative disease and that microscopic total resection is not possible without significant morbidity[24]; however, whether AAs and glioblastomas differ in their infiltrative nature or differ in their response to TMZ therapy remains an open question.[25,26] If such differences exist, one may expect that the benefit of GTR in the AA population may differ from that seen in the glioblastoma population.

In this context, we explored whether the clinical benefit of surgical resection in patients with AA differed from those of glioblastoma patients. Because of the rarity of AAs, we used the SEER population database to identify a cohort of 2755 patients with AA and 21,962 patients with glioblastoma. We found that the patients with AA derive notably greater benefit from GTR relative to patients with glioblastoma, in both relative terms as assessed by hazard of death and in absolute terms as gauged by median survival. This finding bears relevance to surgical decision-making during treatment of patients with AA.

MATERIALS AND METHODS

Data and Study Population

The SEER Program was established by the National Cancer Institute 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 downloaded the dataset as ASCII text files released in April 2013 based on the November 2012 submission.[27]

This study included patients who were diagnosed between 1999 and 2010 with World Health Organization (WHO) Grade III–IV intracranial astrocytomas as the only cancer diagnosis. We used *International Classification of Disease for Oncology*, third edition (ICD-O-3) histology codes 9401 for WHO Grade III AA and 9440–9442 for WHO Grade IV glioblastoma. ICD-O-3 topologic site codes C71.0–C71.9 were used to select for brain tumors. These codes were cross-referenced and validated with **Table 1** of Central Brain Tumor Registry of the United States Statistical Report.[1] Patients were excluded from the study if the surgical status was coded as unknown or if the histology was coded as unconfirmed. After these exclusions, we identified a total of 2,755 AA and 21,962 glioblastoma cases.

Covariates and Extent of Resection

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. We used the following demographic variables in the statistical analysis: age (<18, 18–44, 45–49, 50–54, 55–59, 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 widowed]), and sex (male or female). Clinical variables included tumor size (<5 cm, 5–7 cm or >7 cm), 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, STR, or GTR).

With regards to the extent of resection achieved, we used the following surgery codes from the SEER registry: no surgery (code 00), excisional biopsy (code 20), TR or partial resection (codes 21, 40), or GTR (code 30, 55). Although the exact definition of surgical codes underwent minor modifications with each edition of SEER Program Coding and Staging Manual (1998–2003, 2004–2006, 2007–2009, 2010–present), the general definition remained consistent throughout the various editions.[28,29] The latest definition for surgical codes used at the time of this study can be found in the SEER Program Coding and Staging Manual 2013 released on February 28, 2013 under Appendix C: Surgical Codes for Brain.[30] Historical definitions can also be found on the SEER website.[31] GTR, STR, and biopsy were defined as derived in previously published manuscripts that examined the relative efficacy of GTR and STR in SEER glioblastoma.[28,29]

Statistical Analysis

All analyses were conducted using Stata version 11.2,[32] and the level of statistical significance was set at $P < 0.05$. We performed comparisons of overall survival between AA and glioblastoma patients who underwent STR, GTR, or no surgery. Further analyses were performed to determine the impact of age and TMZ use on the survival benefit associated with GTR. We used the Kaplan-Meier method to generate unadjusted survival curves in both overall and subset analyses. Statistical significance was determined using log-rank test across survival functions.[28] To obtain the multivariate adjusted HR of death, we performed Cox proportional hazard analysis adjusting for demographic and clinical covariates mentioned previously. In addition, we calculated the median survival with 95% confidence interval (CI) in both overall and subset analyses.

RESULTS

Patient and Clinical Characteristics

Patient characteristics are outlined in **Table 1**. From the SEER database, we identified 21,962 patients with glioblastoma and 2775 patients with AA. The median age of diagnosis (interquartile range) was 50 (35–64) for AAs and 61 (52–71) for glioblastomas; 9057 (41.24%) patients with AA and 13,272 (42.37%) with glioblastoma were female. Mortality rates increased with increasing histologic grade with 67.4% mortality for AA and 85.85% for glioblastoma. The most common sites for both AA and glioblastoma were the frontal lobe and the temporal lobe. The demographics of this population are consistent with previous literature.[2]

Of the 2775 patients with AA, 1091 (39.6%) had no surgery, 503 underwent biopsy (18.26%), 624 (22.65%) underwent STR, and 537 (19.49%) underwent GTR. Of the 21,962 patients with