Optic nerve gliomas in adults: a SEER-based study

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Abstract

**Background:** Optic nerve gliomas (ONGs) are uncommon tumors of the central nervous system in adults. The aim of this study was to define their characteristics, prognostic factors, and the impacts of adjuvant radiotherapy (RT) and chemotherapy on outcomes.

**Methods:** Adult patients (age $\geq 18$ years) with ONGs from the Surveillance, Epidemiology, and End Results (SEER) database were included. Univariate and multivariate Cox regression models were utilized to analyze the factors associated with survival. Kaplan-Meier method was used to evaluate the impacts of adjuvant therapies on overall survival (OS).

**Results:** A total of 179 adult patients diagnosed with ONGs were identified between 1991 and 2016, with a median follow-up period of 64.0 months. The median age at diagnosis was 41.0 years. After excluding 18 patients with unknown information, the remaining patients included 142 (88.2%) low-grade tumors and 19 (11.8%) high-grade tumors. Multivariate analysis showed age at diagnosis, tumor grade, adjuvant chemotherapy were significant factors for OS. The 5-year OS rates for patients with low- and high-grade ONGs were 85.5% and 10.5%, respectively. The employment of adjuvant RT or chemotherapy would significantly shorten OS time in the low-grade group and could not prolong OS time in the high-grade group.

**Conclusions:** This is the largest retrospective study of adult ONGs up to date. The overall prognosis of high-grade ONGs in adult patients is still poor despite multi-modality treatments. Adjuvant RT or chemotherapy might not be considered in adult patients with low-grade ONGs unless the malignant transformation or aggressive progression has been confirmed.

Introduction

Optic nerve gliomas (ONGs) are relatively rare neoplasms, accounting for only 1% of all intracranial tumors and 2% - 5% of childhood central nervous system tumors.[1-4] Histopathological types vary, ranging from the most common WHO grade I pilocytic astrocytoma to uncommon grade IV high-grade glioblastoma.[5,6] They are preferentially occurred in the pediatric population, particularly the first decade, and the majority are low-grade lesions.[7] ONGs can either be sporadic[8], or in association with Neurofibromatosis-1 (NF-1)[9], and the typical symptoms include decreased visual acuity, optic nerve atrophy, unilateral visual loss, or proptosis.[10,11]

The optional treatment of ONGs remains controversial, ranging from clinical observation, surgical resection, chemotherapy, and radiotherapy (RT), due to the unpredictable course.[12,1] The treatment is generally commenced when radiological tumor progression or clinical deterioration occurs, especially visual decline.[13] For children, chemotherapy has been the first-line treatment over the past two decades because of fewer adverse side effects than occurs with RT.[14,15,4] While in adults, ONGs are rare, and the treatment for which has historically been approached in a different manner than children.[16-18] However, the definitive efficacy of adjuvant RT or chemotherapy is still inconclusive due to the paucity of
research data. Also, because ONGs are relatively uncommon in adults, it is still challenging to perform prospective studies now or soon.

In the current study, we aim to report the largest series of adult patients with ONGs based on the Surveillance, Epidemiology, and End Results (SEER) database. To better understand these rare tumors, our retrospective study investigated the epidemiology, prognostic factors, and in particular, the impact of adjuvant RT and chemotherapy on outcomes further to define the role of adjuvant therapies in adult ONGs.

Materials And Methods

Study Population

The data information for this study was obtained from the recent SEER database, which provides clinical incidence, treatment, and survival data on many tumors and covering nearly 36.7% of the US population according to the 2010 census, and is maintained by the National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Surveillance Systems Branch. We included data from the incidence SEER 18 registries custom data (with additional treatment fields).

Inclusion Criteria, Exclusion Criteria, and Data Collection

Only adult patients (age ≥ 18 years) diagnosed with glioma (International Classification of Diseases for Oncology, 3rd Edition histology codes 9380 - 9442) and primary site labeled with the optic nerve (code C72.3) between January 1, 1991, and December 31, 2016, were included in the present study. Patients with more than one primary tumor were excluded from the present study. Data collected for analysis included age at diagnosis, gender, marital status, race, year of diagnosis, tumor site, tumor grade, surgery, adjuvant treatment (RT and chemotherapy), and overall survival (OS).

Data Analysis and Statistical Methods

We categorized age as 18 to 29, 30 to 39, 40 to 49, 50 to 59, and ≥ 60 years. The race was categorized into white, others (including black and American Indian/Alaska Native or Asian/Pacific Islander), and unknown. The year of diagnosis was divided into three categorical groups: 1991 – 1999, 2000 – 2009, and 2010 – 2016. The tumor site was categorized into unilateral, bilateral, and unknown. The extent of surgical resection was divided into five groups, including gross total resection (GTR), subtotal resection (STR), biopsy, no surgery, and unknown on the basis of SEER surgery codes guidelines and another previous study.[19] For further survival analysis, patients with the unknown grade, unknown survival time, unknown surgery (code 90 and 99), and unknown radiation record were excluded, and we categorized age as “< 50 years” and “≥ 50 years”, according to the previous literature.[19]

Baseline patient characteristics were summarized by standard descriptive statistics and frequency tabulation. Overall survival analysis was measured by using the Kaplan–Meier method and compared with the log-rank test. Univariate and multivariate Cox regression models were utilized to assess the
effect of variables of interest on OS. All statistical analyses were carried out in SPSS software version 25.0 (IBM Corp., Armonk, NY, USA), and the statistically significant standard was $P < 0.05$. Ethical approval or informed consent was waived for this study because of the de-identified information of the patients included in the SEER.

**Results**

**Clinical Characteristics**

A total of 179 adult patients diagnosed with ONGs were identified between 1991 and 2016. No patients with ONGs were recorded in the SEER database prior to 1991. Of the whole population, the mean and median ages at diagnosis were 42.1 and 41.0 years (range, 18 – 101 years), respectively, with 55.9% of patients being female, 78.2% white people, and 43.6% of married status (Table 1). 116 patients (64.8%) were located unilaterally regarding the tumor site, and 12 patients (6.7%) were bilateral. For tumor grade, 81.6% had a low-grade tumor, and 11.2% had a high-grade tumor. After excluding 18 patients with unknown information, the remaining patients included 142 (88.2%) low-grade tumors and 19 (11.8%) high-grade tumors. In the low-grade tumor group, 78.2% of patients were less than 50 years; however, 89.5% of patients were more than 50 years in the high-grade group.
Table 1
Clinical characteristics of adult patients with optic nerve gliomas

| Characteristic      | n  | %    |
|---------------------|----|------|
| Age at diagnosis (y)|    |      |
| 18–29               | 57 | 31.8 |
| 30–39               | 29 | 16.2 |
| 40–49               | 37 | 20.7 |
| 50–59               | 24 | 13.4 |
| ≥ 60                | 32 | 17.9 |
| Gender              |    |      |
| Female              | 100| 55.9 |
| Male                | 79 | 44.1 |
| Marital status      |    |      |
| Unmarried           | 83 | 46.4 |
| Married             | 78 | 43.6 |
| Unknown             | 18 | 10.0 |
| Race                |    |      |
| White               | 140| 78.2 |
| Others              | 35 | 19.6 |
| Unknown             | 4  | 2.2  |
| Year of diagnosis   |    |      |
| 1991–1999           | 26 | 14.5 |
| 2000–2009           | 84 | 47.0 |
| 2010–2016           | 69 | 38.5 |
| Tumor site          |    |      |
| Unilaterial         | 116| 64.8 |
| Bilateral           | 12 | 6.7  |
| Unknown             | 51 | 28.5 |
| Grade               |    |      |
| Characteristic          | n  | %   |
|------------------------|----|-----|
| Low-grade              | 146| 81.6|
| High-grade             | 20 | 11.2|
| Unknown                | 13 | 7.2 |
| Surgery                |    |     |
| Gross total resection  | 27 | 15.1|
| Subtotal resection     | 11 | 6.1 |
| Biopsy                 | 8  | 4.5 |
| None                   | 130| 72.6|
| Unknown                | 3  | 1.7 |
| Radiotherapy           |    |     |
| No                     | 99 | 55.3|
| Yes                    | 78 | 43.6|
| Unknown                | 2  | 1.1 |
| Chemotherapy           |    |     |
| No                     | 153| 85.5|
| Yes                    | 26 | 14.5|
| Vital status           |    |     |
| Alive                  | 135| 75.4|
| Dead                   | 44 | 24.6|

**Treatment Strategy**

In the present study, 15.1% of the patients underwent GTR, 6.1% of the patients underwent STR, 4.5% had a biopsy, and 72.6% had no surgery. For adjuvant therapies, RT was used in 43.6% of patients, and 26 patients (14.5%) had chemotherapy (Table 1). Besides, according to the different tumor grades, 38.7% and 11.3% of the patients in the low-grade group received adjuvant RT and chemotherapy, respectively. While in the high-grade group, the proportion of the patients who received adjuvant RT and chemotherapy was 68.4% and 47.4%, respectively.

**Overall Survival Analysis**
The median OS time for the whole cohort was not reached with a median follow-up time of 64.0 months, and 44 patients (24.6%) died during follow-up. The 5- and 10-year OS rates for adult patients with ONGs were 75.4% and 73.4%, respectively. Prognostic factors identified in univariate analysis were age at diagnosis, tumor grade, adjuvant RT, and chemotherapy (Table 2). On further multivariate Cox regression, younger age, low-grade tumors, and no adjuvant chemotherapy were significant factors for longer OS (Table 2).
Table 2
Univariate and multivariate analysis of OS

| Variable                  | Univariate analysis |                      | Multivariate analysis |                      |
|---------------------------|---------------------|----------------------|-----------------------|----------------------|
|                           | **HR (95% CI)**     | **Overall P-value**  | **HR (95% CI)**       | **Overall P-value**  |
| Age at diagnosis (y)      | < .001              |                      | < .001                |                      |
| < 50                      | reference           |                      | reference             |                      |
| ≥ 50                      | 10.430 (5.046–21.556) |                      | 4.964 (2.133–11.552)  |                      |
| Gender                    | .896                |                      |                       |                      |
| Female                    | reference           |                      |                       |                      |
| Male                      | 0.959 (0.509–1.807) |                      | 0.959 (0.509–1.807)   |                      |
| Marital status            | .654                |                      |                       |                      |
| Married                   | reference           |                      |                       |                      |
| Unmarried                 | 0.791 (0.411–1.523) |                      | 0.791 (0.411–1.523)   |                      |
| Unknown                   | 0.450 (0.185–2.114) |                      | 0.450 (0.185–2.114)   |                      |
| Race                      | .961                |                      |                       |                      |
| White                     | reference           |                      |                       |                      |
| Others                    | 1.118 (0.513–2.435) |                      | 1.118 (0.513–2.435)   |                      |
| Unknown                   | 0.000 (0.000-9.223E + 15) |                      | 0.000 (0.000-9.223E + 15) |                      |
| Year of diagnosis         | .498                |                      |                       |                      |
| 1991–1999                 | reference           |                      |                       |                      |
| 2000–2009                 | 1.562 (0.615–3.969) |                      | 1.562 (0.615–3.969)   |                      |
| 2010–2016                 | 1.108 (0.390–3.151) |                      | 1.108 (0.390–3.151)   |                      |
| Tumor site                | .953                |                      |                       |                      |
| Unilateral                | reference           |                      |                       |                      |
| Bilateral                 | 1.023 (0.309–3.391) |                      | 1.023 (0.309–3.391)   |                      |
| Unknown                   | 0.895 (0.431–1.857) |                      | 0.895 (0.431–1.857)   |                      |
| Grade                     | < .001              |                      | < .001                |                      |
| Low-grade                 | reference           |                      | reference             |                      |
| Variable                  | Univariate analysis | Multivariate analysis |          |          |
|--------------------------|---------------------|-----------------------|----------|----------|
|                          | HR (95% CI)         | Overall P-value       | HR (95% CI) | Overall P-value |
| High-grade               | 17.630 (9.066–34.282) | .578                  | 6.891 (3.145–15.100) | .548 |
| Surgery                  | reference            |                       |          |          |
| Gross total resection    | reference            |                       |          |          |
| Subtotal resection       | 1.379 (0.402–4.728)  |                       |          |          |
| Biopsy                   | 0.781 (0.162–3.760)  |                       |          |          |
| None                     | 0.700 (0.301–1.627)  |                       |          |          |
| Radiotherapy             | .001                 |                       | .001     | .015     |
| No                       | reference            |                       | reference |          |
| Yes                      | 3.121 (1.580–6.164)  |                       | 1.255 (0.598–2.637) |          |
| Chemotherapy             | < .001               |                       |          |          |
| No                       | reference            |                       | reference |          |
| Yes                      | 6.349 (3.268–12.333) |                       | 2.604 (1.205–5.627) |          |

Due to the possible negative impact of the adjuvant therapies on OS, further analyses were performed in the subgroups of low-grade and high-grade tumors to clarify better the prognosis of these patients who received adjuvant therapies. For the low-grade tumor group, the 5-year OS rate was 85.5%; however, the 5-year OS rate for patients in the high-grade group was only 10.5% (P < 0.001, log-rank test; Fig. 1). Based on the low-grade subgroup analysis, patients with age less than 50 years, no adjuvant RT or chemotherapy had the best OS time, and the difference was significant (P < 0.05, log-rank test; Fig. 2A-C). The results of multivariate Cox regression also showed that younger age, and no adjuvant chemotherapy were significant factors for longer OS (Table 3). However, different results were found in the other subgroup of the high-grade tumor, which demonstrated that only older age resulted in a significantly shorter OS (P < 0.05, log-rank test; Fig. 2D). Moreover, there were no significant differences in OS for high-grade patients who received the adjuvant therapies or not, according to multivariate Cox regression (Table 4, Fig. 2E-F).
Table 3  
multivariate analysis of OS in low-grade group

| Variable              | HR (95% CI)       | Overall P-value |
|-----------------------|-------------------|-----------------|
| Age at diagnosis (y)  | < .001            |                 |
| < 50                  | reference         |                 |
| ≥ 50                  | 5.303 (2.090-13.451) |                 |
| Radiotherapy          | .255              |                 |
| No                    | reference         |                 |
| Yes                   | 1.850 (0.642–5.333) |                 |
| Chemotherapy          | .008              |                 |
| No                    | reference         |                 |
| Yes                   | 4.024 (1.437–11.269) |                 |

Table 4  
multivariate analysis of OS in high-grade group

| Variable              | HR (95% CI)       | Overall P-value |
|-----------------------|-------------------|-----------------|
| Age at diagnosis (y)  | .083              |                 |
| < 50                  | reference         |                 |
| ≥ 50                  | 6.918 (0.777–61.563) |                 |
| Radiotherapy          | .587              |                 |
| No                    | reference         |                 |
| Yes                   | 0.741 (0.250–2.190) |                 |
| Chemotherapy          | .508              |                 |
| No                    | reference         |                 |
| Yes                   | 1.427 (0.497–4.095) |                 |

Discussion

Up to date, most studies of adult ONGs are individual case reports or only include a limited number of patients.[16-18,20-25] The largest research, which included 445 patients, not only mixed pediatric and adult cases, but also focused on the analysis of tumors in the pediatric population.[19] Few investigations have focused explicitly on adults ONGs.[17,25] For all we know, this study, including 179 cases on the basis of the SEER database, is the largest series of adult ONGs and is the only study to
compare the effects of different treatment strategies (including surgery, adjuvant RT, and chemotherapy) on survival with a large number of adult patients. Furthermore, our data identify that both adjuvant treatments (RT and chemotherapy) have a negative impact on the survival and prognosis of adult patients with low-grade tumors.

**Epidemiological and Tumor Characteristics**

ONGs in adults are extremely uncommon and were first described by Hoyt et al. in 1973, which included 15 adult patients with malignant optic glioma.[25] In our study, 70% of the patients were below the age of 50, especially in the low-grade tumors, and the mean age at diagnosis was 42.1 years, which is nearly consistent with the previously limited reported mean age for patients diagnosed at the adulthood of 39 years.[17] However, patients diagnosed with high-grade ONGs usually were older than those with low-grade ONGs, ranging from 57 to 66 years,[23,18,19] the same with our results. In addition, although other studies showed an equal ratio of male and female in the adult population,[25,17] a female predominance was demonstrated in this large study.

In terms of treatment, gross totally surgical resection usually was not the primary treatment option in patients with ONGs, especially for low-grade at any age.[1,19,17] Up to 72.6% of the patients underwent no surgery in the present study. For adjuvant therapies, there were differences between low-grade and high-grade groups. The existing reported data on RT and chemotherapy in patients with low-grade ONGs are mainly limited in the pediatric population.[8,15,26-28] In our study, 38.7% and 11.3% of low-grade adult patients received RT and chemotherapy, respectively. However, for the high-grade group, surgery or biopsy, followed by adjuvant RT and/or chemotherapy, could be considered the standard of care,[18,20,22,23,17] and these two proportions of the adjuvant therapies in current study were 68.4% and 47.4%, respectively.

**Factors Associated with Survival and Tumor Management**

Gender, marital status, race, year of diagnosis, tumor site, and different surgical patterns were not critical predictors of survival in univariate and multivariate analysis. However, age at diagnosis, tumor grade, and adjuvant RT and chemotherapy were significant survival factors in adult patients with ONGs. Although age was not recognized as a prognostic factor in a previous study,[19] our result showed that patients with age ≥ 50 years had a worse prognosis in both low- and high-grade groups, similar to other published series of gliomas.[29,30] It is universally acknowledged that patients with low-grade gliomas have a better survival prognosis, which had a 5-year OS rate of 85.5% compared to 10.5% for patients with high-grade gliomas in our study. Furthermore, although many reported cases of adult ONGs are high-grade, we found most of them remain low-grade tumors, inconsistent with the study by Shofty et al., in which 80% of primary adult ONGs are also low-grade.[17]

Unlike the gliomas in other sites, there is no gold standard in treating both low-grade and high-grade ONGs. The general goal of all individualized treatment strategies is to preserve the patient’s vision as long as possible. Based on this goal, surgical resection might not be a preferred option and is discouraged due
to the inevitable blindness on the affected side or bilateral visual loss risks.[31] Our current results demonstrate no significant differences among various surgical options for patients with any grade ONGs regarding OS. Therefore, initial observation is frequently recommended with ophthalmological evaluation and neuroimaging surveillance to confirm clinical stability, particularly for low-grade ONGs. However, for malignant ONGs or progressive tumors with the aggressively visual decline, it might be appropriate to consider surgical excision to debulk the tumor and obtain a pathological diagnosis before commencing the following adjuvant therapy.[7,1,2]

The role of adjuvant RT and chemotherapy in an adult population remains unclear due to its rarity. To our knowledge, there have been only nine documented cases of low-grade optic pathway gliomas in adults in the past few years.[17,16] The recent case study by Hidalgo et al. demonstrated that an adult patient with low-grade optic pathway glioma who received no adjuvant therapy after STR could survive more than 20 years without tumor progression.[16] In another study that included limited 14 children with optic chiasmatic-hypothalamic gliomas, no significant differences were observed regarding the volume change of tumors treated or not treated with chemotherapy.[32] The critical finding in our study shows that both adjuvant RT and chemotherapy may have potentially adverse effects on survival in adult patients with low-grade ONGs. The concrete reason is unknown because of the limited clinical information included in the SEER database; however, on the grounds of some previously published studies, it is most likely attribute to the systemic side effects and increased risks of malignant progression and visual, neurocognitive and hypothalamic dysfunction after such adjuvant treatments, especially RT.[1,2,33-35,26] Therefore, given the above analysis, we do not recommend to take RT or chemotherapy in adult patients with low-grade ONGs.

For high-grade ONGs in adult patients, the reported average survival ranged from 1 to 2 years, despite aggressive treatment with RT and chemotherapy, similar to that of glioblastoma in other locations. [36,37,23] Our results demonstrate that both adjuvant RT and chemotherapy have no positive effect on patients’ OS. Therefore, given the very limited number of reported and our cases, it can not be confirmed whether adjuvant therapies benefit the adult patient or not. Nevertheless, considering the same histopathological characteristics of high-grade gliomas located in other brain sites, a combination of adjuvant RT and chemotherapy after surgery might remain the most appropriate option that can be adopted for adult patients with ONGs at present. Indeed, large-scale collaborative multicenter prospective studies are still warranted to determine treatment consensus.

**Limitations**

Despite the fact that a huge amount of invaluable data for rare tumors such as ONGs can be acquired in the SEER database, there are still several important limitations to the present study. First, there is no information available on visual outcomes or tumor progression, which is important to be an endpoint for assessing the effects, particularly for the low-grade group. Second, there is a lack of details on the adjuvant treatments, such as chemotherapeutic agents, dose and type of RT, and the exact time of adjuvant treatments. Third, several critical factors, including performance status, systemic disease status,
NF-1 status, or neuroendocrine morbidity, are unable to obtain from the SEER database. Finally, given the impossibly pathological and radiological review of the tumors, it is likely that some tumors may have been misdiagnosed owing to the low interobserver agreement in the diagnosis of different glioneuronal tumors. However, considering the prospective studies not available and not be expected in the near future, because of the scarcity of ONGs, a large retrospective study like this seems to be the best and most useful approach available to define the role of different adjuvant treatments for these lesions. Therefore, although several limitations mentioned above, this is the largest reported series and the best evidence available in regard to adult ONGs up to date.

**Conclusion**

This is the largest retrospective study of adult ONGs, including 179 cases from the SEER database. Our data reaffirms that the low-grade ONGs have a significantly better prognosis than the high-grade, and demonstrates the different role of adjuvant treatments in different grade tumors. Although both adjuvant RT and chemotherapy have no positive effect on patients’ OS in the high-grade group, they may have a potentially negative impact on patient’s survival and prognosis in the low-grade group. Therefore, adjuvant RT or chemotherapy might not be recommended to consider in adult patients with low-grade ONGs, unless the malignant transformation or aggressive progression has been confirmed.

**Declarations**

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**Compliance with Ethical Standards**

**Conflicts of interest:** All authors have no conflicts of interest to declare.

**Ethical approval:** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent:** Informed consent was waived for this study because of the de-identified information of the patients included in the SEER.

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**Data availability:** The data that support the findings of this study is available from the Surveillance, Epidemiology, and End Results (SEER) Program upon application and approval.
Authors’ contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Rong Huang, Yanlin Huang and Jinyun Su. The first draft of the manuscript was written by Rong Huang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Overall survival of adult patients with low- and high-grade optic nerve gliomas.
Figure 2

Impact of age, radiotherapy (RT), and chemotherapy on overall survival of adult optic nerve gliomas. A-C. Low-grade group. D-F. High-grade group.