Oligodendroglioma resection: a Surveillance, Epidemiology, and End Results (SEER) analysis

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OBJECTIVE The available evidence suggests that the clinical benefits of extended resection are limited for chemosensitive tumors, such as primary CNS lymphoma. Oligodendroglioma is generally believed to be more sensitive to chemotherapy than astrocytoma of comparable grades. In this study the authors compare the survival benefit of gross-total resection (GTR) in patients with oligodendroglioma relative to patients with astrocytoma.

METHODS Using the Surveillance, Epidemiology, and End Results (SEER) Program (1999–2010) database, the authors identified 2378 patients with WHO Grade II oligodendroglioma (O2 group) and 1028 patients with WHO Grade III oligodendroglioma (O3 group). Resection was defined as GTR, subtotal resection, biopsy only, or no resection. Kaplan-Meier and multivariate Cox regression survival analyses were used to assess survival with respect to extent of resection.

RESULTS Cox multivariate analysis revealed that the hazard of dying from O2 and O3 was comparable between patients who underwent biopsy only and GTR (O2: hazard ratio [HR] 1.06, 95% confidence interval [CI] 0.73–1.53; O3: HR 1.18, 95% CI 0.80–1.72). A comprehensive search of the published literature identified 8 articles without compelling evidence that GTR is associated with improved overall survival in patients with oligodendroglioma.

CONCLUSIONS This SEER-based analysis and review of the literature suggest that GTR is not associated with improved survival in patients with oligodendroglioma. This finding contrasts with the documented association between GTR and overall survival in anaplastic astrocytoma and glioblastoma. The authors suggest that this difference may reflect the sensitivity of oligodendroglioma to chemotherapy as compared with astrocytomas.

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KEY WORDS oligodendroglioma; extent of resection; gross-total resection; survival; Surveillance, Epidemiology, and End Results; SEER; oncology

IDENTIFICATION of patients who would most likely benefit from resection remains a central tenet in the clinical practice of neurosurgical oncology.^{1,21,25} A key consideration in this regard involves the intrinsic sensitivity of the cancer cells to chemotherapy or radiation therapy. Cancers with exquisite sensitivity to radiation or chemotherapy, such as primary CNS lymphomas (PCNSLs), typically only require a stereotactic needle biopsy for definitive tissue diagnosis.^{10–12,40} In contrast, patients afflicted with cancers of limited radiation or chemotherapy sensitivity, such as high-grade gliomas (HGGs), frequently benefit from maximal safe resection,^{14,16,19,36,37,42} where oligodendroglioma falls in this spectrum of surgical management paradigms remains an open question.

Oligodendroglioma is a rare form of brain cancer that arises from cell populations that give rise to oligodendrocytes;^{8,9,26,38,41,43,47,52} it accounts for 4.9% of malignant adult brain cancers, with an incidence of 1–2 cases per million per year.⁴¹ Oligodendroglioma is further stratified by the WHO on the basis of histological appearance into Grade II (abbreviated in this study as O2) or Grade III (abbreviated in this study as O3).³³ Given the rarity of O2s and O3s, they are often combined into a single entity or grouped with astrocytic tumors during clinical investigations, although the validity of such an approach remains unsubstantiated.^{5,17,30,31,46,48,49}

In this study, we used the Surveillance, Epidemiology, and End Results (SEER; <https://seer.cancer.gov>) popula-

ABBREVIATIONS 75ST = the time in months at which 25% of the original patient population had died; CI = confidence interval; EOR = extent of resection; GTR = gross-total resection; HGG = high-grade glioma; HR = hazard ratio; ICD-O-3 = International Classification of Diseases for Oncology-Third Edition; IQR = interquartile range; O2 = WHO Grade II oligodendroglioma; O3 = WHO Grade III oligodendroglioma; PCNSL = primary CNS lymphoma; SEER = Surveillance, Epidemiology, and End Results; STR = subtotal resection.

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TABLE 1. Patient demographics and clinical characteristics

Variable	O2 Group	O3 Group	Total
No. of patients (%)	2378 (69.82)	1028 (30.18)	3406 (100)
Median age in yrs (IQR)	41 (32–51)	47.5 (38–58)	43 (33–53)
Age category (%)			
<18 yrs	146 (6.14)	19 (1.85)	165 (4.84)
18–44 yrs	1258 (52.9)	418 (40.66)	1676 (49.21)
45–59 yrs	702 (29.52)	376 (36.58)	1078 (31.65)
60–74 yrs	216 (9.08)	177 (17.22)	393 (11.54)
≥75 yrs	56 (2.35)	38 (3.7)	94 (2.76)
Race (%)			
White	1765 (74.22)	753 (73.25)	2518 (73.93)
Black	98 (4.12)	48 (4.67)	146 (4.29)
Asian/Pacific Islander	135 (5.68)	75 (7.3)	210 (6.17)
Hispanic	332 (13.96)	142 (13.81)	474 (13.92)
American Indian/Alaskan Native	26 (1.09)	<10 (<1)	31 (0.91)
Other/unknown, non-Hispanic	22 (0.93)	<10 (<1)	27 (0.79)
Marital status (%)*			
Single	726 (31.54)	219 (22.1)	945 (28.70)
Married	1343 (58.34)	626 (63.17)	1969 (59.79)
Separated, divorced, widowed	233 (10.12)	146 (14.73)	379 (11.51)
Sex (%)			
Male	1325 (55.72)	585 (56.91)	1910 (56.08)
Female	1053 (44.28)	443 (43.09)	1496 (43.92)
Tumor size in cm (%)*			
<5	859 (58)	293 (41.92)	1152 (52.84)
5–7	442 (29.84)	248 (35.48)	690 (31.65)
>7	180 (12.15)	158 (22.6)	338 (15.50)
Tumor site (%)			
Frontal lobe	1257 (52.86)	520 (50.58)	1777 (52.17)
Temporal lobe	453 (19.05)	173 (16.83)	626 (18.38)
Parietal lobe	232 (9.76)	124 (12.06)	356 (10.45)
Occipital lobe	36 (1.51)	18 (1.75)	54 (1.59)
Brain stem	8 (0.34)	3 (0.29)	11 (0.32)
Overlapping lesion of brain	233 (9.80)	134 (13.04)	367 (10.78)
Cerebrum	60 (2.52)	26 (2.53)	86 (2.52)
Brain, NOS	70 (2.94)	22 (2.14)	92 (2.70)
Ventricle, NOS	13 (0.55)	5 (0.49)	18 (0.53)
Cerebellum, NOS	16 (0.67)	3 (0.29)	19 (0.56)
Yr of diagnosis (%)			
1999	139 (5.85)	62 (6.03)	201 (5.90)
2000	210 (8.83)	94 (9.14)	304 (8.93)
2001	213 (8.96)	119 (11.58)	332 (9.75)
2002	234 (9.84)	98 (9.53)	332 (9.75)
2003	221 (9.29)	84 (8.17)	305 (8.95)
2004	213 (8.96)	96 (9.34)	309 (9.07)
2005	172 (7.23)	82 (7.98)	254 (7.46)
2006	213 (8.96)	102 (9.92)	315 (9.25)

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TABLE 1. Patient demographics and clinical characteristics

Variable	O2 Group	O3 Group	Total
Yr of diagnosis (%)			
(cont'd)			
2007	203 (8.54)	58 (5.64)	261 (7.66)
2008	180 (7.57)	82 (7.98)	262 (7.69)
2009	188 (7.91)	76 (7.39)	264 (7.75)
2010	192 (8.07)	75 (7.3)	267 (7.84)
Radiotherapy (%)*			
No	1491 (64.63)	320 (31.97)	1811 (54.75)
Yes	816 (35.37)	681 (68.03)	1497 (45.25)
Surgery (%)			
No surgery	438 (18.42)	128 (12.45)	566 (16.62)
Local excision/biopsy	550 (23.13)	222 (21.6)	772 (22.67)
STR	557 (23.42)	310 (30.16)	867 (25.46)
GTR	833 (35.03)	368 (35.8)	1201 (35.26)
Overall mortality rate (%)			
Living	1788 (75.19)	544 (52.92)	2332 (68.47)
Deceased	590 (24.81)	484 (47.08)	1074 (31.53)

NOS = not otherwise specified.

* Not all patients had complete data.

tion-based database to examine whether extended resection is associated with improved survival for O2s and O3s. We further compared the SEER-based results to a comprehensive search of the published literature, and implications of these findings are discussed.

Methods

Data and Study Population

Data from the SEER database (1999–2010) were used for this study. SEER compiles cancer incidence and survival data from 18 registries in different regions of the US. These registries collect data on 28% of the US population from academic and nonacademic hospitals, and as such, are broadly representative of the US population as a whole (SEER Research Data 1973–2010). Patients were included in this study if they had a diagnosis of oligodendroglioma (International Classification of Diseases for Oncology–Third Edition [ICD-O-3] histology code 9450) or anaplastic oligodendroglioma (ICD-O-3 histology codes 9451 and 9460) and no other cancer diagnosis. Patients of all ages were included.

Primary End Point and Covariates

The primary end point was overall patient survival, defined as the length of time in months from diagnosis to death from any cause or last follow up. All SEER patients with available surgical information were coded as having received 1) no surgery (code 00), 2) biopsy (code 20), 3) subtotal resection (STR; code 40), or 4) gross-total resection (GTR; code 55).^{37,42} Patients who did not undergo surgical intervention were coded as “no surgery.” The operative report was used to distinguish patients who

FIG. 1. Pie charts demonstrating EOR rates for O2 (left) and O3 (right) from 1999 to 2010. EB = excisional biopsy. Figure is available in color online only.

underwent biopsy only versus those with more extended resections (STR and GTR). Determination of GTR versus STR was based on radiographic reports of the postoperative MR images that were entered into the formal medical record. For patients who underwent no surgery, the tissue diagnosis was ascertained through autopsy.

Both demographic and clinical variables were included as covariates in the multivariate hazard ratio (HR) analysis. Demographic variables included sex (male or female), age (< 18, 18–44, 45–59, 60–74, or > 75 years), race (White, Black, Asian/Pacific Islander, Hispanic, American Indian/Alaskan Native, or Other/Unknown), and marital status (single; married; or separated, divorced, or widowed). Clinical variables included tumor size, tumor site, year of diagnosis, use of radiotherapy, and extent of resection (EOR: no surgery, biopsy, STR, and GTR).

Literature Review Search Strategy and Eligibility Criteria

We performed a PubMed electronic database search from 1900 to December 2015 using the following search terms: (“low-grade glioma” OR “anaplastic oligodendroglioma” OR “oligodendroglioma” OR “oligoastrocytoma”) AND (“extent of resection” OR “surgical resection” OR “gross total resection” OR “tumor resection” OR “partial resection” OR “resection”[Title/Abstract]). We excluded all papers that included the word “MRI” in the title, because these papers did not focus on the effect of resection. Studies were also excluded if they met any of the following criteria: 1) not published in English; 2) focused on basic science; 3) involved nonhuman subjects; 4) focused on nonintracranial tumors; 5) focused on a tool or experimental therapy; 6) was an editorial, review, meta-analysis, or case report; 7) included patients < 18 years old; 8) lacked pertinent statistical measures for assessing the association between EOR and overall survival; or 9) combined O2s and O3s into a single variable or included them with other histological tumor subtypes; if other tumor types were included in the study, information was required to be isolatable for O2s and O3s. Articles meeting these criteria were identified by 2 independent reviewers (A.A.A. and M.G.B.) and results were discussed with the senior authors.

Statistical Analysis

All analyses were conducted with commercially available statistical analysis software (Stata SE, version 11.2, StataCorp LP). Statistical significance was set at $p = 0.05$. Univariate analysis of patient demographics and clinical variables by tumor histology was performed using Pearson’s chi-square test. Because median survival was not reached for many of the analyses, the 75th percentile patient survival time by EOR (no resection, biopsy, STR, and GTR) and tumor histology (O2 or O3) was determined.^{15,18,24} Survival was assessed using unadjusted Kaplan-Meier models, and statistical significance was determined using the log-rank test. Finally, a multivariate Cox proportional hazards model was used to assess the hazard of death by EOR, adjusting for patient demographics and clinical covariates. In all comparisons, the biopsy-only category of EOR was used as the reference group.

Results

Patient Demographics and Clinical Characteristics

We identified 2378 patients with O2 and 1028 patients with O3. The median patient age at diagnosis was 41 years for O2 (interquartile range [IQR] 32–51 years) and 48 for O3 (IQR 38–58 years). The male to female ratio was approximately 1:1 for both O2 (1.01) and O3 (1.0). The most common sites for all oligodendroglial types were frontal and temporal lobes. Patient characteristics are described in Table 1. Of the patients with O2, 438 (18%) did not undergo surgery, 550 (23%) underwent biopsy, 557 (23%) underwent STR, and 833 (35%) underwent GTR. Of the patients with O3, 128 (12%) did not undergo surgery, 222 (22%) underwent biopsy, 310 (30%) underwent STR, and 368 (36%) underwent GTR (Fig. 1).

Patient Survival (75th Percentile)

Patient survival in the 75th percentile (the time in months at which 25% of the original patient population had died [75ST]) is an established end point in the study of diseases with prolonged survival.^{34–36} In this study, 75ST was used as an end point because the overall survival of most patients with O2 extended beyond the study period

FIG. 2. Kaplan-Meier curves demonstrating survival in O2 (upper) and O3 (lower) tumors. In both graphs, the difference between the 4 curves was statistically significant according to the log-rank test ($p < 0.0001$). Figure is available in color online only.

such that there was an insufficient number of deaths to determine median survival. The 75ST was 72 months (95% CI 66–79 months) for all O2s and 18 months (95% CI 15–21 months) for all O3s. The survival trends of O2 and O3 differed significantly based on log-rank testing ($p < 0.001$).

Survival Analysis as a Function of Resection

The 75ST for O2 was 38 months (95% CI 28–48 months) for patients who did not undergo surgical intervention, 93 months (95% CI 73–111 months) for patients

who underwent biopsy only, 52 months (95% CI 46–64 months) for patients who underwent STR, and 100 months (95% CI 86–122 months) for patients who underwent GTR (Fig. 2 upper). The 75ST for O3 was 6 months (95% CI 4–10 months) for patients who did not undergo surgical intervention, 24 months (95% CI 21–38 months) for patients who underwent biopsy only, 15 months (95% CI 12–17 months) for patients who underwent STR, and 24 months (95% CI 21–30 months) for patients who underwent GTR (Fig. 2 lower).

TABLE 2. Results of multivariate Cox proportional hazards analysis assessing risk of death with respect to differing EOR

EOR	O2 Group		O3 Group	
	Adjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
No surgery	1.69 (1.15–2.49)	0.008	1.85 (1.18–2.91)	0.008
Local excision/biopsy	1	Reference	1	Reference
STR	1.21 (0.83–1.75)	0.317	1.62 (1.11–2.38)	0.013
GTR	1.06 (0.73–1.53)	0.754	1.18 (0.80–1.72)	0.404

Boldface type indicates statistical significance.

Cox Proportional Hazard Analysis of Survival

To determine whether GTR is associated with increased overall survival after controlling for pertinent demographic and clinical variables, a multivariate Cox proportional hazards analysis was performed. For patients in both the O2 and O3 groups, the HR for death was comparable between the biopsy and the GTR group (Table 2). For patients with O2, the HR of dying from the disease was 1.06 (95% CI 0.73–1.53) for patients who underwent GTR relative to those who underwent biopsy only. For patients with O3, the HR of dying from the disease was 1.18 (95% CI 0.80–1.72) for patients who underwent GTR relative to those who underwent biopsy only.

Literature Review

A comprehensive review of the published literature

was performed to identify studies that examined the association between extended resection and improved overall survival for patients with O2 and O3 (Fig. 3; see *Methods*). There were 5 such papers identified for O2 (Table 3).^{9,26,27,47,52} Of these studies, 4 showed no association between EOR and overall survival ($p = 0.83, 0.90$, nonsignificant, and nonsignificant). The 1 discordant study (Snyder et al.⁴⁷) found an association between GTR and improved overall survival. Notably, the overall survival rate of patients who underwent GTR in this study (62%) was worse than in other published studies and our SEER results.^{9,26,52} We identified 4 papers that examined the association between EOR and overall survival for O3 (Table 3).^{8,27,38,43} While the measures of survival differed in these studies, the 4 studies uniformly concluded there was no association between EOR and improved survival.

FIG. 3. Flow chart demonstrating the technique used to review the literature for articles assessing the association between EOR and survival.

TABLE 3. Results of a review of the literature for studies assessing the association between EOR and survival

Authors & Year	Histological Groups	No. of Pts	Rate of GTR (%)	Overall Survival	Comparison Group	p Value
Yeh et al., 2002	O2	52	13.0	86% (5-yr)	STR (5-yr 78%)	0.83
Lebrun et al., 2004	O2	51	31.40	NA	PR or biopsy	NS
Lebrun et al., 2007	O2	57	19.3	NA	NA	NA†
El-Hateer et al., 2009	O2	69	27.0	HR 0.9	STR	0.9
Snyder et al., 2014	O2	93	45*	90% (5-yr)	STR (5-yr 62%)	0.005
Durando et al., 2013	O3	12	0.0	NA	NA	NS
Puduvalli et al., 2003	O3	106	28.3	NA	NA	NS
Lebrun et al., 2004	O3	49	24.49	16%	PR or biopsy	NS
Nuño et al., 2013	O3	570	36.1	HR 1.03‡	Biopsy	0.79

NA = not available; NS = not significant; Pts = patients.

Boldface type indicates statistical significance.

* GTR defined as >90% resection.

† There was no mention of EOR when significant prognostic variables were discussed, and the univariate and multivariate tables were not provided. We assume that EOR was not mentioned because it was not significant.

‡ Hazard ratio of dying from the disease for GTR relative to patients undergoing biopsy.

Discussion

In neurooncology, surgical paradigms span the spectrum of only biopsy in tumors highly sensitive to chemotherapy and radiation, such as PCNSL,^{10–12,40} to maximal safe resection in HGGs.^{14,16,19,28,37,42} Our analysis of patients with oligodendroglioma in the SEER database suggests that the survival patterns of these tumors more closely resembles that of PCNSL than HGG. In our multivariate model, there was no difference in the hazard of death for patients with oligodendroglioma who underwent a biopsy only versus GTR. These findings are largely consistent with the sensitivity of oligodendroglioma to chemotherapy.^{2,4,13} Notably, the HR of death for patients with oligodendroglioma who underwent STR was found to be higher than the HR of death for those who underwent biopsy or GTR. This result suggests that the inherent patient/tumor characteristics associated with selection for STR are associated with the poor prognosis and/or morbidity associated with STR (for instance, resection terminated due to unfavorable surgical events, or postoperative hemorrhage) negatively influenced overall survival.²³

The finding that GTR did not significantly affect the overall survival of patients with oligodendroglioma is largely consistent with our review of the published literature. Of the 8 articles identified, only the study by Snyder et al. suggested improvement in survival for patients with oligodendroglioma who underwent GTR.⁴⁷ Of note, the 5-year overall survival rate for patients who underwent GTR in the series of Snyder et al. was comparable to all other studies, including this study (80%–90%).^{9,26,52} In contrast, the overall survival rate of patients who underwent STR (62%) was significantly worse than those reported in other published studies and in this report.^{9,26,52} Thus, the statistical difference reported by Snyder et al. was driven more by poor survival of patients who underwent STR than improved survival of patients who underwent GTR.⁴⁷

Studies of rare diseases, such as oligodendroglioma, in a population-based database are particularly instructive because institutional experiences are necessarily limited in sample size. For instance, a sample size of approximate-

ly 1300 patients with O3 would be needed to detect an improvement in survival with GTR relative to biopsy in this population. This is calculated using an α of 0.05, β of 0.8, and an effect size of 10%, which is based on survival estimates provided by our SEER analysis. For the same size effect, approximately 700 patients will be required for the O2 population; such a sample size cannot be achieved by any single institution. In contrast, the SEER database provides outcome data for approximately 2300 patients with O2 and 1300 patients with O3, allowing a sample size sufficient for detection of a 10% survival benefit related to GTR relative to biopsies in both O2 and O3 patient groups.

It is important to interpret the results reported here in the context of the shifting landscape of glioma diagnosis. Since 1999, there has been growing recognition that oligodendrogliomas exhibit favorable response to select chemotherapy regimens,^{3,28,44,50} and the diagnosis of oligodendroglioma qualifies the patient for treatment with these regimens. Consequently, there has been an overall increase in the number of patients diagnosed with oligodendroglioma during the period of our study.³⁷ The available literature suggest that patients with Grade II and III astrocytomas benefit from GTR.^{7,20,22,39} As such, misclassification of Grade II and III astrocytomas as oligodendrogliomas would artificially inflate the survival benefit of GTR in the patients with oligodendroglioma. Despite this consideration, we did not observe any survival benefit for GTR in the patients with oligodendroglioma. In this context, we believe that our results are robust.

However, studies using population databases are not without inherent limitations, including the heterogeneity of clinical practice in participating centers. Furthermore, there is a lack of information on chemotherapeutic regimens, Karnofsky Performance Scale status, and other clinical variables in the SEER database. Additionally, the neurooncology community is largely defining oligodendroglioma based on the presence of genetic events such as isocitrate dehydrogenase mutations and 1p19q loss.^{32,35,45} This information is not available in the current SEER database. This shortcoming is mitigated somewhat by the

high concordance (approximately 80% for isocitrate dehydrogenase and 1p19q) between these genetic events and the histological diagnosis of oligodendroglioma.⁵¹ Another limitation of the SEER data set is that the extent of resection is subjectively assessed without volumetric quantitation. Finally, survival studies, such as the one conducted here, fail to take into consideration nonsurvival clinical benefits associated with extended resection of oligodendroglioma, such as reduction of seizure frequency, neurocognitive function, and quality of life.^{6,34} Nevertheless, our results provide an additional layer of consideration during surgical planning of oligodendroglioma and are of value to the neurosurgical community.

Conclusions

Our SEER-based analysis suggests that GTR is not associated with increased overall survival in patients with oligodendroglioma. This finding contrasts with prior SEER-based analyses of astrocytic tumors, including anaplastic astrocytoma and glioblastoma.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Chen, Alattar, Brandel, Hirshman, Dong, Carter. Acquisition of data: Chen, Alattar, Brandel, Hirshman, Dong. Analysis and interpretation of data: Chen, Alattar, Brandel, Hirshman, Carter. Drafting the article: Chen, Alattar, Brandel, Hirshman. Critically revising the article: Chen, Alattar, Brandel, Hirshman, Carroll, Ali, Carter. Reviewed submitted version of manuscript: Chen, Alattar, Brandel, Hirshman, Dong, Carroll, Carter. Approved the final version of the manuscript on behalf of all authors: Chen. Statistical analysis: Alattar, Hirshman. Administrative/technical/material support: Ali. Study supervision: Chen, Carter.

Supplemental Information

Previous Presentations

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