» This article has been updated from its originally published version to correct the *Results* section of the abstract. See the corresponding erratum notice in this issue, p 1675. «

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CLINICAL ARTICLE

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# Extent of resection, molecular signature, and survival in 1p19q-codeleted gliomas

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**OBJECTIVE** Genomic analysis in neurooncology has underscored the importance of understanding the patterns of survival in different molecular subtypes within gliomas and their responses to treatment. In particular, diffuse gliomas are now principally characterized by their mutation status (IDH1 and 1p/19q codeletion), yet there remains a paucity of information regarding the prognostic value of molecular markers and extent of resection (EOR) on survival. Furthermore, given the modern emphasis on molecular rather than histological diagnosis, it is important to examine the effect of maximal resection on survival in all gliomas with 1p/q19 codeletions, as these will now be classified as oligodendrogliomas under the new WHO guidelines.

The objectives of the present study were twofold: 1) to assess the association between EOR and survival for patients with oligodendrogliomas in the National Cancer Database (NCDB), which includes information on mutation status, and 2) to demonstrate the same effect for all patients with 1p/19q codeleted gliomas in the NCDB.

**METHODS** The NCDB was queried for all cases of oligodendroglioma between 2004 and 2014, with follow-up dates through 2016. The authors found 2514 cases of histologically confirmed oligodendrogliomas for the final analysis of the effect of EOR on survival. Upon further query, 1067 1p/19q-codeleted tumors were identified in the NCDB. Patients who received subtotal resection (STR) or gross-total resection (GTR) were compared to those who received no tumor debulking surgery. Univariable and multivariable analyses of both overall survival and cause-specific survival were performed.

**RESULTS** EOR was associated with increased overall survival for both histologically confirmed oligodendrogliomas and all 1p/19q-codeleted–defined tumors ($p < 0.001$ and $p = 0.002$, respectively). Tumor grade, location, and size covaried predictably with EOR. When evaluating tumors by each classification system for predictors of overall survival, facility setting, age, comorbidity index, grade, location, chemotherapy, and radiation therapy were all shown to be significantly associated with overall survival. STR and GTR were independent predictors of improved survival in historically classified

**ABBREVIATIONS** CSS = cause-specific survival; EOR = extent of resection; GTR = gross-total resection; HGG = high-grade glioma; ICD = *International Classification of Diseases*; *IDH* = isocitrate dehydrogenase; LGG = low-grade glioma; NCDB = National Cancer Database; OS = overall survival; O2 = grade II oligodendroglioma; O3 = grade III oligodendroglioma; SEER = Surveillance, Epidemiology, and End Results; STR = subtotal resection; 75ST = 75% survival time.

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oligodendrogliomas (HR 0.83, p = 0.18; HR 0.69, p = 0.01, respectively) and in 1p/19q-codeleted tumors (HR 0.49, p < 0.01; HR 0.43, p < 0.01, respectively).

**CONCLUSIONS** By using the NCDB, the authors have demonstrated a side-by-side comparison of the survival benefits of greater EOR in 1p/19q-codeleted gliomas.

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**KEYWORDS** oligodendroglioma; IDH; 1pq19; surgery; extent of resection; gross-total resection; survival; oncology

Oligodendrogliomas, historically stratified by histological criteria into grade II (O2) or grade III (O3) tumors, are now currently classified and diagnosed using a molecular signature: mutations in the isocitrate dehydrogenase (*IDH*) gene family and chromosomal 1p/19q codeletion. *IDH* mutations are thought to be an early, nearly ubiquitous prerequisite in the development of oligodendroglioma,[1,2] and their presence carries prognostic significance for progression-free and overall survival (OS),[3,4] as well as other outcome-related measures such as seizure control,[5] better response to radio-/chemotherapy,[6–8] recurrence,[9] and even present targets for oncological vaccination.[47] Whole-arm chromosomal loss of 1p/19q is invariably associated with *IDH* mutations, and *IDH* mutation may even be a prerequisite for its translocation.[10,11] As whole-chromosome analysis has become more efficient and cost-effective, there is great interest in using 1p/19q-codeletion status as a proxy for *IDH* mutation and a prognosticator in oligodendrogliomas.[12–14,48]

While studies have shown that maximal extent of resection (EOR) reliably correlates with improved outcomes in patients with oligodendrogliomas,[15–21] few studies have specifically examined the prognostic value of greater EOR when accounting for molecular characteristics. It has been posited that complete resection is independently associated with a longer progression-free survival in patients with tumors that have *IDH* mutations,[3,22,23] although additional cohorts suggest this effect is less pronounced in *IDH*-wildtype low-grade gliomas (LGG);[24] surgical resection in *IDH*-wildtype LGG does offer a survival benefit when combined with adjuvant radio-/chemotherapy.[25] Indirect evidence suggests that histologically classified *IDH*-wildtype oligodendrogliomas have poorer outcomes with maximal resection than *IDH* mutation, though these cohorts included a higher number of elderly patients and a higher proportion of wildtype tumors, which are factors known to be associated with worse outcomes.[26] These studies have been relatively small, retrospective, single-center analyses that lack external validation. The objective of this study was therefore to query the survival effect of greater resection of oligodendrogliomas in a side-by-side comparison of traditionally codified oligodendrogliomas and 1p/q19-codeleted gliomas given the 2016 classification criteria, with the hypothesis that, contrary to recent studies questioning this effect, greater resection would confer a survival benefit in both of these cohorts.[16,27–29]

# Methods

## Data Sources

The National Cancer Database (NCDB) is a retrospective nationwide data set sponsored by the American College of Surgeons and the American Cancer Society, constituting 70% of incident invasive cancer cases in the United States.[30] Data were collected at over 1500 Commission on Cancer–accredited hospitals between 2004 and 2013. This database has been validated for several variables.[31]

## Sample Selection and Coding

In our initial selection of 1p/19q-codeleted tumors, we queried the NCDB (2016 submission) to identify a convenience sample all cases of oligodendroglioma (*International Classification of Diseases* ICD-O-3 codes 9450), anaplastic oligodendroglioma (ICD-O-3 9451 and 9460), diffuse astrocytoma (ICD-O-3 9400), anaplastic astrocytoma (ICD-O-3 9401), mixed oligoastrocytic tumors (ICD-O-3 9382), and malignant glioma, not otherwise specified (ICD-O-3 9380)[32] within the CNS (ICD-O-3 C70.1–C72.9) diagnosed between January 1, 2004, and December 31, 2014. The last possible date of follow-up for all cases was December 31, 2016. The following variables were collected and coded: facility type, class of case, age at diagnosis, sex, race, Charlson-Deyo score, ICD-O-3 histology, primary site, collaborative stage extension, tumor size, surgery at primary site, radiation therapy, chemotherapy, and collaborative stage site-specific factor 5 (chromosome 1p: loss of heterozygosity) and 6 (chromosome 19q: loss of heterozygosity). Cases with zero days of or no follow-up were excluded (including all patients diagnosed after January 1, 2014), as these patients either did not undergo surgery at all or did not survive long enough to see an effect of management. We excluded cases if all of their treatment decisions were not done at the reporting facility or if treatment location was not specified, to increase the quality of the data with regard to treatment history. For our primary analysis, we included only tumors with 1p and 19q codeletion. Finally, we eliminated cases with unknown chemotherapy status, radiotherapy status, or EOR.

Each facility reporting cases to the NCDB is assigned a category of classification by the Commission on Cancer Accreditation Program, labeled as "Community Cancer Program," "Comprehensive Community Cancer Program," "Academic/Research Program," "Integrated Network Cancer Program," or "unknown/other." We coded facility setting as "academic," "nonacademic," or "unknown." Patient demographics, including age at diagnosis, sex, and race are recorded as indicated in the medical record. We defined race as "white," "black," or "other." Comorbid conditions mapped from ICD-9-CM or ICD-10 secondary diagnosis codes are weighted and summed. These scores are catego-

rized as 0, 1, 2, and 3 or more. Tumor grade was coded as II, III, or unknown based on ICD-O-3 histology codes. Collaborative stage extension describes contiguous growth (extension) of the primary tumor within the organ or origin or its direct extension into neighboring organs. In the brain, this variable defines supratentorial and infratentorial location by the ICD-O-3 topological site. Tumor location was coded as "supratentorial," "infratentorial involvement," or "unknown" based on the ICD-O-3 topography code for site of origin and the collaborative stage extension variables. The "unknown" category included tumors for which location in relation to the tentorium cerebelli was unclear. Tumor size is also recorded as a part of the Collaborative Stage Data Collection System and is described by the most accurate measurement of a solid primary tumor, usually measured on the resected specimen, based on the largest diameter in millimeters. Tumor size was coded as < 5 cm, ≥ 5 cm, or unknown.

The Commission on Cancer programs are required to identify treatment their patients received from all sources. All cancer-directed treatment was recorded only if it was given as part of the initial course of treatment to destroy, modify, control, or remove cancerous tissue. Treatment may be recorded if administered within 1 year of the initial diagnosis and if it is part of the initial treatment plan before tumor progression or recurrence or discontinuation of the first course of treatment. If a patient has had multiple surgeries, the most definitive surgical procedure or the cumulative effect of the surgeries on the primary site is recorded. Patients were classified as having had a "debulking surgery" if they received cancer-directed resection procedures with the endorsed goal of modifying, controlling, removing, or destroying cancerous tissue at the primary site. EOR is reported qualitatively, rather than volumetrically. EOR was based on definitions in the American College of Surgeons Commission on Cancer's Facility Oncology Registry Data System manual;[33] EOR was coded into 3 categories based on the Surgery at Primary Site variable: "no surgery" (code 00 [no surgery of the primary site]), "subtotal resection" (STR) (codes 20 [local excision or excisional biopsy], 21 [STR], 40 [partial resection of the lobe of the brain when surgery cannot be coded as 20–30]), and "gross-total resection" (GTR) (codes 30 [radical, total, gross resection of the tumor], 55 [GTR of a lobe of the brain]), consistent with prior studies.[28,34–37] Radiation therapy and chemotherapy were coded dichotomously as "radiation" or "no radiation" and "chemotherapy" or "no chemotherapy."

We conducted a second query for historically classified histological oligodendrogliomas (ICD-O-3 9450) or anaplastic oligodendrogliomas (ICD-O-3 9451 and 9460)[32] within the CNS (ICD-O-3 C70.1-C72.9), applying the same initial exclusion criteria, with the exception of 1p/19q-codeletion status.

### Primary Outcome

The primary outcome in our study was OS. Survival time was calculated as the months between the date of diagnosis and the date on which the patient was last contacted or died. Vital status is recorded at the date of last contact or death. Participant registries report patient follow-up to the NCDB annually.

### Statistical Analysis

All statistical analyses were carried out using the SPSS Statistics software package (IBM Corp.) and Stata version 14 (StataCorp LLC). Median survival times were determined using the Kaplan-Meier method, and significance was determined using the log-rank test. A 75th percentile patient survival time (75ST) was used as a surrogate marker of survival when median survival time was not reached.[16,38] Univariable and multivariable analyses of both OS and cause-specific survival (CSS) were conducted using the Cox proportional hazards ratios model. The 95% confidence intervals are expressed next to the corresponding hazard ratios. Associations between treatment and other variables were determined using Pearson's chi-square test, and column proportions were compared using Bonferroni correction to adjust for multiple comparisons. Tests with two-tailed p values < 0.05 were considered statistically significant. Demographic and clinical features associated with survival or that approached significance, using $p = 0.10$ as a cutoff, were included in multivariable analyses. Propensity score analysis was carried out for survival data using Stata inverse-probability weighting with a probit model based on significant variables in univariable analysis, with GTR as dependent variable. Average treatment effect was calculated. This analysis was conducted separately for both 1p/19q-codeleted and oligodendroglioma populations.

## Results

### Demographic and Clinical Characteristics

The NCDB was first queried for all cases of oligodendroglioma, then again for all cases of gliomas with 1p/19q deletion status. As shown in Fig. 1, 2514 cases of oligodendrogliomas were identified after exclusion criteria. Of these, 90% occurred in Caucasian patients, with a slight male preponderance (56%), and mostly with a low comorbidity index (Charlson-Deyo score 0 in 81%). Roughly 50% of the tumors for which size was recorded were smaller than 5 cm. Nearly 11% of patients received no surgery, whereas 51% underwent STR and 38% underwent GTR. The median follow-up duration was 33.9 months; there were 480 deaths (19%) in that time period. Additional demographic data for oligodendrogliomas is shown in Supplemental Table 1.

Overall, 1067 tumors with 1p/19q-codeletion status were extracted from the NCDB, as shown in Fig. 1. Demographic variables were grossly similar to those for all oligodendrogliomas: 56% male, 92% Caucasian, and 83% with low comorbidity index (see Supplemental Table 2). Of those codeleted tumors for which tumor size was available, 50% were smaller than 5 cm (a cutoff used in similar large-database studies).[16,27] Only 8.5% of this group did not undergo surgery (STR 53%, GTR 39%), and 61% received chemotherapy and 45% received radiation. The median follow-up duration was 36.0 months; there were 143 deaths in that time period.

A breakdown of codeletion status based on glioma histology is represented in Supplemental Table 3. Codeletion status was largely unknown for gliomas not otherwise specified and astrocytomas. However, molecular subtype

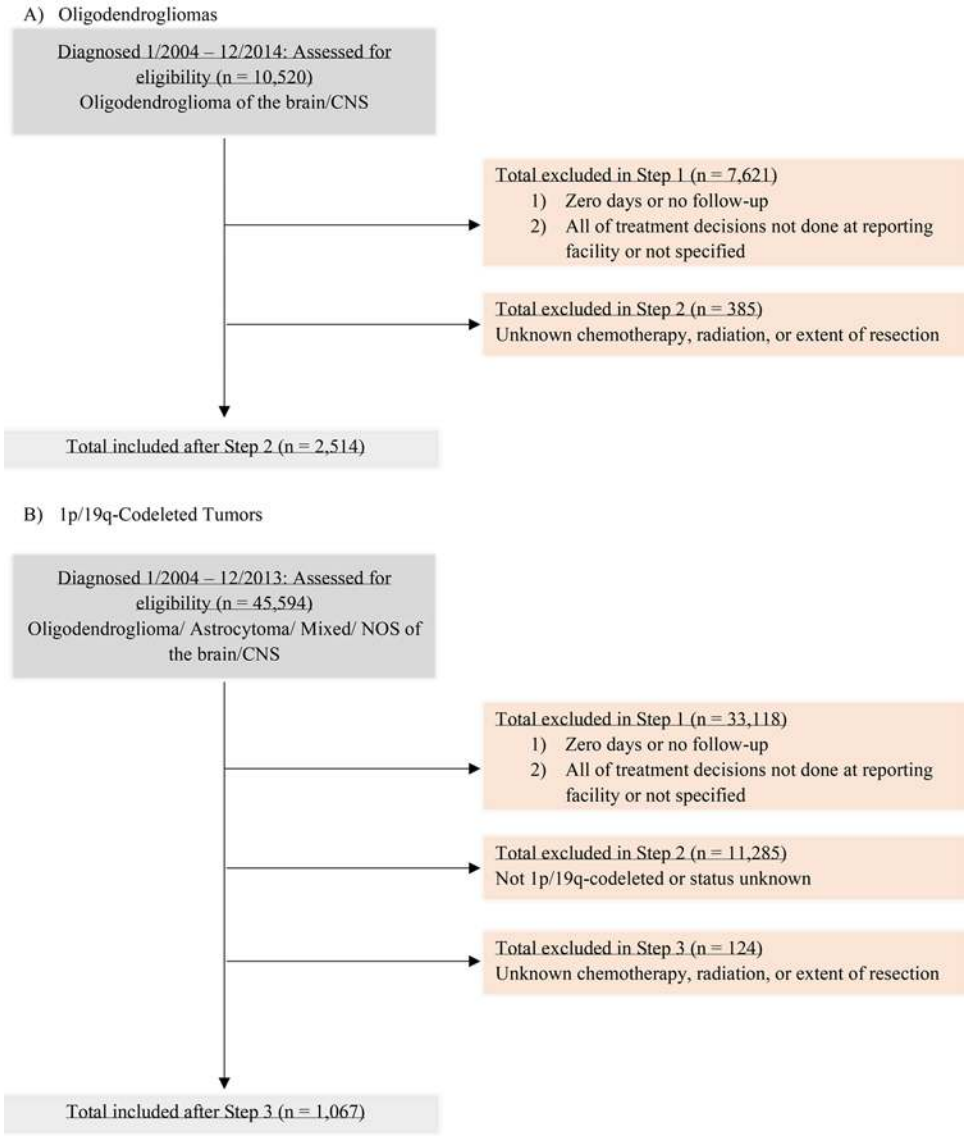


**FIG. 1.** Patient selection flowchart. NOS = not otherwise specified. Figure is available in color online only.

was available for nearly half of mixed gliomas (16.9% codeleted) and oligodendrogliomas (low-grade, 31.5% codeleted; anaplastic, 35.4% codeleted); of the O2 and O3 tumors with reported codeletion status, 72.5% of O2 and 76.9% of O3 were codeletion positive. Consistent with analyses from other national databases, among all 1p19q-codeleted tumors, nearly 70% were low-grade or anaplastic oligodendrogliomas.[1] Our final cohort of 1p/19q-codeleted tumors included 804 (75.4%) histologically classified oligodendrogliomas.

### Histologically Classified Oligodendrogliomas

EOR was shown to be associated with several demographic variables (Table 1). Patients younger than 49 years of age had lower rates of no-debulking surgery (a database term used to describe the absence of cancer-directed surgery) (8.3% vs 13.6%) and higher rates of GTR (40.3% vs 35.1%) compared to older patients. Treatment at academic centers was associated with greater EOR ($p < 0.001$). There were no differences in EOR between sex, race, and comorbidity index. Tumors later diagnosed with a higher histological grade were observed to undergo more extensive resection intraoperatively (grade II vs grade III [no debulking]: 7% vs 13%; STR: 53% vs 51%; GTR: 40% vs 37% [Supplemental Table 4]). Supratentorial tumors were more likely to undergo GTR than infratentorial tumors (39% vs 20%); infratentorial tumors had higher rates of no-debulking surgery (26% vs 10%). Larger tumors (> 5 cm) were more likely to undergo STR than smaller ones (55% vs 47%) and were less likely to undergo GTR (38% vs 43%). Finally, chemotherapy rates did vary by EOR, such that higher rates of chemotherapy were observed in STR (54% vs 49%) and lower rates after GTR (36% vs 40%).

Median OS time for all patients was not reached. The 75ST and 5-year survival rate were 54.8 months and

**TABLE 1. Demographic factors associated with EOR in oligodendrogliomas**

| Variable | No Debulking (A) | | STR (B) | | GTR (C) | | p Value |
|---|---|---|---|---|---|---|---|
| | Count | % | Count | % | Count | % | |
| Facility setting | | | | | | | |
| Academic | 107 | 10.0 | 544 | 51.0 | 415 | 38.9 | **<0.001** |
| Nonacademic | 117[B,C] | 15.1 | 376 | 48.4 | 284 | 36.6 | |
| Unknown | 49 | 7.3 | 370[A] | 55.1 | 252[A] | 37.6 | |
| Age (yrs) | | | | | | | |
| 0–48 | 109 | 8.3 | 673[A] | 51.4 | 528[A] | 40.3 | **<0.001** |
| ≥49 | 164[B,C] | 13.6 | 617 | 51.2 | 423 | 35.1 | |
| Sex | | | | | | | |
| Female | 151 | 10.7 | 726 | 51.6 | 530 | 37.7 | 0.94 |
| Male | 122 | 11.0 | 564 | 50.9 | 421 | 38.0 | |
| Race | | | | | | | |
| White | 245 | 10.9 | 1154 | 51.1 | 859 | 38.0 | 0.64 |
| Black | 17 | 13.2 | 70 | 54.3 | 42 | 32.6 | |
| Other | 11 | 8.7 | 66 | 52.0 | 50 | 39.4 | |
| Charlson-Deyo score | | | | | | | |
| 0 | 213 | 10.4 | 1048 | 51.2 | 784 | 38.3 | 0.10 |
| 1 | 49[B,C] | 14.8 | 164 | 49.4 | 119 | 35.8 | |
| 2 or greater | 11 | 8.0 | 78 | 56.9 | 48 | 35.0 | |
| Histology | | | | | | | |
| O2 | 214[B,C] | 12.8 | 847 | 50.5 | 616 | 36.7 | **<0.001** |
| O3 | 59 | 7.0 | 443[A] | 52.9 | 335[A] | 40.0 | |
| Tumor location | | | | | | | |
| Supratentorial | 236 | 9.9 | 1214[A] | 51.1 | 927[A,B] | 39.0 | **<0.001** |
| Infratentorial | 12[B,C] | 26.1 | 25 | 54.3 | 9 | 19.6 | |
| Unknown | 25[B,C] | 27.5 | 51[C] | 56.0 | 15 | 16.5 | |
| Tumor size | | | | | | | |
| <5 cm | 111 | 10.7 | 484 | 46.8 | 439[B] | 42.5 | **<0.001** |
| ≥5 cm | 54 | 7.3 | 406[A] | 54.6 | 283[A] | 38.1 | |
| Unknown | 108[B,C] | 14.7 | 400[C] | 54.3 | 229 | 31.1 | |
| Chemotherapy | | | | | | | |
| No | 150[B] | 11.8 | 620 | 48.6 | 506[B] | 39.7 | **0.02** |
| Yes | 123 | 9.9 | 670[A,C] | 54.1 | 445 | 35.9 | |
| Radiation | | | | | | | |
| No | 163 | 11.5 | 705 | 49.7 | 551 | 38.8 | 0.16 |
| Yes | 110 | 10.0 | 585 | 53.4 | 400 | 36.5 | |

Superscripted letters refer to statistically significant differences between treatment groups in the straddle heads.
Boldface indicates statistical significance.

70.3%, respectively. STR (75ST 49.2 months, $p = 0.006$) and GTR (75ST = 61.3 months, $p < 0.001$) were associated with significantly increased OS over no surgical debulking (75ST = 33.7 months, $p < 0.001$ for overall comparison, Fig. 2A).

In univariable and multivariable analyses to determine factors associated with OS in patients with oligodendrogliomas, being treated at a nonacademic center conferred higher risk than an academic one (HR 1.37, $p = 0.001$) (Table 2). Older age was associated with an increased risk (HR 1.06 per year, $p < 0.001$), whereas sex and race were not. Patients with more comorbidities had poorer survival (Charlson-Deyo score 1: HR 1.83, $p < 0.001$; Charlson-Deyo Score > 1: HR 2.84, $p < 0.001$). Anaplastic tumors and infratentorial tumors were associated with poorer survival (HR 1.96, $p < 0.001$ and HR 2.61, $p < 0.001$, respectively), whereas tumor size was not associated with survival. Critically, increasing EOR was shown to improve OS in a stepwise fashion in the univariable analysis (STR: HR 0.70, $p = 0.006$, GTR: HR 0.51, $p < 0.001$). Each of the associated variables was included in a subsequent multivariable analysis: age (HR 1.06), sex (HR 1.28), comorbidity index (Charlson-Deyo > 1: HR 2.00), tumor location (infratentorial: HR 2.15), and GTR (HR 0.69) continued to

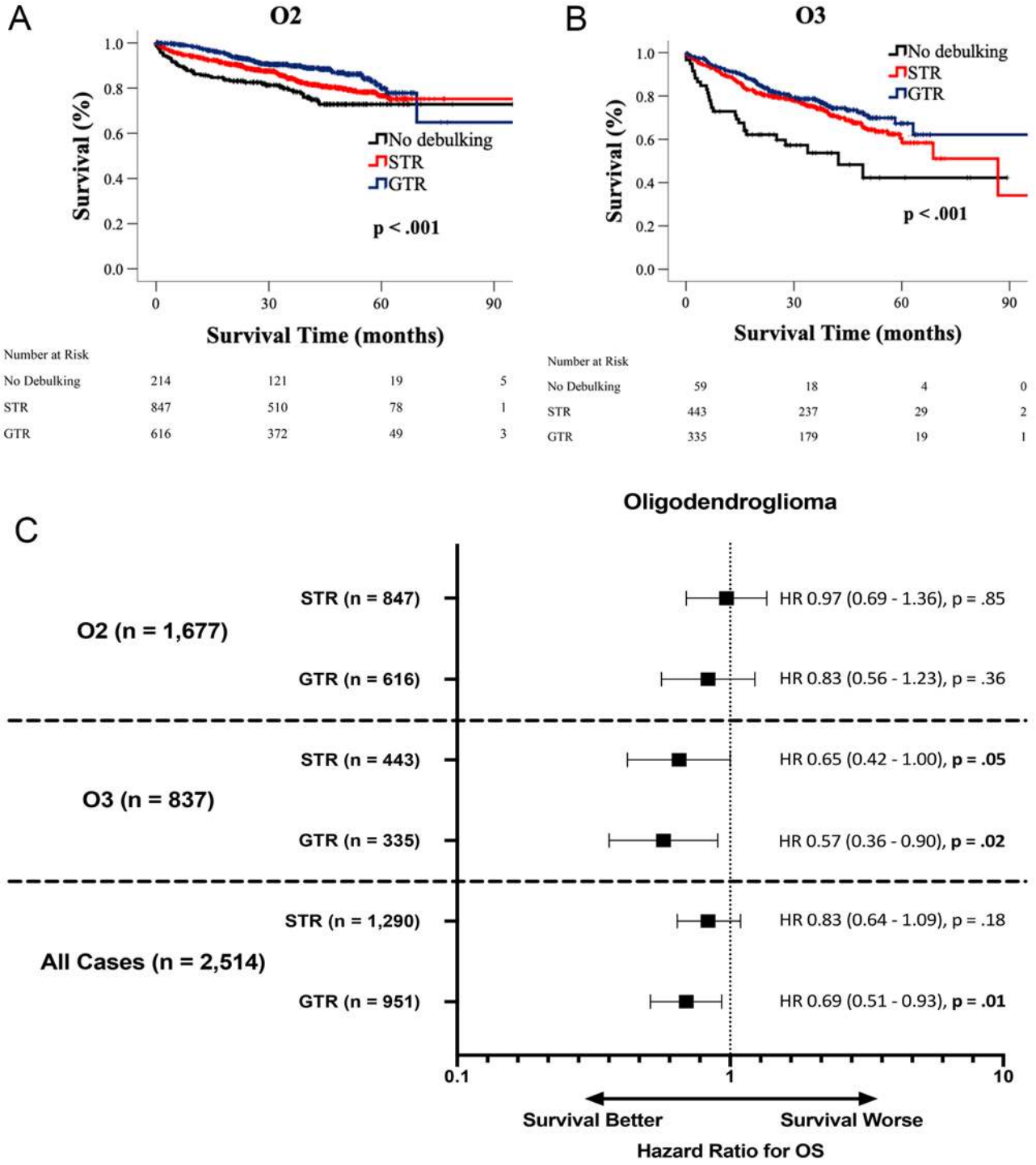


**FIG. 2.** Kaplan-Meier curves for overall survival based on EOR for O2 (**A**) and O3 (**B**) tumors. Forest plot for side-by-side comparison of hazard ratios. HRs are presented with their 95% CIs. Boldface p values indicate statistical significance (**C**). Figure is available in color online only.

be associated with survival. Radiation therapy was associated with decreased survival in the univariable (HR 2.04) and multivariable (HR 1.54) analyses.

In order to further assess the potential survival benefit of progressively greater EOR, a subgroup analysis was performed in which hazard ratios were compared between STR and GTR for different histological subtypes of oligodendrogliomas (Fig. 2A and B). The effect on survival was most pronounced for higher-grade oligodendrogliomas: Among O3 tumors, GTR conferred a HR of 0.57, whereas STR conferred a HR of 0.65 ($p = 0.02$ and $p = 0.05$, respectively). However, the same effect was not significant for

**TABLE 2. Univariable and multivariable analysis of OS for oligodendrogliomas**

| | | Univariable | | | | Multivariable | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Variable | Reference | p Value | HR | Lower | Upper | p Value | HR | Lower | Upper |
| Facility setting | Academic | **<0.001** | — | — | — | **0.009** | — | — | — |
| Nonacademic | | **0.001** | 1.37 | 1.13 | 1.66 | 0.10 | 1.18 | 0.97 | 1.43 |
| Unknown | | **<0.001** | 0.36 | 0.27 | 0.48 | **0.004** | 1.71 | 1.19 | 2.47 |
| Age | | **<0.001** | 1.06 | 1.06 | 1.07 | **<0.001** | 1.06 | 1.05 | 1.07 |
| Sex (female) | Male | 0.07 | 1.19 | 0.99 | 1.42 | **0.008** | 1.28 | 1.07 | 1.54 |
| Race | White | 0.15 | | | | — | | | |
| Black | | 0.17 | 0.73 | 0.46 | 1.15 | — | — | — | — |
| Unknown | | 0.15 | 0.71 | 0.44 | 1.14 | — | — | — | — |
| Charlson-Deyo score | 0 | **<0.001** | | | | **<0.001** | | | |
| 1 | | **<0.001** | 1.83 | 1.44 | 2.31 | 0.14 | 1.20 | 0.94 | 1.53 |
| ≥2 | | **<0.001** | 2.84 | 2.12 | 3.80 | **<0.001** | 2.00 | 1.49 | 2.69 |
| Histology (O3) | O2 | **<0.001** | 1.96 | 1.64 | 2.34 | **<0.001** | 1.55 | 1.27 | 1.90 |
| Location | Supratentorial | **<0.001** | | | | **<0.001** | | | |
| Infratentorial | | **<0.001** | 2.61 | 1.65 | 4.13 | **0.001** | 2.15 | 1.35 | 3.42 |
| Unknown | | **<0.001** | 2.45 | 1.74 | 3.46 | **<0.001** | 1.94 | 1.36 | 2.76 |
| Tumor size | <5 cm | 0.46 | | | | — | | | |
| ≥5 cm | | 0.40 | 1.10 | 0.89 | 1.36 | — | — | — | — |
| Unknown | | 0.23 | 1.14 | 0.92 | 1.43 | — | — | — | — |
| EOR | No debulking | **<0.001** | | | | **0.04** | | | |
| STR | | **0.006** | 0.70 | 0.54 | 0.90 | 0.18 | 0.83 | 0.64 | 1.09 |
| GTR | | **<0.001** | 0.51 | 0.39 | 0.68 | **0.01** | 0.69 | 0.51 | 0.93 |
| Chemotherapy | No chemotherapy | **0.01** | 1.26 | 1.06 | 1.51 | 0.26 | 0.89 | 0.72 | 1.09 |
| Radiation | No radiation | **<0.001** | 2.04 | 1.70 | 2.45 | **<0.001** | 1.54 | 1.26 | 1.89 |

— = not applicable.
Boldface type indicates statistical significance.

O2s. Yet again, when aggregating histological subtypes, GTR was associated with improved survival for oligodendrogliomas (HR 0.69) (Fig. 2C).

Propensity score analysis with inverse proportional weights comparing GTR to biopsy showed estimated survival time for average treatment effect to be 11.3 months longer for patients who had undergone GTR than those who had undergone biopsy alone ($p = 0.007$). The average treatment effect on the treated patients was 10.9 months longer if all patients in the population had undergone GTR ($p = 0.017$). Observations were matched for age, academic center, Charlson-Deyo score, histology, location, size, chemotherapy treatment, and radiation treatment.

### 1p/19q-Codeleted Gliomas

Median OS time for all cases was not reached. The 75ST and 5-year survival rate were 68.7 months and 74%, respectively. STR (75ST 68.7 months, $p = 0.05$) and GTR (75ST not reached, $p < 0.001$) were associated with significantly increased OS over no surgical debulking (75ST 60.0 months, $p = 0.002$ for overall comparison, Fig. 3). In 1p/19q-codeleted tumors, academic centers, sex, race, and comorbidity index did not correlate with EOR (Supplemental Table 4). However, age was significantly associated with EOR ($p = 0.05$). Grade 3 tumors were less likely to receive no debulking surgery when compared with low-grade tumors (5% vs 10%). Supratentorial tumors were more likely to undergo GTR (40% vs 23%), while infratentorial tumors were more likely to not undergo any debulking surgery (18% vs 8%). Furthermore, smaller tumors (< 5 cm) had lower rates of STR (46% vs 56%) and higher rates of GTR (46% vs 38%). Patients who received no chemotherapy were more likely to have undergone GTR (45% vs 35%) than patients who received chemotherapy.

In the univariable analysis, age (HR 1.06, $p < 0.001$), comorbidity index (Charlson-Deyo score 1: HR 1.85, $p = 0.006$; Charlson-Deyo score > 1: HR 3.59, $p < 0.001$), tumor grade (HR 2.35, $p < 0.001$), infratentorial location (HR 4.75, $p < 0.001$), and receipt of chemotherapy (HR 1.52, $p = 0.02$) and radiotherapy (HR 2.56, $p < 0.001$) were associated with poorer survival. Treatment at an academic center (HR 0.77, $p = 0.18$) and tumor size (HR 1.33, $p = 0.17$) approached but did not reach significance. STR (HR 0.63, $p = 0.05$) and GTR (HR 0.40, $p = 0.001$) were associated with improved survival. In multivariable analysis, STR (HR: 0.49, $p = 0.005$) and GTR (HR 0.43, $p < 0.003$) had a positive relationship with increased survival times. Older age (HR: 1.07), worse comorbidities (Charlson-Deyo score > 1: HR 2.98), anaplastic grade (HR 1.8), infratentorial location (HR 5.11), and receipt of radiotherapy

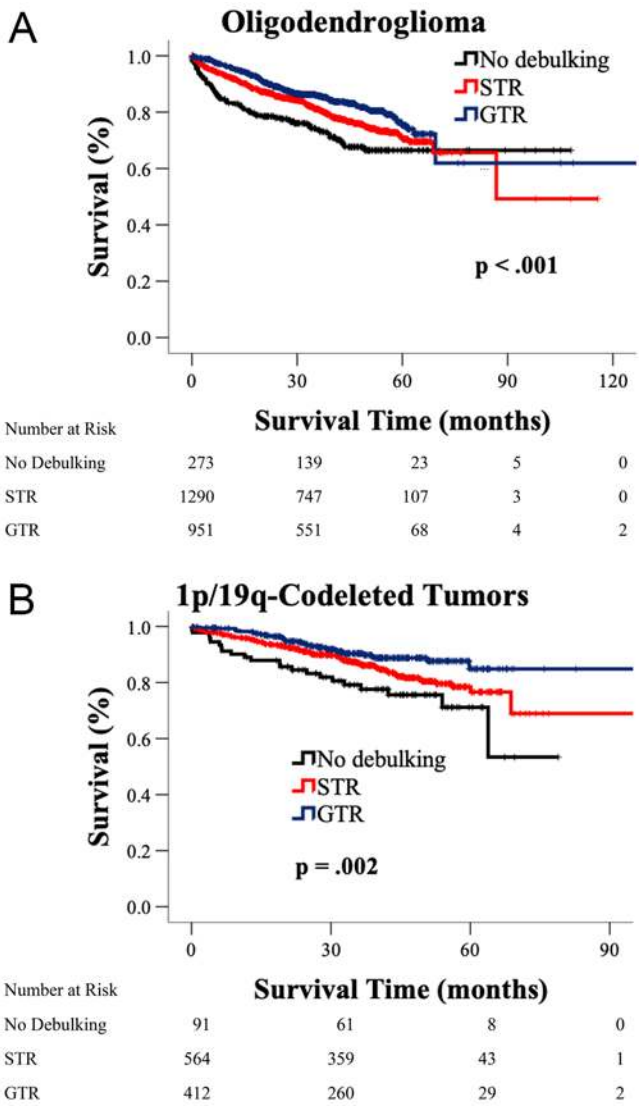


**FIG. 3.** Kaplan-Meier curves for all OS based on EOR for oligodendrogliomas (**A**) and 1p/19q-codeleted tumors (**B**). Figure is available in color online only.

(HR 1.87) were all associated with poorer survival. These findings are shown in Table 3.

Although database queries are convenience samples and our selection was not specifically powered to evaluate EOR in subgroups of 1p/19q-codeleted tumors, we conducted an exploratory analysis of grade II and III tumors (Supplemental Fig. 1A and B). As with the above, the effect on survival was most profound for grade III tumors (STR: HR 0.11, $p < 0.001$; GTR: HR 0.09, $p < 0.001$); the same effect was not observed in grade II tumors (Supplemental Fig. 1B).

Propensity score analysis with inverse probability weights showed the average treatment effect estimated survival time to be 5.2 months longer for patients who underwent GTR compared to those who underwent biopsy alone ($p = 0.002$). The average treatment effect on the treated showed survival time to be 5.5 months longer in this cohort if all patients had undergone GTR ($p < 0.001$). Observations were matched for age, tumor grade, tumor location, and radiation treatment.

## Discussion

Here we present one of the largest population-based studies examining EOR and survival in in patients with oligodendrogliomas. The NCDB, aside from including more covariates than similar population databases such as the Surveillance, Epidemiology, and End Results (SEER) Program, enables for coding of oligodendrogliomas and/or 1p/19q-codeleted tumors. Here, we show that greater EOR improves survival in both categories, consistent with national guidelines. In this study, we demonstrated that even with molecular specification of 1p/19q-codeleted tumors (as opposed to histological classification of oligodendrogliomas), the survival benefit with greater EOR remains. It should be noted that there is an inherent skew toward resection throughout the database, as only 10.9% of oligodendrogliomas and 8.5% of codeleted tumors did not undergo surgery. However, as GTR is associated with a greater survival benefit relative to STR, greater EOR likely improves outcomes, suggesting maximal safe resection remains the optimum strategy for these tumors.

Given recent findings that, on the basis of molecular signature, up to 35% of oligodendrogliomas are historically misclassified when compared with molecular signature, it is important to reaffirm the survival benefit of greater EOR in 1p/19q-codeleted tumors, specifically.[4,16,39,49] It is possible that this misclassification could have previously contributed to false-positive trials when comparing molecularly diagnosed oligodendrogliomas to historical histologically diagnosed tumors;[39] however, our findings suggest that regardless of traditional histological classification compared to chromosomally classified oligodendrogliomas, EOR remains a significant predictor of survival. Furthermore, while previous studies using the NCDB have generally found survival benefits to GTR, STR alone often is not associated with improved outcomes for glioblastoma.[40] While we demonstrated similar findings in oligodendrogliomas, in our examination of 1p/19q-codeleted tumors, GTR and STR both significantly improved OS in multivariable models. We hypothesize that the STR group had substantial resections of at least 80% of tumor, based on previous reports on the impact of EOR in gliomas, accounting for the increased survival in this group.

Interestingly, in subgroup analyses, it appears that some of the survival benefit in both traditionally codified oligodendrogliomas and 1p/19q-codeleted tumors may be driven by the effect observed in higher-grade tumors (e.g. grade III oligodendrogliomas and gliomas). The median follow-up time for O2 tumors was 35 months, whereas median survival appears to be well over 90 months. This problem was more pronounced in codeleted grade II tumors, where 5-year survival was 88% and only 44 events were recorded. In our previous analysis of the SEER database, GTR was associated with improved survival in O2 tumors.[16] In the current study, there were only 9 patients with 90-month follow-up compared to 372 in our previous study. The survival curves are nearly identical until 30 months of follow-up, at which point they diverge. Thus, while it is possible that the survival advantages of GTR

**TABLE 3. Univariable and multivariable analysis of OS for 1p/19q-codeleted tumors**

| | | Univariable | | | | Multivariable | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Variable | Reference | p Value | HR | Lower | Upper | p Value | HR | Lower | Upper |
| Facility setting | Academic | **<0.001** | | | | 0.37 | | | |
| Nonacademic | | 0.18 | 0.77 | 0.52 | 1.13 | 0.51 | 0.87 | 0.58 | 1.31 |
| Unknown | | **<0.001** | 0.25 | 0.14 | 0.44 | 0.43 | 1.37 | 0.63 | 2.94 |
| Age | | **<0.001** | 1.06 | 1.05 | 1.08 | **<0.001** | 1.07 | 1.05 | 1.09 |
| Sex (female) | Male | 0.66 | 1.08 | 0.78 | 1.50 | — | — | — | — |
| Race | White | 0.26 | | | | — | | | |
| Black | | 0.25 | 1.56 | 0.73 | 3.34 | — | — | — | — |
| Unknown | | 0.21 | 1.54 | 0.78 | 3.03 | — | — | — | — |
| Charlson-Deyo score | 0 | **<0.001** | | | | **0.001** | | | |
| 1 | | **0.006** | 1.85 | 1.19 | 2.86 | 0.35 | 1.25 | 0.79 | 1.99 |
| ≥2 | | **<0.001** | 3.59 | 2.08 | 6.18 | **<0.001** | 2.98 | 1.70 | 5.25 |
| Grade | II | **<0.001** | | | | **0.001** | | | |
| III | | **<0.001** | 2.35 | 1.58 | 3.48 | **0.009** | 1.80 | 1.16 | 2.81 |
| Unknown | | **<0.001** | 2.56 | 1.67 | 3.90 | **<0.001** | 2.34 | 1.51 | 3.64 |
| Location | Supratentorial | **<0.001** | | | | **<0.001** | | | |
| Infratentorial | | **<0.001** | 4.75 | 2.49 | 9.06 | **<0.001** | 5.11 | 2.62 | 9.99 |
| Unknown | | **0.001** | 2.87 | 1.50 | 5.47 | **0.03** | 2.11 | 1.08 | 4.13 |
| Tumor size | <5 cm | 0.08 | | | | 0.15 | | | |
| ≥5 | | 0.17 | 1.33 | 0.89 | 2.00 | 0.63 | 1.11 | 0.72 | 1.72 |
| Unknown | | **0.03** | 1.61 | 1.06 | 2.44 | 0.06 | 1.51 | 0.98 | 2.32 |
| EOR | No debulking | **0.002** | | | | **0.007** | | | |
| STR | | **0.05** | 0.63 | 0.39 | 1.01 | **0.005** | 0.49 | 0.30 | 0.81 |
| GTR | | **0.001** | 0.40 | 0.24 | 0.68 | **0.003** | 0.43 | 0.24 | 0.74 |
| Chemotherapy | No chemotherapy | **0.02** | 1.52 | 1.06 | 2.20 | 0.68 | 0.92 | 0.61 | 1.38 |
| Radiation | No radiation | **<0.001** | 2.65 | 1.87 | 3.77 | **0.001** | 1.87 | 1.28 | 2.73 |

Boldface indicates statistical significance.

are attenuated in grade II tumors due to their longer survival times, the question cannot be adequately answered in the current study. Future studies on low-grade tumors with longer follow-up times are warranted.

This is one of the first studies to look at prognostic factors in 1p/19q codeleted tumors on a population-level. A recent, similar study queried the NCDB for 1p/19q-codeleted tumors to evaluate EOR, and only observed a significant survival benefit for greater EOR in tumors without codeletions.[41] However, our findings elaborate upon these in several meaningful ways. First, we were able to show a side-by-side comparison between oligodendrogliomas as traditionally coded in NCDB and those that were 1p/19q-codeleted lesions.[39] When delineating the tumors in this manner, the hazard ratios for mortality were significantly lower in both STR and GTR after controlling for confounders in a multivariable analysis. Second, previous work has only examined cases that satisfy WHO grade II histological criteria;[41] as our data accounts for grade III diagnoses, we were able to validate the findings across both LGG and HGG in 1p/19q-codeleted tumors. Where previous, small-scale studies have suggested that resection may not affect survival in higher-grade codeleted tumors, the data provided here appear to affirm national guidelines.[42] Finally, our analysis was able to account for predictors of EOR as well as survival, showing that certain factors (including tumor grade) independently predict EOR and therefore may be important to account for as potential future confounders in studies on survival, given the association between EOR and survival.

There are limitations in using a large database such as the NCDB in our work. The retrospective nature of the data prevents clarification and recoding of data. It is also difficult to create a truly objective measure by which resection is reported, given the variability between individual provider interpretations. Definitions of EOR were nonvolumetric and, therefore, not consistent with the most modern definitions of EOR. It is also important for future studies to account for *IDH* mutation status to validate these findings. Although *IDH* mutations are highly co-occurrent with 1p/19q codeletion, the most accurate interpretation of 2016 WHO guidelines would necessitate both pieces of information.[29] Additionally, we would be remiss not to call attention to the dramatic racial bias in the tumors pulled from the NCDB, given that 90% of oligodendrogliomas were in Caucasian patients. Although race was not observed to correlate with either EOR or survival, the skewed distribution of patients across race raises some

question as to the lack of power in observing an effect of race on these variables. This analysis is not unique in its findings, as similar studies have documented this underrepresentation of minority populations.[43,44]

There are also advantages to large population-based data sets. As there will likely never be a randomized clinical trial examining the impact of variability in resection on survival in patients with gliomas, validating these hypotheses in large databases is an important second-line step in establishing practice. The NCDB is ideal to address our objective because it includes molecular characteristics of tumors as well as covariate data (e.g., demographics, comorbidities, adjunct treatment, and so on). Compared to similar projects using SEER, the NCDB is more adequately equipped to address the question of EOR and survival in the modern age with molecular signature classification.[16,27,28] Furthermore large sample size increases power, lending credence to the validity of these results when compared to smaller, single institution–based studies. Population-based studies also reflect treatment patterns across the country, reducing the influence of single-institution or systemic bias.[45,46] While recognizing the limitations of national databases, we find that these results make an important contribution to validating current guidelines given ongoing uncertainty about the effect of greater EOR amid the reclassification of oligodendrogliomas.[39]

## Conclusions

We conducted a twofold analysis using a large national database in which we first looked at tumors traditionally classified as "oligodendrogliomas," then looked at all gliomas bearing the molecular hallmark of oligodendrogliomas under the current WHO guidelines. In a univariable analysis, STR was associated with a trend toward improved survival. In a multivariable analysis, however, among tumors that are 1p/19q codeleted, greater EOR improves survival while only GTR, not STR, improves outcomes in traditionally codified oligodendrogliomas. These findings support current treatment practices at the national level.

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## Author Contributions

Conception and design: Garton, Kinslow, Canoll, Wang. Acquisition of data: Kinslow, Mehta, Sonabend. Analysis and interpretation of data: Garton, Kinslow, Rae. Drafting the article: Garton, Kinslow, Magge, Pannullo, Ramakrishna. Critically revising the article: Garton, Kinslow, Rae, Mehta, Pannullo, Magge, Ramakrishna, McKhann, Sisti, Bruce, Sonabend, Wang. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Garton. Statistical analysis: Garton, Kinslow, Rae, Mehta, Cheng, Sonabend. Administrative/technical/material support: Canoll, Cheng, Sonabend, Wang. Study supervision: Canoll, Cheng, Sonabend, Wang.

## Supplemental Information

### Online-Only Content

Supplemental material is available with the online version of the article.

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