

Significance of Necrosis in Grading of Oligodendroglial Neoplasms: A Clinicopathologic and Genetic Study of Newly Diagnosed High-Grade Gliomas

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A B S T R A C T

Purpose

High-grade gliomas (HGGs; WHO grades 3-4) are highly diverse, with survival times ranging from months to years. WHO 2000 grading criteria for high-grade oligodendroglial neoplasms [anaplastic oligoastrocytoma (AOA) and anaplastic oligodendroglioma (AO)] remain subjective, and the existence of grade 4 variants is controversial.

Patients and Methods

Overall survival (OS) of 1,093 adult patients with a cerebral HGG newly diagnosed between 1990 and 2005 was analyzed by univariate and multivariate models for significance of the following factors: patient age, surgery type, year of diagnosis, endothelial proliferation, necrosis, oligodendroglial histology, treatment center, and chromosome 1p, 19q, 7p (*EGFR*), and 10q (*PTEN*) abnormalities by fluorescence in situ hybridization (FISH).

Results

Necrosis was a statistically significant predictor of poor OS on univariate and multivariate analyses in AOA but not in AO. Median OS for patients with necrotic AOA (22.8 months) was significantly worse than for patients with non-necrotic AOA (86.9 months; $P < .0001$) but was better than conventional glioblastomas (9.8 months; $P < .0001$). In addition to patient age, the following were significant independent prognostic factors ($P \leq .001$): grade and surgery type for the entire HGG cohort; modified grade for AOA (3 v 4); and modified grade, 1p/19q codeletion status, and oligodendroglial histology for the 586 HGGs analyzed by FISH.

Conclusion

Stratification of AOA, but not of pure AO, into grades 3 and 4 on the basis of necrosis is prognostically justified and is more powerful than the current approach. Both routine histology and genetic testing provide independent, prognostically useful information.

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INTRODUCTION

Diffuse, infiltrative gliomas are the most common primary intracranial neoplasms, accounting for 40% of all primary and 78% of all malignant CNS tumors.¹ More than 80% of these tumors are considered high grade (grades 3 and 4) when diagnosed according to criteria established by WHO in 2000.² Four distinct, diffuse, high-grade gliomas (HGGs) are currently recognized and are distinguished by morphologic evidence of differentiation along astrocytic [anaplastic astrocytoma (AA), WHO grade 3; and glioblastoma (GBM), WHO grade 4], oligodendroglial [anaplastic oligodendroglioma (AO), WHO grade 3], or mixed [anaplastic oligoastrocytoma (AOA), WHO grade 3] lineages. In contrast to the high-grade astrocytomas (HGAs), the existence of

grade 4 high-grade oligodendroglial neoplasms (HGOs) remains a subject of debate.

Classification and grading criteria for astrocytic neoplasms are well established, having been refined periodically over the last 80 years. WHO 2000 uses mitotic activity to distinguish AA from its WHO grade 2 counterpart. Endothelial proliferation (EP) and/or necrosis are distinguishing features of GBM. These morphologic criteria have enhanced reproducibility for HGA and serve as prognostically useful predictors of overall survival (OS).³⁻⁵

Since its original description,⁶ oligodendroglioma has become a well-recognized clinicopathologic entity, with increasing clinical interest in this important subclass over the last 20 years.⁷⁻⁹ The two forms of HGO, AO and AOA, are distinguished from their low-grade counterparts, oligodendroglioma and oligoastrocytoma, by the presence of any of

the following histologic features: brisk mitotic activity, EP, and necrosis. Nonetheless, the grading remains subjective and is considerably less reproducible than for HGA,^{3-5,8,10} with survivals ranging widely from less than 1 to more than 10 years.²

Strong associations of chromosome 1p and 19q codeletion with therapeutic responsiveness and improved prognosis have made accurate histopathologic and molecular genetic characterization of HGO of paramount importance for proper treatment planning and enhanced prognostic accuracy.¹¹⁻¹⁴ 1p/19q codeletion most frequently (50% to 90%) occurs in morphologically classical AO. A subset (approximately 20%) of AOA also harbors 1p/19q codeletion,¹³ although its prognostic utility remains less well defined in this setting. Despite these advances, diagnostic discrepancies remain frequent.^{3-5,8,10} For example, small-cell astrocytoma (SCA) is considered a variant of GBM that commonly mimics HGO; however, its clinical behavior is similar to conventional GBM (median OS of approximately 1 year), even when EP and necrosis are not present.^{15,16} Identification of characteristic molecular genetic alterations in SCA, such as amplification of chromosome 7p (*EGFR*) and chromosome 10q (*PTEN*) deletion, is diagnostically useful in challenging patients.

The present study was designed to address the natural history and prognostic factors of diffuse HGG diagnosed according to current WHO 2000 criteria. Genetic studies were performed in a subset of patients, and the main objective was to determine whether HGO could be further stratified histologically into grade 3 and 4 variants.

PATIENTS AND METHODS

Study Participants

With institutional review board approval (Washington University School of Medicine [WUSM] Human Studies Committee 04-1270), the surgical neuropathology and consult files were searched for primary HGGs diagnosed between 1990 and 2005. Patients less than 20 years of age and those having tumors located within the diencephalon, cerebellum, or spinal cord were excluded. Recurrent HGGs were also excluded to eliminate confounding effects of prior therapy, such as radiation necrosis. An additional 10 study patients with HGO with pseudopalisading necrosis (PPN) were obtained from the Mayo Clinic. In total, 1,093 adult patients with diffuse cerebral HGG were studied. Subsets of these patients have been previously reported.^{13,16-18}

Information was extracted from medical records. Dates of death were obtained from these records or the Social Security Death Index. OS was

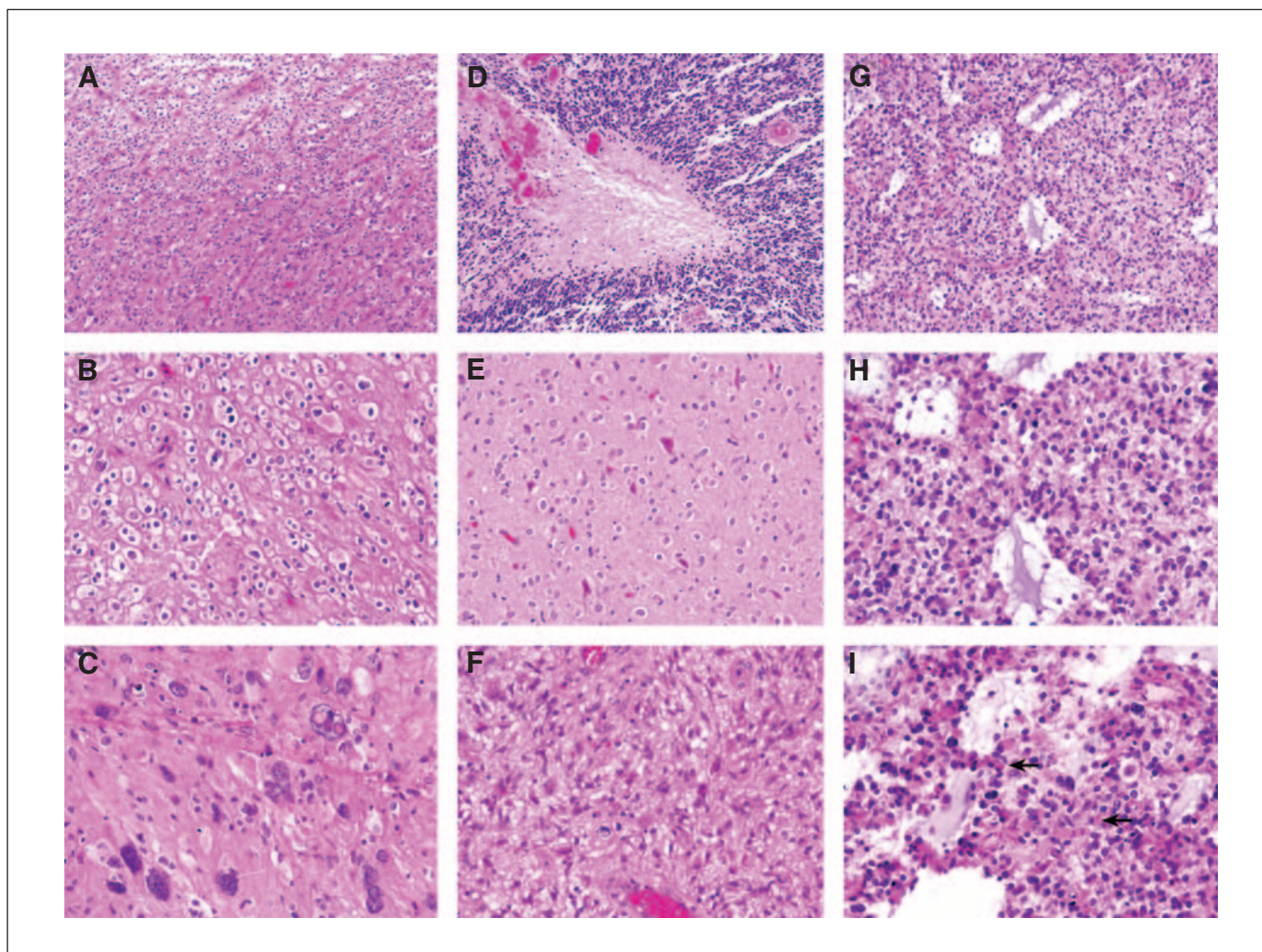


Fig 1. Morphologic features of four separate anaplastic oligoastrocytomas (A to C, D, E to F, and G to I). The biphasic, compact variant contains distinct oligodendroglial (A, top; B, and E) and astrocytic (A, bottom; C, and F) components. The tumor in D features pseudopalisading necrosis. The diffuse variant contains intermingled oligodendroglial and astrocytic components (G to I). This example also has mucin-rich microcystic spaces and mini-gemistocytes (arrows).

calculated from the date of surgery to either the date of death or the last follow-up date documented in the patient's medical record.

Histopathology

Tumors were diagnosed according to WHO 2000 criteria² with the criterion of brisk mitotic activity for AO and AOA further defined as a minimum of six mitoses per 10 high-powered fields either focally or diffusely.¹⁹ Given controversies within the neuropathology community over diagnostic criteria for AOA, morphologic examples are illustrated in Figure 1. Additional details regarding our approach to glioma classification are found in the Appendix.

Molecular Cytogenetics

Dual-color fluorescence in situ hybridization (FISH) was performed and interpreted as previously described.^{13,17,18,20} In the vast majority of patients, the data were collected prospectively as part of the routine diagnostic work-up. Retrospective analysis was undertaken in selected patients who predated the routine application of FISH at WUSM in 1999 or were from the Mayo Clinic.

Statistics

All statistical analyses were performed using Intercooled STATA, version 9.2 (STATA Corp, College Station, TX). χ^2 or Fisher's exact tests were used for comparisons of proportions, and Student's *t* test was used for mean comparisons of continuous variables such as age. All statistical tests were two sided, and *P* < .05 was considered significant unless otherwise stated. Kaplan-Meier survival curves were plotted, and log-rank tests and Cox proportional hazards analysis were used for univariate and multivariate comparisons of median OS. Additional methodologic details are available in the Appendix.

RESULTS

Patients

Characteristics of 1,093 study patients are listed in Table 1. Among the tumors, 13 (2.2% of GBMs or 1.2% of all HGGs) were

Table 1. Patient Characteristics and Histopathologic Features

| Characteristic | WHO 2000 Diagnosis (% of patients) | | | | |
|------------------------------|------------------------------------|----------------|-------------------|------------------|-----------------|
| | All HGG (N = 1,093) | HGA | | HGO | |
| | | AA (n = 81) | GBM* (n = 581) | AOA (n = 215) | AO (n = 216) |
| Age, years | | | | | |
| Mean | 52.4 | 43.3 | 59.5 | 44.0 | 45.4 |
| Median | 52 | 39 | 61 | 42 | 44.5 |
| Range | 21-90 | 22-82 | 22-90 | 21-85 | 23-81 |
| ≤ 40 | 25 | 52 | 9 | 46 | 39 |
| 40-60 | 41 | 32 | 39 | 42 | 48 |
| ≥ 60 | 34 | 16 | 52 | 12 | 13 |
| Sex | | | | | |
| Male | 58 | 54 | 60 | 53 | 56 |
| Female | 42 | 46 | 40 | 47 | 44 |
| Diagnosis year | | | | | |
| 1990-1995 | 15 | 5 | 21 | 9 | 6 |
| 1996-1999 | 14 | 14 | 17 | 10 | 11 |
| 2000-2005 | 71 | 81 | 62 | 81 | 83 |
| Treatment center | | | | | |
| Academic | 79 | 78 | 89 | 67 | 67 |
| WUSM | 64 | 56 | 83 | 42 | 15 |
| Nonacademic | 21 | 22 | 11 | 33 | 33 |
| Type of surgery | | | | | |
| Needle biopsy | 22 | 38 | 31 | 7 | 7 |
| Resection | 76 | 60 | 68 | 91 | 89 |
| Unknown | 2 | 2 | 1 | 2 | 4 |
| Patients alive at study end† | 46 | 65 | 19 | 67 | 85 |
| Follow-up | | | | | |
| Mean, years | 1.4 | 1.7 | 1.0 | 1.8 | 1.9 |
| Median, years | 0.8 | 1.4 | 0.7 | 0.8 | 0.6 |
| Maximum, years | 14.4 | 11.6 | 11.5 | 14 | 13.5 |
| Completeness of follow-up | 62 | 63 | 68 | 60 | 58 |
| Patients with 100% follow-up | 61 | 46 | 85 | 38 | 24 |
| EP | 73 | NA | 91 | 66 | 60 |
| Necrosis | 59 | NA | 85 | 33 | 35 |
| Necrosis type | | | | | |
| Geographic | 52 | NA | 49 | 56 | 68 |
| PPN | 48 | NA | 51 | 44 | 32 |

Abbreviations: HGG, high-grade glioma; HGA, high-grade astrocytoma; HGO, high-grade oligodendroglioma; AA, anaplastic astrocytoma; GBM, glioblastoma multiforme; AOA, anaplastic oligoastrocytoma; AO, anaplastic oligodendroglioma; WUSM, Washington University School of Medicine; EP, endothelial proliferation; NA, not applicable; PPN, pseudopalisading necrosis.

*Includes 120 small-cell astrocytomas (20.7%) and 13 gliosarcomas (2.2%).

†Includes censored patients.

gliosarcomas, and 120 (20.7% of GBMs or 11.0% of all HGGs) were SCAs. Two hundred fifteen tumors (48.8% of HGOs; 19.7% of all HGGs) were AOA. These latter two disproportionately high percentages reflected a consultation bias encountered by one of the authors (A.P.), given that SCA and AOA represented only 4.1% and 18.0%, respectively, of all in-house HGGs at WUSM versus 18% and 28.8%, respectively, of all consult HGGs ($P < .001$ for each). Growth of the consult service over time is also reflected in the significantly greater fraction of patients obtained after the year 2000 (71%; $P \leq .001$). More patients with HGO (AOA and AO) were diagnosed since 2000 (82% of 431 patients; $P < .001$), again likely reflecting a consultation bias because HGOs are more often submitted for second opinion and genetic analysis than HGAs. The mean age of GBM patients was 59.5 years and was significantly higher than the ages of patients with AA, AOA, or AO ($P < .05$). A significantly greater fraction of patients aged more than 60 years had GBM (52%; $P < .05$).

Roughly half of patients (555 patients; 51%) received their treatment at WUSM, and the GBM cohort was largely drawn from this group (428 patients; 74%). The majority of AOA and AO patients (72% and 85%, respectively) received care elsewhere. Most patients (76%) underwent resection; however, more HGA patients (32%) were diagnosed on stereotactic needle biopsy than HGO patients (7%; $P < .05$). Five hundred ninety-five patients (54%) died by the end of the study, and 58 (5.3%) were alive with longer than 5 years of follow-up. Mean follow-up time was 1.4 years for the entire cohort and varied with WHO 2000 diagnosis, patient age, diagnosis year, and treatment institution (Appendix Table A1, online only). Complete follow-up (C statistic = 100%) was obtained for 61% of patients, and 17% of patients were lost to follow-up after surgery ($C \leq 5\%$).

Histopathologic and Molecular Cytogenetic Features

Histopathologic features are listed in Table 1. EP and necrosis were more frequently found in GBM than in either AOA or AO

($P < .001$). There were no significant differences in the frequencies of either EP or necrosis between AOA and AO ($P > .05$).

Molecular cytogenetic features are summarized in Appendix Figures A1 through A3 (online only). Decreasing frequencies of 1p/19q codeletion were found in AO (89%), AOA (19%), and AA/GBM (0%; Appendix Fig A2; $P < .001$). Polysomies (gains) of 1p or 19q were more frequent in HGA than in AO (data not shown; $P < .001$). *EGFR* amplification and 10q deletion were evident most frequently in GBM (Appendix Fig A3; $P < .001$). *EGFR* amplification was more frequent in SCA (63%) than other GBM subtypes (19%; $P < .001$). 10q deletion was identified in 82% of 141 HGAs but only 26% of 81 HGOs ($P < .001$). Additional information regarding the molecular cytogenetic features is available in the Appendix.

Univariate Analysis of Prognostic Factors

Clinical, histopathologic, and genetic factors were examined for their associations with OS in the entire HGG patient cohort and in each of the four separate diagnostic entities (Table 2). Patient age was the only prognostic factor significant in all five cohorts ($P < .01$), whereas year of diagnosis and solitary 19q deletion were the only examined factors nonsignificant in all five cohorts. Needle biopsy was a poor prognostic indicator in GBM patients compared with resection (5.6 v 11.7 months, respectively; 95% CI, 4.4 to 7.0 and 10.2 to 13.0 months, respectively; $P < .0001$). GBM patients treated at WUSM showed a small ($P = .039$) difference in median OS time (9.5 months; 95% CI, 9.4 to 12.9 months) compared with GBM patients treated elsewhere (10.8 months; 95% CI, 8.4 to 11.1 months), likely because of the fact that GBM patients from WUSM were more often diagnosed by needle biopsy (34% of 426 patients) than non-WUSM patients (22% of 147 patients; $P = .006$).

Both the presence of any type of necrosis (Fig 2A) and PPN alone (Fig 2B) were statistically significant negative prognostic factors only in patients with AOA ($P \leq .0001$; Table 2). Median OS time for

Table 2. Univariate (log-rank) Analysis of Prognostic Factors

| Factor | P | | | | |
|---------------------------|---------|--------|--------|--------|--------|
| | All HGG | AA | GBM | AOA | AO |
| Clinical | | | | | |
| Age group | .0001* | .0003* | .0001* | .0001* | .0001* |
| Surgery type | .0001* | .3 | .0001* | .3 | .2 |
| Diagnosis year group | .02 | .5 | .06 | .6 | .5 |
| Treatment center | .0001* | .2 | .04 | .10 | .6 |
| Histopathology | | | | | |
| EP | .0001* | NA | .01 | .10 | .4 |
| Necrosis | .0001* | NA | .3 | .0001* | .4 |
| PPN | .0001* | NA | .2 | .0001* | .3 |
| Cytogenetics | | | | | |
| 1p deletion | .0001* | NA | .7 | .12 | .2 |
| 19q deletion | .0001* | .3 | .6 | .3 | .12 |
| 1p/19q codeletion | .0001* | NA | NA | .12 | .06 |
| Solitary 19q deletion | .8 | .3 | .6 | .9 | .4 |
| <i>EGFR</i> amplification | .0001* | .5 | .9 | .2 | NA |
| 10q deletion | .0002* | .4 | .8 | .3 | .8 |
| <i>EGFR</i> amp/10q del | .003* | .4 | .5 | .4 | NA |

Abbreviations: HGG, high-grade glioma; AA, anaplastic astrocytoma; GBM, glioblastoma multiforme; AOA, anaplastic oligoastrocytoma; AO, anaplastic oligodendroglioma; EP, endothelial proliferation; NA, not applicable; PPN, pseudopalisading necrosis.

*Statistically significant ($P \leq .01$).

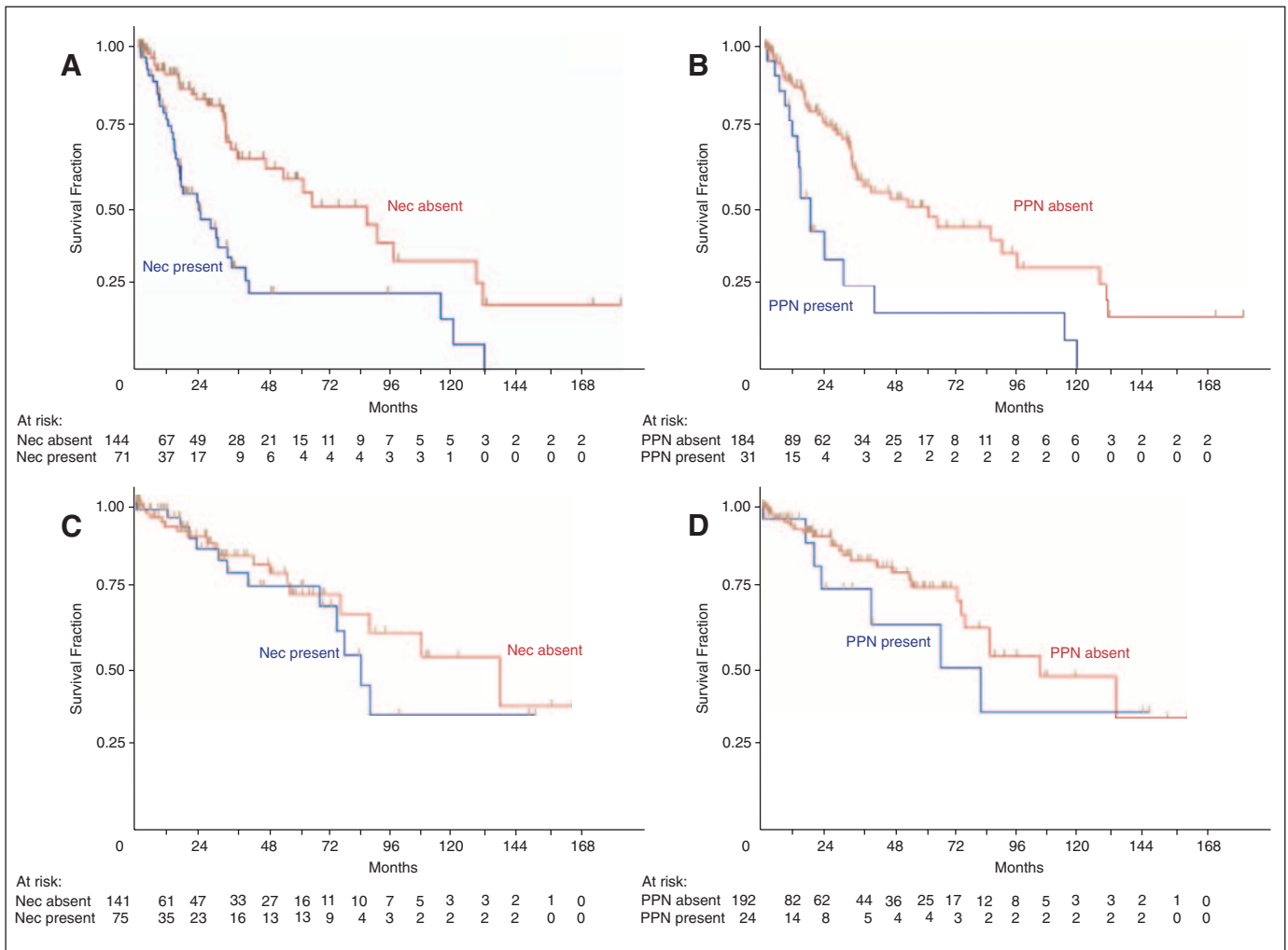


Fig 2. Kaplan-Meier survival curves for (A and B) anaplastic oligoastrocytomas (AOA) and (C and D) anaplastic oligodendroglioma (AO) diagnosed by WHO 2000 criteria and stratified by (A and C) any type of necrosis (Nec) or (B and D) pseudopalisading necrosis (PPN) alone. Both factors were highly significant on log-rank analysis for AOA ($P < .0001$) but not for AO ($P \geq .32$).

patients with necrotic AOA was significantly shorter (22.8 months; 95% CI, 14.9 to 33.8 months) compared with patients with non-necrotic AOA (86.9 months; 95% CI, 48.4 to 129 months). Similarly, median OS time for patients whose tumors featured PPN was significantly shorter (15.6 months; 95% CI, 10.5 to 30.1 months) compared with patients without PPN (62.8 months; 95% CI, 35.2 to 97.1 months). In contrast, neither necrosis nor PPN alone were significantly associated with OS in AO patients ($P \geq .32$; Figs 2C and 2D, Table 2). Small-cell histology did not significantly influence median OS time in GBM patients (11.5 v 9.4 months for SCA and conventional GBM, respectively; 95% CI, 9.7 to 14.1 and 8.3 to 11.0 months, respectively; $P = .43$).

As shown in Appendix Figure A5A (online only), trends were evident for 1p/19q codeletion in AOA ($P = .12$) and AO ($P = .06$) patients. Median OS time for patients with 1p/19q-deleted AOA was 132 months (95% CI, 29.5 months to upper limit undefined) compared with 42.0 months (95% CI, 33 to 86.9 months) for patients lacking 1p/19q codeletion. Similarly, median OS times for AO patients with and without 1p/19q codeletions were 135 months (95% CI, 76.0 months to upper limit undefined) and 68.2 months (95% CI, 26.3

months to upper limit undefined), respectively. However, only 19% of 189 AOA patients harbored 1p/19q codeletion, and 12% of 200 AO patients lacked 1p/19q codeletion, and few of these patients had died (13 of 58 patients; 22%), limiting the statistical power in these individual subsets. Therefore, a combined analysis of 1p/19q codeletion in all HGO patients was performed (Appendix Fig A5B) and showed significantly prolonged median OS time in 1p/19q codeleted HGO patients (132 months; 95% CI, 77.4 months to upper limit undefined) compared with patients without codeletion (49.6 months; 95% CI, 33.1 to 86.8 months; $P < .0001$).

Chromosomal abnormalities, including 1p, 19q, and 10q deletions, *EGFR* amplification, 1p/19q codeletion, and combined *EGFR* amplification/10q deletion, were each highly associated with OS for all HGG patients ($P \leq .003$) but did not reach statistical significance within individual diagnostic categories ($P \geq .12$; Table 2).

Multivariate Analysis of Prognostic Factors

Because both necrosis (any type) and PPN alone were significant prognostic factors in AOA, we hypothesized that these tumors could be substratified (modified grading scheme), with necrosis (any type or

PPN) distinguishing grade 4 mixed oligoastrocytomas (MOA4) from grade 3 mixed oligoastrocytomas (MOA3). As shown in Table 3, both modified grading factors were significant in mixed tumors ($P \leq .028$). However, prognostic accuracy (C index) was slightly higher for grade based on any type of necrosis (0.72) than for either WHO 2000 grading (0.69) or PPN (0.70). Furthermore, more of the variability in OS was captured in the model based on age and necrosis (31%) than in models containing either age alone (WHO 2000, 23%) or age and PPN (29%). 1p/19q codeletion did not quite reach statistical significance in any of the three AOA models ($P = .17$ to $.26$). In contrast, age and 1p/19q codeletion were significant independent prognostic factors in AO ($P \leq .056$; Table 3).

A multivariate comparison of the WHO 2000 versus modified grading schemes was conducted with the entire HGG cohort (Table 3). Age, grade, and surgery type were included in these two models, but cytogenetic factors were omitted because of limited availability of 1p/19q data (54% of all HGGs). All three factors were significant in both models ($P < .001$). Both models were equally accurate and accounted for similar percentages of variation in OS, but the hazard ratio (HR) for grade was greater for the modified approach (4.3; 95% CI, 3.4 to 5.6) than the WHO 2000 scheme (3.8; 95% CI, 3.0 to 4.8).

Kaplan-Meier curves using the WHO 2000 criteria are shown in Figure 3A. Median OS times of patients with GBM, AA, AOA, and AO were 9.8 months (95% CI, 8.9 to 11.3 months), 40.1 months (95% CI, 26.8 months to upper limit undefined), 41.9 months (95% CI, 33.1 to 86.9 months), and 86.8 months (95% CI, 74.5 months to upper limit

undefined), respectively. Three statistically separable curves were evident because all pairwise comparisons among diagnostic entities were significant ($P < .0001$) except AA versus AOA ($P = .73$). In contrast, the modified scheme (Fig 3B) yielded four statistically separable survival curves (GBM, MOA4, AA, and AO; $P \leq .038$ for all pairwise comparisons), and a trend towards statistical significance was evident for MOA3 versus AO ($P = .21$).

The significant survival advantage for patients with 1p/19q codeleted HGO (Appendix Fig A5B) prompted a multivariate analysis of age, grade (WHO 2000 v the modified scheme), oligodendroglial histology (HGO v HGA), and 1p/19q codeletion in the subset of genetically analyzed patients ($n = 570$). As shown in Table 3, age and 1p/19q codeletion were significant independent prognostic factors ($P < .001$). Modified grading was statistically significant (HR = 2.1; 95% CI, 1.4 to 3.3; $P < .001$), whereas WHO 2000 grading only showed a trend towards significance (HR = 2.1; 95% CI, 0.9 to 4.7; $P = .073$). Moreover, the presence of an oligodendroglial component (HGO v HGA) was significant when analyzed in the context of the modified scheme (HR = 0.6; 95% CI, 0.4 to 0.9; $P = .026$) but not the WHO 2000 scheme (HR = 0.8; 95% CI, 0.3 to 1.7; $P = .49$).

DISCUSSION

To our knowledge, this represents the largest retrospective analysis of both histopathologic and molecular genetic features of HGG since the

Table 3. Multivariate Comparison of Grading Schemes

| Prognostic Factor | All HGG (n = 1,070) | | AOA (n = 213) | | AO (n = 204) | FISH Patients (n = 570) | |
|--|------------------------|------------|------------------|--------------------------|-----------------|----------------------------|-----------------------|
| | WHO 2000 | Modified | WHO 2000 | Modified Necrosis PPN | WHO 2000 | WHO 2000 | Modified, Necrosis |
| Age group: ≤ 40 , 40-60, ≥ 60 years | | | | | | | |
| HR | 2.0 | 2.0 | 2.6 | 2.4 | 2.5 | 2.9 | 2.2 |
| 95% CI | 1.7 to 2.2 | 1.7 to 2.3 | 1.7 to 4.0 | 1.5 to 3.7 | 1.6 to 3.9 | 1.6 to 5.2 | 1.8 to 2.8 |
| P | .001* | .001* | .001* | .001* | .001* | .001* | .001* |
| Surgery type | | | | | | | |
| HR | 0.6 | 0.6 | | | | | |
| 95% CI | 0.5 to 0.8 | 0.5 to 0.7 | | | | | |
| P | .001* | .001* | | | | | |
| Grade: 3 v 4 | | | | | | | |
| HR | 3.8 | 4.3 | | 2.2 | 2.3 | | 2.1 |
| 95% CI | 3.0 to 4.8 | 3.4 to 5.6 | NA | 1.2 to 3.8 | 1.1 to 4.9 | NA | 0.9 to 4.7 |
| P | .001* | .001* | | .006* | .028* | | .073* |
| 1p/19q codeletion | | | | | | | |
| HR | | | | | 0.41 | 0.3 | 0.4 |
| 95% CI | | | | | 0.16 to 1.02 | 0.2 to 0.6 | 0.2 to 0.7 |
| P | | | | | .056* | .001* | .001* |
| Oligodendroglial histology: HGO v HGA | | | | | | | |
| HR | | | | | | 0.8 | 0.6 |
| 95% CI | | | | | | 0.3 to 1.7 | 0.4 to 0.9 |
| P | | | | | | .49 | .026* |
| C index | 0.75 | 0.75 | 0.69 | 0.72 | 0.70 | 0.74 | 0.78 |
| R ² | 0.43 | 0.44 | 0.23 | 0.31 | 0.29 | 0.39 | 0.52 |

Abbreviations: HGG, high-grade glioma; AOA, anaplastic oligoastrocytoma; AO, anaplastic oligodendroglioma; FISH, fluorescence in situ hybridization; PPN, pseudopalisading necrosis; HR, hazard ratio; NA, not applicable; HGO, high-grade oligodendroglioma; HGA, high-grade astrocytoma; C index, prognostic accuracy; R², explained variation.

*Statistically significant ($P \leq .05$).

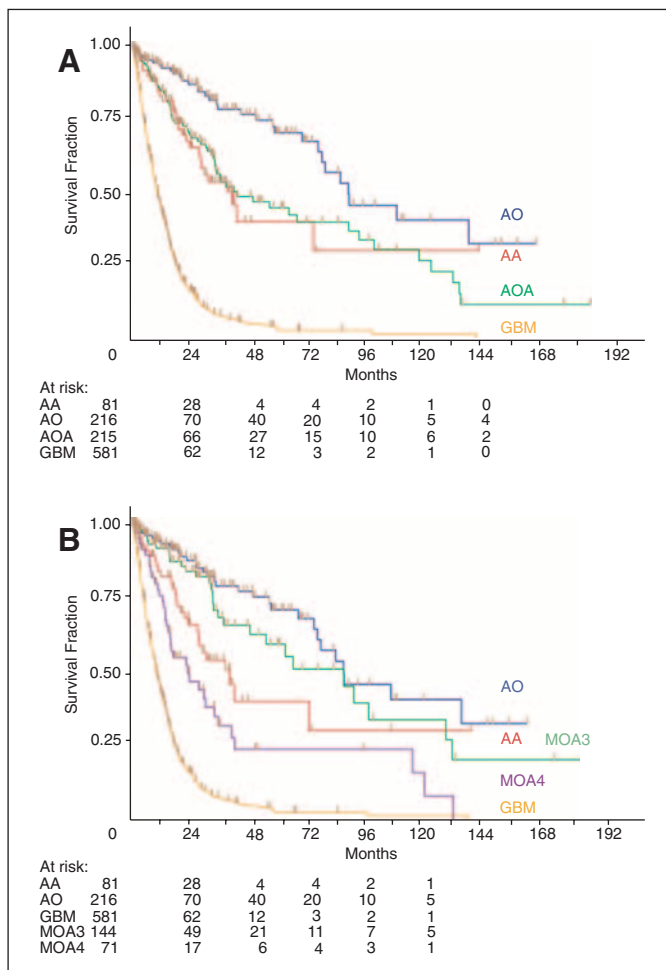


Fig 3. Kaplan-Meier overall survival (OS) curves for 1,093 HGG patients diagnosed by (A) WHO 2000 or (B) modified criteria. Median OS times were 9.8 months for glioblastoma multiforme (GBM), 22.8 months for grade 4 mixed oligoastrocytoma (MOA4), 40.1 months for anaplastic astrocytoma (AA), 41.9 months for anaplastic oligoastrocytoma (AOA), 86.8 months for anaplastic oligodendrogloma (AO), and 86.9 months for grade 3 mixed oligoastrocytoma (MOA3; log-rank, $P < .0001$). (A) AA and AOA and (B) AO and MOA3 were the only statistically nonsignificant pairwise comparisons ($P \geq .21$).

publication of the WHO 2000 classification scheme. Patient demographics and genetic data are consistent with prior publications. As detailed in the Appendix, therapeutic records were not available for most of the non-WUSM patients; therefore, a potential weakness of this study is that the effects of individual therapies on OS could not be further evaluated. However, an important new finding was that necrosis stratified AOA into two groups with distinct OS, independent of age and 1p/19q status. Median OS time for AOA was significantly shorter for tumors with necrosis than for tumors without necrosis ($P < .0001$) but was still considerably longer than the OS time of patients with conventional GBM ($P < .0001$). This finding is consistent with results of a phase III clinical trial of adjuvant procarbazine, lomustine, and vincristine in newly diagnosed HGO patients, which also identified necrosis as an independent prognostic factor.²¹ In the present study, PPN was likewise found to be a significant predictor of poor OS. However, use of any type of necrosis was preferable compared with PPN for AOA grading for the following reasons: it was more prevalent (33% v 15%, respectively), yielded slightly greater

diagnostic accuracy (C index, 0.72 v 0.70, respectively), accounted for more variation in OS (R^2 , 31% v 29%, respectively), and conformed to the approach currently used in grading HGA.

Based on these data, we propose the following modified classification of mixed HGGs, which is similar to the current WHO 2000 classification of HGA: a grade 3 variant (AOA, MOA3) without necrosis and a grade 4 variant with necrosis (MOA4). MOA4 has a worse prognosis than conventional MOA3 (WHO 2000 AOA) but a better prognosis than standard GBM, even in the absence of 1p/19q codeletions. The optimal terminology for this tumor type is unclear, although GBM with oligodendroglial features is one possibility that is already in common use. In line with the notion that GBM is an astrocytic tumor, this term would imply a grade 4 variant with a mixture of both cell types.

In contrast to AOA, neither necrosis nor PPN were found to be independent prognostic factors in AO. Similar findings were evident in a recently published retrospective series of 98 AOs.²² Although additional follow-up on the most recently diagnosed AO patients (2000 to 2005) will be required to make a definitive conclusion, these preliminary data suggest that such patients retain a favorable prognosis despite these otherwise ominous features and, in line with the current WHO scheme, support the existence of only a single high-grade pure oligodendroglioma (AO, WHO grade 3). In diagnostically challenging patients, genetic studies can be useful for distinguishing AO (1p/19q codeletion) from SCA (*EGFR* amplification, 10q deletion). Whereas the latter chromosomal abnormalities do not provide prognostic information independent of histology and grade, 1p/19q codeletion enhances both the diagnostic accuracy of AO and provides independent prognostic information.

Of additional interest, patients in the current series with HGO lacking codeletion still had a more favorable outcome than patients with HGA of similar grade, emphasizing the importance of both accurate histologic classification and ancillary genetic testing. For example, the median OS time of 5.7 years (95% CI, 2.2 years to upper limit undefined) for AO without deletions was considerably higher than the 1 to 3 years reported previously.^{21,23} This difference supports the notion that OS estimates for HGO without deletions have been artificially lowered by the inadvertent inclusion of SCA.^{15,16} Additionally, our MOA3 and MOA4 cohorts without deletions survived longer (median OS time, 55 and 22.8 months, respectively; 95% CI, 33.4 to 97.1 and 14.9 to 42.0 months, respectively) than AA (median OS time, 40 months; 95% CI, 26.8 months to upper limit undefined) and conventional GBM patients undergoing resection (median OS time, 11.7 months; 95% CI, 10.2 to 13.2 months). In fact, these differences are even greater if one considers that the application of pure astrocytoma grading criteria to MOA3 would have resulted in an alternate diagnosis of GBM in 66% of patients due to the presence of EP (Table 1). These data argue against the opinions of some that oligodendroglial tumors lacking 1p/19q deletions are merely astrocytomas and that the diagnosis of a mixed glioma should be avoided whenever possible. Because independent prognostic value was noted for oligodendroglial histology on multivariate analysis of the modified grading cohort with FISH data (Table 3), this further supports the contention that cytogenetic features alone cannot replace histologic definitions of oligodendroglial differentiation, despite the inherent subjectivities of the latter.

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Acknowledgment

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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