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The Misclassification of Diffuse Gliomas: Rates and Outcomes

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Abstract

Background: The integrated histopathological and molecular diagnoses of the 2016 WHO classification of CNS tumors have revolutionized patient care by improving diagnostic accuracy and reproducibility; however, the frequency and consequences of misclassification of histologically-diagnosed diffuse gliomas are unknown.

Methods: Patients with newly-diagnosed ICD-O-3 histologically-encoded diffuse gliomas from 2010-2015 were identified from the National Cancer Database—the misclassification rates and overall survival (OS) of which were assessed by WHO grade and 1p/19q status. Additionally, misclassification rates by IDH, ATRX, and p53 statuses were examined in an analogous multi-institutional cohort of registry-encoded diffuse gliomas.

Results: Of 74,718 diffuse glioma patients, only 74.4% and 78.8% of molecularly-characterized WHO grade II and III oligodendrogliomas were in fact 1p/19q-codeleted. Additionally, 28.9% and 36.8% of histologically-encoded grade II and III "oligoastrocytomas", and 6.3% and 8.8% of grade II and III astrocytomas had 1p/19q-codeletion, thus molecularly representing

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oligodendrogliomas if also IDH-mutant. OS significantly depended on accurate WHO grading and 1p/19q status.

Conclusions: Based on 1p/19q, IDH, ATRX, and p53, the misclassification rates of histologically-encoded oligodendrogliomas, astrocytomas, and glioblastomas are ~21-35%, ~6-9%, and ~9%, respectively; with significant clinical implications. Our findings suggest that when compared to historical histology-only classified data—in national registry, as well as, institutional databases—there is the potential for false-positive results in contemporary trials of molecularly-classified diffuse gliomas, which could contribute to a seemingly positive phase II trial (based on historical comparison) failing at the phase III stage. Critically, findings from diffuse glioma clinical trials and historical cohorts using prior histology-only WHO schemes must be cautiously re-interpreted.

Keywords

Diffuse Glioma; Molecular Classification; Astrocytoma; Oligodendroglioma; Glioblastoma; Outcomes

INTRODUCTION

The molecular characterization for a spectrum of cancer types has revolutionized oncologic diagnostics and therapeutics and is increasingly becoming a critical component of clinical care for cancer patients. In 2016, the World Health Organization (WHO) histological classification of tumors of the central nervous system (CNS; 4th edition) was revised to synthesize our growing understanding of the molecular basis of CNS tumors—principally made possible by advances in next-generation sequencing and gene expression analysis—with histology into a diagnostic and prognostic classification scheme that is more objective and accurate.(1) The changes have been particularly groundbreaking for diffuse gliomas (*i.e.* gliomas with a diffusely infiltrative pattern of growth) for which *IDH1/IDH2* gene mutational status and the presence or absence of chromosomal whole-arm codeletion of 1p and 19q have important prognostic and therapeutic implications.(2) The accurate diagnosis of diffuse gliomas faces several challenges, including an overlapping spectrum of histomorphologies and substantial intratumoral histologic heterogeneity. These challenges can commonly be compounded by tumor under-sampling and the limited specimen available for evaluation due to the surgical complexity of safely accessing many of these tumors. As a result, relying on histology alone for the classification of diffuse gliomas can lead to erroneous diagnoses. In addition to CNS tumors, molecular markers are now critical for the accurate diagnosis and treatment of hematopoietic and lymphoid, soft tissue and bone, renal, melanoma, lung, and various other malignancies; each accompanied by major recent revisions to their WHO classification schema.(3–5)

In an effort to systematically collect cancer patient data in the United States, including that of glioma patients, cancer registry reporting standards were developed and employed by North American Association of Central Cancer Registries, including the American College of Surgeons' National Cancer Database program (NCDB), the National Cancer Institute's Surveillance, Epidemiology, and End Results program, and the Center for Disease Control's National Program for Cancer Registries and Central Brain Tumor Registry of the United

States.(6–8) These cancer registries, crucially, have vastly improved our understanding of cancer epidemiology, but have lagged in incorporation of key molecular drivers for a range of cancer types. U.S. cancer registries encode cancer diagnoses using WHO/IARC International Classification of Diseases for Oncology (ICD-O) v3—the codes and histologic definitions of which were defined in the *WHO International Histological Classification of Tumours* "Blue Books" published through 2010 (*i.e.* through the 4th edition).(9) For CNS tumors, the 4th edition was published in 2007 and classified diffuse gliomas solely based on their histological appearances.(10) Consequently, cancer registry data cannot presently differentiate between IDH-mutant and IDH-wildtype diffuse gliomas. Additionally, many of the key clinical trials of diffuse gliomas, as well as studies using historical cohorts, relied on older histology-only classification schemes. Nevertheless, the magnitude of potential coding errors and diagnostic misinterpretations in these databases are not fully appreciated or taken into consideration.(11–27) Herein, we examine the accuracies of cancer registry-encoded diffuse gliomas by WHO grade and 1p/19q status, in addition to IDH, ATRX and p53 status; we explore the associations between misclassification, tumor characteristics, and survival outcomes; and we demonstrate the important need for incorporating molecular data into registries, historical cohorts, and clinical trials of cancer patients.

METHODS

The NCDB, a hospital-based nationwide cancer database, comprises >70% of newly-diagnosed cancers in the U.S. Patients with newly-diagnosed diffuse gliomas between 2010 and 2015 were identified by ICD-O-3 histological codes coupled with a "/3" malignant behavior code as presented in Table 1, inclusive of all brain site codes (*i.e.* 71.0-71.9). Patients were excluded if previously diagnosed with cancer or if they were diagnosed at an index institution but received treatment entirely elsewhere. Primary brain-specific factors included the loss of heterozygosity (LOH)/deletion of chromosome arms 1p and 19q (first encoded in 2010) and WHO grade. Cases were designated as 1p/19q-codeleted if both arms were coded for LOH/deletion, although the methodology utilized for this determination was not recorded in the NCDB.

In order to evaluate the accuracy of diagnoses based on additional molecular alterations, 150 diffuse glioma patients (25 per year, from 2010 to 2015) were randomly queried from the cancer registry-submitted data from each of three tertiary care institutions (Brigham and Women's Hospital, Dana-Farber Cancer Center, and Massachusetts General Hospital) using ICD-O-3 codes. The neuropathologist-assigned integrated diagnosis and WHO grade were evaluated for each of the 450 patients, along with the status of 1p/19q, IDH, ATRX, and p53, as determined by immunohistochemistry and/or molecular assays (*e.g.* next generation sequencing panels, array comparative genomic hybridization, and fluorescence *in situ* hybridization).

Statistical Analyses

The clinicopathologic factors of age at diagnosis, histology, tumor location, 1p/19q status, and WHO grade were summarized and then compared by χ^2 test, t-test, and ANOVA as appropriate. The primary outcome was concordance rate between the histological

classification of diffuse gliomas and their encoded WHO grade and 1p/19q molecular status. Unadjusted differences in overall survival (OS) were estimated by Kaplan-Meier methods and compared by log-rank tests. The NCDB excludes survival data for patients diagnosed in the final year of the dataset due to limited follow-up, which for this release was 2015. OS was measured from date of diagnosis with the endpoint assigned as date of death, with patients censored at the date of most recent follow-up. The end date for follow-up in this release was 12/31/2015. A secondary outcome was the concordance rate between the histological classification of institutional cases included in the cancer registry and their corresponding neuropathologist-assigned integrated histological and molecular diagnoses. Statistical analyses were conducted using STATA (v. 14.2, StataCorp), with 2-sided p-values <0.05 denoted as significant. This study was approved by the Partners HealthCare institutional review board (2015P002352).

RESULTS

Diffuse Gliomas Often Demonstrate Discordance between Histological Diagnosis and WHO Grade

From 2010 to 2015 NCDB data, there were 74,718 patients newly-diagnosed with diffuse gliomas following exclusion (Table 1). For ICD-O-3-encoded diffuse oligodendrogliomas and astrocytomas (*i.e.* grade II), only 86.3% (n=2,742) and 65.7% (n=2,748) were coded as WHO grade II (Table 2). In anaplastic oligodendrogliomas and astrocytomas (*i.e.* grade III), the concordance rates between ICD-O-3 coding and WHO grade improved to 90.0% (n=1,361) and 90.4% (n=5,090), respectively. The age at diagnosis and OS significantly differed between WHO grades for each ICD-O-3-encoded oligodendroglioma and astrocytoma group: diffuse oligodendrogliomas and astrocytomas that were in fact coded as WHO grade II demonstrated significantly improved OS and younger age at diagnosis than those that were coded as WHO grade III (both p<0.001). The highest concordance rate (98.7%, n=39,828) between ICD-O-3 coding and WHO grade was observed in glioblastomas (GBMs, grade IV).

Diffuse Gliomas Often Demonstrate Discordance between Histological Diagnosis and 1p/19q-codeletion Status

The 2016 WHO recognized that 1p/19q-codeletion in combination with IDH mutation is a pathognomonic feature of oligodendrogliomas, with clinical guidelines therefore recommending molecular testing for all diffuse gliomas. For cases with known 1p/19q status, only 74.4% (n=1,001) and 78.8% (n=523) of WHO grade II diffuse oligodendrogliomas and WHO grade III anaplastic oligodendrogliomas (as encoded by both ICD-O-3 histology and WHO grade), respectively, were truly 1p/19q-codeleted; suggesting that the remainder were likely inappropriately encoded astrocytomas or non-diffuse glioma subtypes (Table 3). Correspondingly, the histologically-encoded oligodendrogliomas with confirmed 1p/19q-codeletion were associated with significantly younger age at diagnosis, greater predilection for the frontal lobe, and improved OS than histologically-encoded “oligodendrogliomas” with retained 1p/19q (all p<0.05). In our multi-institutional cohort, when integrating 1p/19q, IDH, ATRX, and p53 molecular statuses, 23.1% (n=6) of registry-encoded WHO grade II diffuse oligodendrogliomas were reclassified: 3.8% as WHO grade

II diffuse astrocytoma IDH-mutant and 19.2% as WHO grade IV glioblastoma IDH-wildtype—often with an oligodendroglioma-like histological component (Table 4). Likewise, 35.0% (n=7) of registry-encoded WHO grade III anaplastic oligodendrogliomas were also reclassified: 15.0% as WHO grade III anaplastic astrocytoma IDH-mutant, 5.0% as WHO grade III anaplastic astrocytoma IDH wild-type, 10.0% as WHO grade IV glioblastoma IDH-wildtype (also commonly with an oligodendroglioma-like component), and 5.0% as a high-grade glioma without 1p/19q or IDH status.

In histologically-encoded "mixed gliomas" (*i.e.* oligoastrocytoma), 28.9% (n=163) of WHO grade II and 36.8% (n=168) of WHO grade III tumors, respectively, had 1p/19q-codeletion, therefore likely representing oligodendrogliomas; whereas the remaining 1p/19q-retained cases were likely astrocytomas (Table 3). Within our multi-institutional cohort, when incorporating the integrated molecular status, 92.9% (n=39) of registry-encoded "mixed gliomas" were reclassified as either WHO grade II oligodendroglioma 1p/19-codeleted and IDH-mutant (9.5%), diffuse astrocytoma IDH-mutant (21.4%), and diffuse astrocytoma IDH-wildtype (4.8%), or WHO grade III anaplastic oligodendroglioma 1p/19q-codeleted and IDH-mutant (14.3%), anaplastic astrocytoma IDH-mutant (23.8%), and anaplastic astrocytoma IDH-wildtype (19.0%). Similarly, 47.8% (n=11) of registry-encoded "malignant gliomas" (*i.e.* high-grade gliomas) could be re-assigned to a 2016 CNS WHO subtype when integrating molecular status.

1p/19q status was reported in only a minority of histologically-encoded WHO grade II diffuse astrocytomas and WHO grade III anaplastic astrocytomas, but of these cases, 6.3% (n=34) and 8.8% (n=72), respectively, demonstrated 1p/19q-codeletion and would now be reclassified as oligodendrogliomas in the presence of an IDH mutation (Table 3). Additionally, applying integrated molecular approaches to our multi-institutional registry-encoded WHO grade II diffuse astrocytomas revealed that 41.7% (n=15) were IDH-wildtype and 36.1% (n=13) were IDH-mutant, and 2.8% (n=1) were in fact *BRAFV600E*-mutant (IDH-wildtype) pilocytic astrocytomas; whereas for the WHO grade III anaplastic astrocytomas, 60.0% (n=45) were re-classified as IDH-wildtype and 26.7% (n=20) were IDH-mutant. Of the encoded GBMs with reported 1p/19q status, 9.4% (n=227) displayed 1p/19q-codeletion (and would be reclassified as anaplastic oligodendrogliomas if IDH-mutant); these were associated with significantly improved OS compared to the encoded GBMs with retained 1p/19q. Among the multi-institutional registry-encoded GBMs, 3.7% were found to be IDH-mutant, with another 0.9% and 0.4% found to be the giant cell and gliosarcoma variants of GBM IDH-wildtype.

DISCUSSION

WHO 2016 molecular classification for diffuse gliomas

The 2016 WHO made several significant changes to the classification of diffuse gliomas, primarily by integrating *IDH1/IDH2* mutation and 1p/19q-codeletion status with histology into a diagnostically and prognostically more accurate scheme (Table 5). The most frequent isocitrate dehydrogenase (IDH) driver mutation in diffuse glioma, occurring in approximately 90% of cases, is an arginine to histidine missense mutation at codon 132 of the *IDH1* gene, which can be reliably detected with an IDH1 R132H immunohistochemical

stain.(28,29) In IDH-mutant gliomas, 1p/19q-codeletion is pathognomonic for oligodendroglioma. This biomarker and *MGMT* promoter methylation status are the only brain cancer-specific molecular data encoded in cancer registry data as of 2010. Data on IDH mutation status are notably not yet reported in the U.S. cancer registries, but have started to be collected in 2018. Grading of diffuse gliomas was made on the basis of histologic features such as mitotic activity, tumor necrosis, and microvascular proliferation, with these conventions retained in the 2016 revised 4th edition. Herein, we examine the accuracies of cancer registry-encoded diffuse gliomas by WHO grade and 1p/19q status, and demonstrate how misclassification may impact survival outcome estimates.

Diffuse astrocytoma (WHO grade II) and anaplastic astrocytoma (WHO grade III) are 1p/19q-retained and can be further subclassified on the basis of their IDH status: mutant, wildtype, or NOS (Table 4). The IDH status has important prognostic value, as IDH-mutant infiltrating astrocytomas are associated with a better survival, as well as increased sensitivity to chemoradiation.(30,31) The majority of WHO grade II and III infiltrating astrocytomas harbor IDH mutations. These IDH-mutant astrocytomas almost always have concurrent inactivating *TP53* and *ATRX* mutations. The Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy—Not Official WHO (cIMPACT-NOW) was established in 2016 to translate the 2016 CNS WHO criteria into diagnostic guidelines and recommends that for diffuse gliomas with astrocytoma-like histology, demonstrating IDH1 (R132H) mutation with loss of nuclear ATRX expression and/or strong diffuse p53 expression by immunohistochemistry is sufficient for rendering a diagnosis of IDH-mutant astrocytoma, without necessitating 1p/19q testing.(32–34) If the immunohistochemical results or clinicopathologic features are non-canonical for IDH-mutant astrocytomas, then additional testing for alternative IDH mutations, other molecular hallmarks, or chromosomal alterations may be indicated. A subset of tumors that were initially diagnosed as grade II or grade III IDH-wildtype infiltrating astrocytomas can be reclassified after molecular testing as other glioma subtypes, including pilocytic astrocytomas, gangliogliomas, glioblastomas, and diffuse midline gliomas (H3 K27M-mutant).(35) We found that 1p/19q status was only reported in a minority of astrocytomas, but that a significant subset had 1p/19q-codeletion, likely representing miscoded oligodendrogliomas in most examples (*i.e.*, if IDH-mutant). Additionally, the integrated molecular testing of multi-institutional registry-encoded astrocytomas demonstrated that the prognostically-relevant IDH status varied substantially.

Oligodendroglioma (WHO grade II) and anaplastic oligodendroglioma (WHO grade III) are IDH-mutant and 1p/19q-codeleted (Table 4).(36,37) In contrast to IDH-mutant astrocytomas, oligodendrogliomas often have *TERT* promoter mutations, and *p53* and *ATRX* genetic aberrations are not characteristic. The 2016 CNS WHO and cIMPACT-NOW recommend that all diffuse gliomas with oligodendroglioma-like histology or mixed oligodendroglioma-astrocytoma histology be evaluated for 1p/19q-codeletion and IDH status. In clinical trials, IDH-mutant 1p/19q-codeleted oligodendrogliomas are associated with significantly improved response to chemotherapy, as compared to IDH-mutant and IDH-wildtype astrocytomas.(38–40) Herein, only 74% and 79% of grade II and III oligodendrogliomas, respectively, were in fact coded as 1p/19q-codeleted. These codeleted cases were associated with significantly younger age, more frequent localization to the frontal lobe, and more favorable OS as compared to the 1p/19q-retained subset of miscoded

astrocytomas or other glial tumors. The differences in clinical characteristics and outcome between 1p/19-codeleted and 1p/19q-retained gliomas in this cohort highlight the importance of accurate integration of molecular data with histology. Furthermore, when 1p/19q, IDH, ATRX, and p53 statuses were incorporated, we observed similar rates of re-classification in our multi-institutional cases of registry-encoded oligodendrogliomas.

Importantly, under the 2016 WHO scheme, a diagnosis of oligoastrocytoma should be exceedingly rare, reserved for instances in which the tumor demonstrates distinct areas with histologic and genetic features of astrocytoma and oligodendroglioma, respectively.(41,42) Instead, nearly all diffuse gliomas with mixed astrocytic and oligodendroglial morphology can be reclassified as either astrocytomas or oligodendrogliomas when incorporating molecular and cytogenetic data.(43) For example, we found that 29% and 37% of WHO grade II and III histologically-encoded “oligoastrocytomas” had 1p/19q-codeletion, therefore likely representing grade II and III oligodendrogliomas, assuming that they also had IDH mutations. In our multi-institutional series, 93% and 48% of registry-encoded “oligoastrocytomas” and “malignant gliomas”, respectfully, could be re-assigned to a 2016 CNS WHO subtype when integrating molecular status.

In key trials of chemotherapy (*e.g.* RTOG9802 trial of radiotherapy combined with procarbazine, lomustine, and vincristine [NCT00003375] and RTOG0424 trial of radiotherapy combined with temozolomide [NCT00114140]) and radiotherapy (*e.g.* EORTC22845 timing trial and NCCTG/RTOG/ECOG dose trial) for grade II diffuse gliomas, tumors were classified only histologically as oligodendroglioma, oligoastrocytoma, or astrocytoma, and 1p/19q status was not addressed in survival analyses.(44–47) Based on our results, up to 29% of “oligoastrocytomas”, approximately 6% of “astrocytomas”, and only 74% of “oligodendrogliomas” in these trials would have likely represented WHO grade II 1p/19q-codeleted oligodendrogliomas—if also IDH mutant—and thus would have been associated with improved OS, as also suggested by the improved progression-free survival by 1p/19q-codeleted status in EORTC22033-26033 of temozolomide versus radiotherapy (NCT00182819).(38) Additionally, our findings suggest that grade II diffuse “astrocytomas” in these trials actually comprised a combination of prognostically-distinct WHO grade II IDH-mutant and IDH-wildtype diffuse astrocytomas, as well as suggesting that up to 3% of the diffuse “astrocytomas” may have in fact represent pilocytic astrocytomas. Correspondingly, updated subgroup analyses by 1p/19q status in clinical trials for grade III diffuse gliomas (*e.g.* EORTC26951 and RTOG9402 [NCT00002569] trials of radiotherapy combined with procarbazine, lomustine, and vincristine) demonstrated improved OS with 1p/19q-codeletion, which was reflected in our results: 79% and 49% 5-year OS for 1p/19q-codeleted and non-codeleted WHO grade III gliomas, respectively.(39,40)

Glioblastoma (WHO grade IV) can also be subclassified by IDH status (Table 4). However, unlike the lower grade infiltrating astrocytomas, most GBMs (*i.e.* >90%) are IDH-wildtype. IDH-wildtype GBMs frequently have *TERT* promoter mutations, recurrent copy number alterations including polysomy 7 and monosomy 10 (with loss of *PTEN*), amplification of *EGFR*, and loss of tumor suppressors *CDKN2A* and *CDKN2B*. IDH-mutant GBMs, representing approximately 4% of registry-encoded GBMs in our cohort, may progress from grade II or III diffuse astrocytomas and are associated with a better prognosis and younger

age at time of diagnosis compared to IDH-wildtype GBMs.(28,48,49) The distinction between IDH-mutant and IDH-wildtype GBMs is not permitted by current cancer registry encoding. We found that only a fraction of encoded "GBMs" included 1p/19q status, of which 9% were 1p/19q-codeleted and were associated with significantly improved OS. These cases may have been previously interpreted within the now-defunct "GBM with oligodendroglial component" category (*i.e.*, the grade IV counterpart of oligoastrocytoma), but would now be more appropriately reclassified as WHO grade III anaplastic oligodendrogliomas when IDH-mutant.(50)

In 2018, NAACCR began incorporating all of the 2016 WHO ICD-O coding and definitions for diffuse gliomas, including the new entity diffuse midline glioma characterized by the H3 K27M mutation (Table 4); although incorporation of registry data into databases for public analysis usually lags by approximately 3 years. Additionally, IDH status will be collected as a site-specific variable. Together, these crucial updates will permit cancer registries to more accurately stratify diffuse glioma patients, which in turn will enable clinically-relevant evaluations of contemporary glioma epidemiology and management.

Limitations

The cancer registry-based databases, although extensive in their scope, are constrained by several limitations. For CNS tumors, molecular data are limited only to *MGMT* promoter methylation status and 1p/19q status, with IDH status notably lacking despite now being essential for accurate diagnosis. To help address this challenge, we included the diagnostic accuracy results for 450 registry-encoded diffuse gliomas from three tertiary care institutions, based on canonical 1p/19q, IDH, ATRX, and p53 statuses. Also, although 1p and 19q LOH variables are included, registry data lack details about the diagnostic methodologies used: for instance, it is known that only whole arm deletions correlate with the biologically favorable oligodendrogliomas; however, smaller deletions are seen in a subset of astrocytic tumors, which might be construed as a false-positive in FISH assays that only assess one probe per arm. The databases additionally only include data from a patient's initial presentation and initial treatment courses, precluding evaluation of subsequent treatments, progression, recurrence, or metastasis.

Conclusions

Cancer registries are critical to our understanding of the epidemiology, oncogenesis, and treatment of a wide spectrum of tumor types. However, many diffuse gliomas are inappropriately classified, with significant implications for OS estimates. Based on 1p/19q, IDH, ATRX, and p53 statuses, the overall rates of misclassified oligodendrogliomas, astrocytomas, and GBMs based on histology-only classification are approximately 21-35%, 6-9%, and 9%, respectively. Our rapidly expanding understanding of the genetic landscape of diffuse gliomas highlights the importance of integrating histology with molecular data for diagnosis. Our findings suggest that when compared to historical histology-only classified data, there is the potential for false-positive results in contemporary therapeutic trials of molecularly-classified diffuse gliomas. These issues may be true for institutional historical databases, as well as national registry-based sources, and could also contribute to a seemingly positive phase II trial (based on historical comparison) failing at the phase III

stage. Critically, the findings from diffuse glioma clinical trials, registry-based studies, and historical cohorts using prior histology-based WHO classification schemes must be cautiously re-interpreted and tempered in light of the integrated diagnoses defined in the revised 2016 WHO. Particularly for institutional historical comparison groups, we recommend that investigators consider using immunohistochemical evaluation (and chromosomal/molecular testing if indicated) of archival formalin-fixed paraffin-embedded samples in order to appropriately re-classify historical cohorts. Our results highlight the pressing need to design preclinical investigations, clinical trials, and national cancer registries moving forward that incorporate key molecular data across all cancer types.

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Statement of Translational Relevance:

The molecular characterization for a spectrum of cancer types—principally made possible by advances in next-generation sequencing and gene expression analysis—has revolutionized oncologic diagnostics and therapeutics, and is increasingly becoming a critical component of clinical care for cancer patients. The changes have been particularly groundbreaking for diffuse gliomas in which *IDH1/IDH2* gene mutational status and the presence of chromosomal codeletion of 1p/19q have important prognostic and therapeutic implications. Our findings suggest that when compared to historical histology-only classified data, there is the potential for false-positive results in contemporary therapeutic trials of molecularly-classified diffuse gliomas. Critically, findings from diffuse glioma clinical trials, registry-based studies, and historical cohorts using prior WHO schemes based on histology alone must be cautiously re-interpreted. Our results highlight the pressing need to design preclinical investigations, clinical trials, and national cancer registries moving forward that incorporate key molecular data across all cancer types.

TABLE 1.

Diffuse Glioma ICD-O-3 Coding and Histologies Presently Available in Registry-Derived Databases from 2010 to 2015 (*i.e.* pre-WHO 2016 Classification)

ICD-O-3 Code/Behavior	ICD-O-3 Histology	n	% with WHO grade	% with 1p/19q codeletion data
9380/3	Glioma, malignant	3,956	23.2	4.0
9381/3	Gliomatosis cerebri	217	49.8	6.9
9382/3	Mixed glioma	2,688	94.8	43.0
9400/3	Astrocytoma, NOS	5,135	81.4	11.9
9401/3	Astrocytoma, anaplastic	5,977	94.2	15.2
9410/3	Protoplasmic astrocytoma	20	95.0	10.0
9411/3	Gemistocytic astrocytoma	436	93.3	12.2
9420/3	Fibrillary astrocytoma	924	93.2	8.7
9440/3	Glioblastoma, NOS	48,730	82.8	5.4
9441/3	Giant cell glioblastoma	422	90.3	5.2
9442/3	Gliosarcoma	1,177	89.2	3.7
9450/3	Oligodendroglioma, NOS *	3,456	91.9	44.9
9451/3	Oligodendroglioma, anaplastic	1,580	95.7	46.7
	Total	74,718	81.8	10.7

"/3" behavior code designates a malignant tumor; NOS: Not otherwise specified;

* In ICD-O-3, this diagnosis is synonymous with oligodendroglioma, diffuse.

TABLE 2.

Discordance between ICD-O-3 Histological Diagnosis and WHO Grade in Diffuse Gliomas

ICD-O-3 Histology	Have WHO grade (n)	WHO grade	n	%	Age (years)			Overall Survival (months)		
					Median	IQR	*p-value**	5 yr-OS	95% CI	*p-value***
Diffuse OG	3,176	I	51	1.6	36	(22-52)	***<0.001***	87.2	(71.9-94.5)	***<0.001***
		II	**2,742**	**86.3**	41	(32-51)		88.1	(86.1-89.8)	
		III	241	7.6	47	(36-57)		61.2	(51.2-69.8)	
		IV	142	4.5	56	(46-66)		31.2	(22.5-40.2)	
Anaplastic OG	1,512	I	2	0.1	46	(42-50)	***0.01***	no observations		***<0.001***
		II	25	1.7	39	(28-54)		65.3	(34.6-84.3)	
		III	**1,361**	**90.0**	48	(38-58)		69.6	(65.9-72.9)	
		IV	124	8.2	51	(41-60)		37.9	(25.0-50.7)	
Diffuse AC	4,182	I	170	4.1	31	(18-49)	***<0.001***	77.5	(68.8-84.1)	***<0.001***
		II	**2,748**	**65.7**	40	(29-55)		63.8	(61.4-66.0)	
		III	760	18.2	52	(38-64)		29.3	(25.7-32.9)	
		IV	504	12.1	62	(52-70)		9.8	(7.1-13.0)	
Anaplastic AC	5,628	I	5	0.1	41	(34-72)	***<0.001***	53.3	(6.8-86.3)	***<0.001***
		II	51	0.9	39	(27-58)		57.1	(36.1-73.5)	
		III	**5,090**	**90.4**	50	(35-64)		33.3	(31.5-35.2)	
		IV	482	8.6	54	(40-67)		18.8	(14.4-23.7)	
Glioblastoma	40,333	I	83	0.2	62	(51-71)	***0.008***	10.6	(2.7-24.9)	*0.08*
		II	66	0.2	60	(46-69)		10.8	(2.5-26.0)	
		III	356	0.9	62	(53-72)		9.6	(5.7-14.5)	
		IV	**39,828**	**98.7**	62	(54-71)		7.6	(7.1-8.0)	

** p-value from a log-rank test using Kaplan-Meier survival analysis

* p-value from an ANOVA test;

OG: oligodendroglioma, AC: astrocytoma, IQR: interquartile range, OS: overall survival, CI: confidence interval;

TABLE 3.

Discordance between ICD-O-3 Histological Diagnosis and 1p/19q-codeletion Status in Diffuse Gliomas

WHO grade	ICD-O-3 Histology	Have 1p/19q data (n)	1p/19q-codeleted			Age (years)			Male		Frontal lobe		Overall Survival (months)		
				n	%	Median	IQR	*p-value**	%	*p-value***	%	*p-value***	5yr-OS	95% CI	*p-value****
II	**Diffuse OG**	1,345	Yes	1,001	74.4	39	(29-49)	***<0.001***	57.6	*0.44*	74.8	***<0.001***	90.9	(87.4-93.4)	***0.01***
			No	344	25.6	42	(33-51)		55.2		58.2		84.9	(78.6-89.5)	
	Diffuse AC	544	Yes	34	6.3	36	(29-46)	*0.43*	52.9	*0.77*	57.7	*0.72*	81.4	(57.5-92.6)	*0.85*
			No	510	93.8	39	(29-51)		55.5		53.7		70.6	(62.1-77.6)	
III	**Mixed Glioma**	564	Yes	163	28.9	35	(29-45)	***0.001***	46.6	***0.003***	76.5	***<0.001***	83.8	(75.0-89.7)	*0.09*
			No	401	71.1	43	(32-51)		60.4		58.8		74.7	(67.8-80.3)	
	Anaplastic OG	664	Yes	523	78.8	44	(32-58)	***0.05***	59.9	*0.95*	76.9	***0.001***	78.5	(72.5-83.2)	***<0.001***
			No	141	21.2	48	(38-57)		59.6		62.9		48.6	(35.4-60.6)	
	Anaplastic AC	815	Yes	72	8.8	42	(31-56)	*0.10*	47.2	*0.23*	51.0	*0.10*	53.7	(34.5-69.6)	*0.86*
			No	743	91.2	47	(33-57)		54.6		52.9		48.5	(42.6-54.1)	
	Mixed Glioma	456	Yes	168	36.8	41	(31-55)	*0.39*	52.4	*0.13*	74.2	*0.17*	72.6	(63.5-79.8)	***0.004***
			No	288	63.2	44	(33-55)		59.7		63.9		56.8	(49.4-63.4)	
IV	**Glioblastoma**	2,427	Yes	227	9.4	60	(52-69)	***0.03***	63.9	*0.05*	43.4	*0.66*	18.1	(10.5-27.4)	***0.01***
			No	2,220	91.5	59	(49-68)		57.1		38.7		10.9	(8.70-13.4)	

*** p-value from a log-rank test using Kaplan-Meier survival analysis

** p-value from a chi-square test;

* p-value from a t-test;

OG: oligodendroglioma, AC: astrocytoma, IQR: interquartile range, OS: overall survival, CI: confidence interval;

TABLE 4.

Molecular Status of Multi-Institutional Registry-Derived Diffuse Glioma Patients from 2010 to 2015 (*i.e.* pre-WHO 2016 Classification)

Cases from Registry Data			Corresponding Data from Institutional Neuropathology Reports								
ICD-O-3 Code/ Behavior	**ICD-O-3 Histology**	**n**	**% with WHO grade**	**% with 1p/19q status**	**% 1p/19q codeleted**	**% with IDH status**	**% IDH mutant**	**% with p53 status**	**% p53 pos**	**% with ATRX status**	**% ATRX loss**
9380/3	Glioma, malignant	23	73.9	47.8	0	100	21.7	56.5	53.9	47.8	36.4
9381/3	Gliomatosis cerebri	3	100	33.3	0	66.7	100	33.3	100	0	0
9382/3	Mixed glioma	42	100	88.1	27.0	97.6	75.6	61.9	50.0	21.4	66.7
9400/3	Astrocytoma, NOS	36	91.7	36.1	0	94.4	38.2	63.9	56.5	30.6	45.5
9401/3	Astrocytoma, anaplastic	75	100	46.7	2.9	90.7	32.4	61.3	63.0	36.0	48.2
9410/3	Protoplasmic astrocytoma	1	100	100	0	100	100	100	100	0	n/a
9411/3	Gemistocytic astrocytoma	none									
9420/3	Fibrillary astrocytoma	1	100	0	n/a	100	0	100	100	100	0
9440/3	Glioblastoma, NOS	217	99.1	35.5	0	87.1	3.7	51.6	34.8	26.3	8.8
9441/3	Giant cell glioblastoma	1	100	0	n/a	0	n/a	0.0	n/a	0.0	n/a
9442/3	Gliosarcoma	5	100	40.0	0	60.0	0	60.0	100	40.0	0
9450/3	Oligodendroglioma, NOS *	26	100	100	76.9	96.2	80.0	69.2	16.7	57.7	0
9451/3	Oligodendroglioma, anaplastic	20	95.0	95.0	68.4	90.0	83.3	60.0	25.0	15.0	33.3
	Total	450	97.3	49.3	19.8	90.0	28.6	56.9	44.1	30.2	25.0

"/3" behavior code designates a malignant tumor; NOS: Not otherwise specified;

* In ICD-O-3, this diagnosis is synonymous with oligodendroglioma, diffuse.

TABLE 5.

Revised ICD-O-3 Coding from the 2016 WHO for Diffuse Gliomas

ICD-O-3 Code/Behavior	Revised ICD-O-3 Histology
9382/3	Anaplastic oligoastrocytoma, NOS
9382/3	Oligoastrocytoma, NOS
9385/3	Diffuse midline glioma, H3 K27M-mutant
9400/3	Diffuse astrocytoma, IDH-mutant
9400/3	Diffuse astrocytoma, IDH-wildtype
9401/3	Anaplastic astrocytoma, IDH-mutant
9401/3	Anaplastic astrocytoma, IDH-wildtype
9411/3	Gemistocytic astrocytoma
9440/3	Epithelioid glioblastoma
9440/3	Glioblastoma, IDH-wildtype
9441/3	Giant cell glioblastoma
9442/3	Gliosarcoma
9445/3	Glioblastoma, IDH-mutant
9450/3	Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
9451/3	Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted

“/3” behavior code designates a malignant tumor; NOS: Not otherwise specified