Completeness and concordancy of WHO grade assignment for brain and central nervous system tumors in the United States, 2004–2011

Ryan L. Lym[1], **Quinn T. Ostrom**[2,3], **Carol Kruchko**[3], **Marta Couce**[2,4], **Daniel J. Brat**[5], **David N. Louis**[6], and **Jill S. Barnholtz-Sloan**[2,3]

Ryan L. Lym: rll63@case.edu; Jill S. Barnholtz-Sloan: jsb42@case.edu

[1]Case Western Reserve University School of Medicine, 11100 Euclid Avenue, Cleveland, OH, USA

[2]Case Comprehensive Cancer Center, Case Western Reserve University School of Medicine, 11100 Euclid Avenue, Wearn 152, Cleveland, OH, USA

[3]Central Brain Tumor Registry of the United States, Hinsdale, IL, USA

[4]Department of Pathology, University Hospitals Case Medical Center, Cleveland, OH, USA

[5]Department of Pathology, Emory University School of Medicine, Atlanta, GA, USA

[6]Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Abstract

Central nervous system (CNS) tumors are categorized and graded for clinical and research purposes according to the World Health Organization (WHO) scheme which segregates tumors by histological type and predicted biological behavior. However, reporting of WHO grade in pathological reports is inconsistent despite its collection in cancer registration. We studied the completeness, concordancy, and yearly trends in the collection of WHO grade for primary CNS tumors between 2004 and 2011. Data from the Surveillance, Epidemiology and End Results program were analyzed for the percentage of histologically diagnosed primary CNS tumor cases with concordantly documented WHO grades between 2004 and 2011. Yearly trends were calculated with annual percentage changes (APC) and 95 % confidence intervals (95 % CI). Completeness and concordancy of the collection of WHO grade varied significantly by histological type and year. The percentage of cases with documented WHO grade increased significantly from 2004 to 2011: 39.0 % of cases in 2004 had documented WHO grade, while 77.5 % of cases had documented grade in 2011 (APC, 10.3; 95 % CI: 9.0, 11.5). Among cases with documented WHO grade, the percentage graded concordantly increased significantly from 89.1 % in 2004 to 93.7 % in 2007 (APC, 1.8; 95 % CI: 1.0, 2.6) and these values varied over time by histological type. One common trend among all histologies was a significant increase in the

Correspondence to: Ryan L. Lym, `rll63@case.edu`; Jill S. Barnholtz-Sloan, `jsb42@case.edu`.

Conflict of interest There are no conflicts of interest to report.

percentage of cases with documented WHO grade. A sizeable proportion of reported CNS tumors collected by cancer registrars have undocumented WHO grade, while a much smaller proportion are graded discordantly. Data collection on grade has improved in completeness and concordancy over time. Efforts to further improve collection of this variable are essential for clinical care and the epidemiological surveillance of CNS tumors.

Keywords

World Health Organization (WHO) grade; World Health Organization (WHO) histological type; Central nervous system tumors; Neuropathology; Cancer registry

Introduction

There are over 100 histologically distinct types of primary central nervous system (CNS) tumors, each with its own spectrum of clinical presentations, treatments, and outcomes. The first edition of the World Health Organization (WHO) *Classification of Tumours of the Central Nervous System* was published in 1979 as a unifying system for classifying CNS tumors [1]. It has been revised three times, most recently in 2007 [2–4], and has become the international standard for the categorization of CNS tumors. The WHO classification system acts as a common language for communication between clinical and basic science investigators worldwide [5–7].

Unlike most other cancers, CNS neoplasms are not staged and, therefore, grading takes on a heightened importance for patient management [8]. Grading assignment is achieved through the WHO classification system which provides a grading scheme in order to indicate predicted clinical behavior based on morphologic features (WHO grade I–IV) [5, 7]. As such, the WHO grade often estimates clinical outcomes and guides the management of some CNS tumors [5, 6]. Updates to WHO classification and grading result in improved correlations between histological grade and outcomes and can affect changes in diagnostic and clinical practice [7, 9]. WHO grading is also used in population and epidemiological studies to identify patterns of diagnosis for CNS tumors. For example, a substantial change from the 1993 to 2000 WHO classification and grading scheme for meningiomas resulted in an increase in the frequency of diagnosis and thus the incidence of grade II meningiomas, a tumor which carries a poorer prognosis than grade I meningiomas [10].

However, despite its clinical and epidemiological use, reporting of WHO grade remains optional in both pathology reports and cancer registration [5, 6]. The College of American Pathologists (CAP) recommends, but does not require, that WHO grade be assigned in pathological reports [8]. Grading is also not a required item by either of the two major cancer registry programs in the United States: the Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries (NPCR) and the National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results (SEER) program.

A previous study by Kruchko, et al. analyzed the completeness and concordance of WHO grading for primary CNS tumor cases from 2004 to 2008 within 18 SEER cancer registries and revealed a substantial frequency of undocumented or discordant WHO grades [11]. The

objective of this report is to expand and update this analysis by describing the completeness, concordancy and trends in the collection of WHO grade for primary CNS tumor cases from 2004 to 2011 using SEER data.

Materials and methods

Data collection

This study used data from the SEER program of the NCI, which includes ~28 % of cancer cases for the US population [12]. Specifically, the SEER 18 Registries Research Data set (Nov 2013 submission) containing data updated to year 2011 was used [13]. Non-malignant tumors were also included in this analysis. 2004 was selected as the start year of this study since the collection of these tumors was initiated on January 1, 2004. Adoption of this practice was the direct result of the passage of the Benign Brain Tumor Cancer Registries Amendment Act (Public Law 107–260) which mandated that all non-malignant CNS tumors be registered within the United States [14, 15]. In addition, WHO grade which is recorded in the SEER cancer registry as Collaborative Stage Site Specific Factor 1 [16] was available from 2004 and onward [13]. For these reasons, primary years of analysis were from 2004 to 2011.

Regarding cancer registration guidelines for WHO grade, SEER records WHO grade based on instructions from the Collaborative Stage Data Collection Manual [15] which states that WHO grade is recorded from a pathology report; WHO grade is not recorded if the diagnosis is made radiographically [16]. Information from the pathology report is first recorded by tumor registrars from treatment centers and cancer care programs who then send this information to central (state) cancer registries who submit it to SEER [17]. Tumor registrars and central cancer registries are held under quality controls checks to ensure that the information reported to SEER is as accurate and complete as possible.

Primary CNS tumors were identified for WHO grade analysis based on the *International Classification of Diseases for Oncology*, 3rd edition (ICD-O-3) site codes (C70.0–72.9, C75.1–75.3) [15]. CNS tumor groups were selected based on their overall incidence over the time period and by clinical interest [11] and listed according to ICD-O-3 histology and behavior codes (Table 2). Since the histology and grade of CNS tumors are more accurately determined when they are microscopically confirmed, this study primarily focused on cases with microscopic (e.g. histopathologic) confirmation [17, 18]. Cases in which the histological diagnosis is assigned without microscopic confirmation, such as those identified radiographically without surgical resection and which are also reported to cancer registries, were included but not the focus of this study. Designated WHO grades for specific histological types were based on the 2007 WHO grading scheme [5] and did not differ substantially from the 2000 grading scheme for these selected histologies [7].

Statistical analysis

SEER*Stat 8.1.5 statistical software (http://seer.cancer.gov/seerstat) was used to generate counts and proportions to analyze completeness, concordancy, and time trends of WHO grading. Completeness of WHO grade was determined by the percentage of tumor cases

with documented WHO grade (I–IV). Cases in which WHO grade was not assigned, was assigned but not documented in the pathology report, or was assigned, documented, but not recorded within cancer registries were classified as cases with undocumented WHO grade. Concordancy was determined by the percentage of tumor cases with a documented WHO grade and with concordant grading in relation to the WHO grading scheme, which directly assigns each specific histological diagnosis with a defined WHO grade. For example, the WHO grading scheme directly assigns tumors with a histological diagnosis of pilocytic astrocytoma as a grade I tumor and so pathological reports for this tumor with a grade I were deemed concordant, and reports with grades II, III, IV were deemed discordant. Thus, the grade is determined to be concordant if the pathologist assigned a WHO grade for a specific histological diagnosis that corresponds with the WHO grading scheme. Time trends in data collection for WHO grade were determined by tracking these two variables between 2004 and 2011. The Joinpoint Regression Program 4.1.1 (htttp://surveillance.-cancer.gov/joinpoint/) was used to determine trends by calculating an annual percentage change (APC) and 95 % confidence interval (95 % CI).

Results

Overall WHO Grade completeness and concordancy

Completeness and concordancy of WHO grade were calculated for all selected histologies as a group (Table 1). From 2004 to 2011 there were a total of 86,080 cases, of which 57,480 (66.8 %) were microscopically confirmed and 28,600 that were not (33.2 %). Among all tumor cases, 39.7 % had documented WHO grade, and 93.6 % of those with documented WHO grade were graded concordantly.

Among microscopically confirmed cases, 58.5 % had documented WHO grade, and 93.6 % of these cases with documented WHO grade were graded concordantly. Cases that were not microscopically confirmed had 1.9 % of cases with documented WHO grade of which 95.9 % of these cases were graded concordantly. These included cases where the histological diagnosis was done radiographically, and a WHO grade was still recorded in the SEER registry. However, these cases were not further analyzed in regards to specific histologies or trends.

Histology-Specific WHO Grade completeness and concordancy

Selected histologic groups were analyzed individually for completeness and concordancy in WHO grade from 2004 to 2011 (Table 2). The percentage of microscopically confirmed tumor cases ranged from a low of 46.0 % for non-malignant meningioma to 100.0 % for anaplastic ependymoma.

Completeness of WHO grade varied by histological type. More than 80 % of all cases had grade documented for anaplastic astrocytoma, oligodendroglioma, anaplastic oligodendroglioma, and oligoastrocytoma/anaplastic oligoastrocytoma, whereas less than 25 % of all cases had WHO grade documented for craniopharyngioma and hemangioblastoma.

Concordancy of WHO grade also varied based on histological type. Among cases that were graded, more than 98 % of craniopharyngioma and hemangioblastoma were graded

concordantly in contrast to anaplastic/malignant meningioma in which only 55.8 % were graded concordantly.

Time trends in WHO Grade completeness and concordancy

Yearly percentages of documented and concordant WHO grade were determined overall for microscopically confirmed CNS tumor cases for each year between 2004 and 2011 (Fig. 1). There was a significant decrease in the percentage of cases microscopically confirmed each year beginning with 71.9 % in 2004 and ending with 64.3 % in 2011 (APC, −1.6; 95 % CI −2.1, −1.1). Among specific histologies analyzed for yearly trends, non-malignant meningioma was the only histology that resulted in a significant decrease in the percentage of microscopically confirmed cases overtime. The percentage of cases with documented WHO grade significantly increased each year: 39.0 % of cases in 2004 had documented WHO grade, and in 2011, 77.5 % of cases had documented grade (APC, 10.3; 95 % CI 9.0, 11.5). Among those with documented grade, the percentage of cases graded concordantly increased significantly from 2004 (89.1 %) to 2007 (93.7 %) (APC, 1.8; 95 % CI 1.0, 2.6). From 2007 to 2011 this percentage did not change significantly and remained stable at roughly 94 % (APC, 0.2; 95 % CI −0.3, 0.7).

Specific histologies were also analyzed for yearly trends in WHO grade between 2004 and 2011 based on incidence and clinical interest. These included glioblastoma/giant cell glioblastoma/gliosarcoma, non-malignant meningioma, atypical meningioma, and anaplastic/malignant meningioma (Fig. 2). For glioblastoma/giant cell glioblastoma/ gliosarcoma, there was no significant change in the percentage of microscopically confirmed cases over time (APC, 0.3; 95 %CI 0.0, 0.5), but there were significant increases in the percentage of cases with documented WHO grade (APC, 7.2; 95 % CI 6.2, 8.2) and with concordant grades among those cases (APC 0.7; 95 % CI 0.4, 0.9). For non-malignant meningioma, there was a significant decrease in the percentage of cases being microscopically confirmed (APC, −3.1; 95 % CI −3.8, −2.5) and a significant increase in the percentage of cases with documented WHO grade (APC, 18.3; 95 % CI 13.8, 22.9). Among cases that had documented WHO grade, there was no significant change in the percentage of cases being graded concordantly between 2004 and 2006 (APC, 0.7; 95 % CI −1.0, 2.3), but this finding was followed by a significant decrease between 2006 and 2011 (APC, −0.6; 95 % CI −0.9, −0.2). For atypical meningioma, there were significant increases in the percentage of microscopically confirmed cases (APC, 1.3; 95 %CI 0.2, 2.4) and in cases with documented WHO grade (APC, 11.8; 95 % CI 7.9, 15.8). However, there was no significant change in the number of cases being graded concordantly (APC, 0.5; 95 % CI −0.8, 1.8). Anaplastic/malignant meningioma followed a similar pattern. Between 2004 and 2011, there were significant increases in the percentage of microscopically confirmed cases (APC, 2.9; 95 % CI 1.7, 4.2) and in cases with documented WHO grade (APC, 9.8; 95 % CI 4.5, 15.4). However, there was no significant change in the number of cases being graded concordantly (APC, 3.8; 95 % CI −4.2, 12.4). These specific histologies displayed wide variability in time trends. However, one common trend observed among all four histologies (glioblastoma/giant cell glioblastoma/gliosarcoma, non-malignant meningioma, atypical meningioma, and anaplastic/malignant meningioma) was a significant increase in the

percentage of cases with documented WHO grade between 2004 and 2011. APCs and 95 % CIs for time trends are summarized in Table 3.

Discussion

A significant number of CNS tumor cases reported to SEER registries from 2004 to 2011 had undocumented WHO grade; however, among cases that were graded, over 90 % were graded concordantly (Table 1). All CNS tumor types had cases with undocumented or discordantly assigned WHO grade, yet completeness and concordancy of WHO grading varied by histological type of tumor (Table 2).

The inclusion of WHO grade on pathology reports remains optional in the United States [5, 6]. Although clinicians are using WHO grading in their practices, WHO grade may not be documented on pathological reports. Furthermore, according to the College of American Pathologists (CAP) guidelines, neuropathologists have options in reporting–including: choosing to assign a WHO grade, reporting grade as not applicable, reporting grade as cannot be determined, or not assigning a WHO grade–that may affect documentation and, therefore, further impede the registrar's ability to consistently collect this variable [8].

Although the *WHO Classification of Tumours of the Central Nervous System* establishes a defined WHO grade for each histological diagnosis, neuropathologists make the final assignment of grades on a case by case basis [8] further complicating the documentation process. As a result, pathologists may choose to assign a WHO grade that deviates from the grading scheme (SEER registries record WHO grades based on the assignment of the working pathologist even if it deviates from the defined grading scheme [15]). Tumors with deviated WHO grade would, therefore, contribute to the number of cases determined to be discordantly graded. However, we found that, overall, most diagnosed tumors conform to the WHO grading scheme and so these cases probably only account for a small proportion [5]. Finally, one cannot dismiss that errors in cancer registration are also a possible cause for both undocumented and discordant WHO grades. For example, if a pathologist assigns a concordant WHO grade on a pathology report, recording of grade in the registries could have been overlooked or recorded erroneously resulting in a tumor case with an undocumented or discordant WHO grade within the SEER database.

Only a small portion of all CNS tumor cases between 2004 and 2011 were discordantly graded, as most were either undocumented or assigned the concordant WHO grade (Tables 1, 2). In other words, the large majority of these cases either had no documented WHO grade or were graded concordantly. This may indicate that neuropathologists are more likely to leave a WHO grade unassigned in a pathology report than assign a discordant WHO grade as it may be difficult to assign grade for tumors with histological features that are problematic to interpret or do not readily fit into a definitive grade [19].

Microscopically confirmed cases had a higher proportion of documented WHO grade when compared to cases that were not microscopically confirmed (Table 1). Cases that were not microscopically confirmed (e.g. CNS tumors identified radiographically but did not result in surgery for histologic confirmation) had WHO grade documented in 1.9 % of the cases. This

finding most likely reflects the current practice in which WHO grade cannot be assigned for tumors that are diagnosed radiographically. Furthermore, many non-malignant CNS tumors may not receive surgery as their first course of treatment prohibiting microscopic (i.e. histopathologic) confirmation of their disease. These results reaffirm that microscopic confirmation is necessary for the assignment of histological type and grade for CNS tumors [17, 18].

Overall, from 2004 to 2011 an increasing proportion of cases each year were documented and assigned with the concordant WHO grade (Fig. 1). A factor which most likely contributed to the increase of documented and concordant WHO grade over time was the impetus in cancer centers to use a standardized protocol provided by the CAP in reporting the results of surgically biopsied or resected CNS tumors. This protocol was developed to assist pathologists in reporting useful and relevant information and consists of a checklist that specifies factors such as primary tumor site, histological diagnosis, and WHO grade [8]. WHO grade has been included in this protocol since its early versions before 2004 and the current version published in 2014 also includes the most updated WHO grading scheme as a reference for working pathologists. The rise in documented WHO grade may in part be explained by the mandate in January 1, 2004 by the Commission on Cancer (CoC), a program of the American College of Surgeons, for the use of the CAP protocol as part of its Cancer Program Standards for Approved Cancer Programs that allows for CoC accreditation which recognizes a cancer care program for comprehensive, high-quality patient centered care [8]. Current Cancer Program Standards for CoC accreditation requires that CAP protocol elements such as WHO grade are reported in at least 90 % of pathology reports. This mandate may have led to an increase in the number of treatment centers and cancer care programs seeking CoC accreditation to use the CAP protocol in pathology reports.

Time trends for specific histologies such as glioblastoma and non-malignant meningioma show that improvements over time in completeness and concordancy of WHO grade vary significantly based on histology (Fig. 2). Of particular note is the significant increase in the percentage of cases with documented WHO grades for grade I, II, and III meningiomas. This may reflect the changes in the 2000 WHO classification system in which the diagnosis of these tumors is correlated directly with grade and, therefore, contribute to making WHO grade documentation straightforward and reproducible [20]. Furthermore, these changes have helped clarify the determination of grade for the histological subtypes of meningioma, such as microcystic (grade I), chordoid (grade II), and papillary (grade III) meningiomas.

Variable trends in non-malignant meningioma (grade I), atypical meningioma (grade II), and anaplastic/malignant meningioma (grade III) most likely reflect changes in the diagnostic approach or classification of these tumors. The significant decrease in the percentage of cases with microscopic confirmation for non-malignant meningioma, the most common among the three types, may be the result of increased dependence or reliability on neuroimaging as the method of diagnosis for these tumors. Given that non-malignant meningioma accounts for an overwhelming majority of CNS tumor cases (Table 2), a decrease in the percentage of non-malignant meningiomas with microscopic confirmation would cause a significant decrease in the overall percentage of microscopically confirmed cases seen in CNS tumors over the years (Fig. 1). Yearly variability in the percentage of

cases with concordant grading for atypical and anaplastic/malignant meningioma most likely reflects the continuing difficulty in establishing a system that consistently and appropriately classifies and grades these tumors. Multiple studies have shown that reassessment of meningiomas based on updated WHO classification and grading criteria have led to the reclassification of histological diagnosis and grade for these tumors. For instance, a study in 2006 by Simon, et al. studied the impact of the revised WHO 2000 classification system by analyzing 57 cases of meningioma that were previously classified and graded based on the WHO 1993 criteria [21]. They found that a significant number of cases previously diagnosed as atypical and anaplastic/malignant meningioma were classified and graded differently based on the WHO 2000 criteria in which the study suggested that more stringent criteria be established in the classification and grading of these tumors. A similar study by Yang, et al. in 2007 revealed parallel results [22] and another by Rosenberg, et al. in 2009 stated that the WHO 2000 and 2007 definitions for grade III meningiomas classify a substantially different group of tumors when compared to previous definitions [23]. Difficulty in the classification and grading of meningiomas will continue to produce variations in the diagnosis, grading, and epidemiology of these tumors.

Differences in diagnostic, prognostic, or therapeutic approach may influence the application of WHO grade for individual histologies and account for the variability seen in WHO grade assignment (Table 2). For instance, WHO grade can be a consistent predictor of clinical outcomes for some but not all tumors. For certain tumors, other characteristics such as molecular markers may be better at predicting clinical outcomes and guiding management [19]. Tumors with a higher percentage of documented WHO grade most likely represent histologies in which grade has been found to be clinically useful for prognosis and therapeutic management. Additionally, for histologies with similar or overlapping names, WHO grade may be more frequently assigned because it can act as a safety check to insure that the appropriate histological diagnosis was made. For instance, the assignment of WHO grade II for oligodendroglioma on a pathology report would help differentiate it from anaplastic oligodendroglioma which is assigned a WHO grade III. For histologies in which the name is distinct and only a single WHO grade is assigned, such as craniopharyngioma, the grade is implied in pathology report diagnosis and so the assignment of WHO grade might be considered redundant in the clinical setting and thus grade would be less often documented. Continued investigations in identifying patterns of completeness and concordancy in documentation of WHO grade would be useful in further understanding its clinical use and in determining if certain CNS tumors warrant reassignment of grade or classification.

Overall, improvements in completeness and concordance of WHO grading are being seen overtime and efforts to continue this trend should be made. Pathologists should continue to use standardized protocols such as those offered by the CAP to ensure more consistent collection of this variable. Programs such as the CoC that accredits cancer care programs and cancer registries should also set high standards for the collection of grade and other cancer related elements, such as newer molecular markers, as these will be important in epidemiological and research studies. Updates to the WHO classification and grading system that adapt to the growing body of knowledge revolving around CNS tumors are essential, as this system has become the standard by which the neuro-oncology community

diagnoses and grades tumors. By ensuring that grade accurately reflects tumor behavior and prognosis, clinicians will be more inclined to use it in their practices as a reliable indicator of patient outcomes, and thereby affecting its inclusion in the medical record and eventual collection by tumor registrars.

Strengths and limitations

This analysis provides important information on the use of WHO grade in clinical practice and the concordancy of its collection in a population-based cancer registry representing ~28 % of brain and CNS tumor cases in the United States in a selected time period, 2004–2011.

An important limitation of this study is that, although quality control checks exist for cancer registries [17], there is no mechanism for central pathology review. Trained cancer registrars abstract information on WHO grade directly from pathology reports which represent the opinions of individual pathologists and may influence the number of cases with concordantly/discordantly assigned WHO grade in spite of our focus on microscopically confirmed cases.

Similarly, the lack of central pathology review implies that there is uncertainty in whether an error in the assignment of WHO grade versus the histological diagnosis was made in cases in which the grade was discordant for the given histology. In this study, the histological diagnosis assigned by the pathologist was assumed to be accurate in which concordancy of WHO grade was subsequently determined. Implementation of a central pathology review system at the level of individual treatment centers and their registrars, central cancer registries, and with SEER would encourage complete, accurate, and reliable collection of WHO grade along with other useful and relevant cancer elements such as histological diagnosis and molecular markers.

Based on current guidelines, WHO grade and histological diagnosis ideally should have been directly recorded from pathology reports. However, this may not always be the case and the SEER*Stat statistical program used for this analysis is unable to verify if recorded WHO grades or histological diagnoses were in fact directly abstracted from pathology reports. Thus, any errors in the recording of WHO grade or histology that would be present in the SEER database would also be present in this analysis. Microscopically confirmed cases were chosen to be analyzed because SEER guidelines place priority in using pathological reports to record the histological diagnosis and WHO grade for these cases.

The inability to identify the cause on why certain cases were recorded with an undocumented WHO grade within the SEER registry was also a limitation of this study. It would be interesting to explore these cases to determine if WHO grades are primarily undocumented within registries because they are not being assigned by pathologists or because of errors in cancer registration. Determining these patterns would help identify areas of improvement and strategies for the collection of WHO grade. A special study looking at individual records would be needed in order to investigate the collection of WHO grade from clinical records in order to provide a clear evaluation of collection practices.

Conclusions

This study revealed that overall, primary CNS tumors reported to central cancer registries have a significant proportion of cases with undocumented WHO grade. For those cases with microscopic confirmation, even though discordant WHO grades were low, improvements in both the completeness and concordancy of WHO grading have been made over time. Neuropathologists and cancer registrars should continue their efforts to ensure that documentation of WHO grade is complete and concordant. The collection of this variable is important for cancer surveillance efforts and for performing a population-based calculation of clinical outcomes, as well as for clinical care and research purposes [20–23].

For clinicians and neuropathologists, assigning WHO grade holds significant clinical value for patient care in neuro-oncology. This is the case even in the context of testing for molecular markers which have currently been identified for several histologic types of CNS tumors and which will likely be used in combination with WHO grade to assign diagnosis and therapy, and to predict prognosis [6, 8, 19]. Along with histological identification, WHO grade will continue to provide important information for the prognosis and management of CNS tumors. For cancer surveillance, it is important that the collection of WHO grade continues to improve over time. Comprehensive and consistent inclusion of this variable in cancer databases helps to increase the clinical utility of cancer surveillance for population and epidemiological studies. Gaining a better understanding of trends of WHO grade collection in population-based registries may also prove useful in evaluating its application in clinical practices in the United States. Furthermore, this study provides documentation which may be useful to revisions of future grading schemes of the *WHO Classification of Tumours of the Central Nervous System* so that improved correlations between histological grade and outcomes continue to be made.

Acknowledgments

References

1. Zulch, KJ. International histological classification of tumours. Geneva: World Health Organization; 1979. Histological typing of tumours of the central nervous system.

2. Kleihues, P.; Burger, PC.; Scheithauer, BW.; Zulch, KJ. Histological typing of tumours of the central nervous system. 2nd edn.. Berlin: Springer-Verlag; 1993.

3. Kleihues, P.; Cavenee, WK. International Agency for Research on Cancer. Pathology and genetics of tumours of the nervous system. Lyon: IARC Press; 2000.

4. Louis, DN.; Ohgaki, H.; Wiestler, OD.; Cavenee, WK. World Health Organization classification of tumours. 4th edn.. Lyon: International Agency for Research on Cancer; 2007. WHO classification of tumours of the central nervous system.

5. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol. 2007; 114:97–109. doi:10.1007/s00401-007-0243-4. [PubMed: 17618441]

6. Pollo B. Neuropathological diagnosis of brain tumours. Neurol Sci. 2011; 32(Suppl 2):S209–S211. doi:10.1007/s10072-011-0802-2. [PubMed: 22009244]

7. Brat DJ, Parisi JE, Kleinschmidt-DeMasters BK, Yachnis AT, Montine TJ, Boyer PJ, Powell SZ, Prayson RA, McLendon RE. CoAP Neuropathology Committee. Surgical neuropathology update: a review of changes introduced by the WHO classification of tumours of the central nervous system, 4th edition. Arch Pathol Lab Med. 2008; 132:993–1007. doi:10.1043/1543-2165. [PubMed: 18517285]

8. Parisi JE, Miller DV, Boyer PJ, Brat DJ, Cochran EJ, Cohen ML, Demasters BK, Dolinak D, McComb RD, McLendon RE, Powell SZ, Prayson RA, Vinters HV, Yachnis AT. Members of Cancer Committee CoAP. Protocol for the examination of specimens from patients with tumors of the brain/spinal cord. Arch Pathol Lab Med. 2008; 132:907–912. doi:10.1043/1543-2165. [PubMed: 18517271]

9. Combs SE, Schulz-Ertner D, Debus J, von Deimling A, Hartmann C. Improved correlation of the neuropathologic classification according to adapted world health organization classification and outcome after radiotherapy in patients with atypical and anaplastic meningiomas. Int J Radiat Oncol Biol Phys. 2011; 81:1415–1421. doi:10.1016/j.ijrobp.2010.07.039. [PubMed: 20932661]

10. Willis J, Smith C, Ironside JW, Erridge S, Whittle IR, Everington D. The accuracy of meningioma grading: a 10-year retrospective audit. Neuropathol Appl Neurobiol. 2005; 31:141–149. doi:10.1111/j.1365-2990.2004.00621.x. [PubMed: 15771707]

11. Kruchko, C.; Dolecek, TA.; McCarthy, BJ. A Review of the Collection of WHO Grade for Brain and CNS Tumors in Cancer Registration. Poster presented at: Society for Neuro-Oncology Annual Scientific Meeting and Education Day; Nov 17–20, 2011; Orange County, California. 2011.

12. Surveillance Research Program—National Cancer Institute. SEER… as a Research Resource. 2010. http://seer.cancer.gov/about/factsheets/SEER_Research_Brochure.pdf

13. Surveillance Epidemiology and End Results (SEER) Program SEER*Stat Database: Incidence—SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2013 Sub (1973–2011 varying)—Linked To County Attributes—Total U.S., 1969–2012 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2014, based on the November 2013 submission.

14. [Accessed 4 June 2014] Benign Brain Tumor Cancer Registries Amendment Act. 2002. http://www.gpo.gov/fdsys/pkg/PLAW-107publ260/pdf/PLAW-107publ260.pdf

15. Surveillance Epidemiology and End Results (SEER) Program. [Accessed 4 June 2014] SEER Program Coding and Staging Manual 2013. 2013. http://seer.cancer.gov/archive/manuals/2013/SPCSM_2013_maindoc.pdf

16. Collaborative Stage Data Collection System. [Accessed 5 June 2014] Brain: CS Site-Specific Factor 1, World Health Organization (WHO) Grade Classification. 2013. http://web2.facs.org/cstage0205/brain/Brain_jpo.html

17. Ostrom QT, Gittleman H, Liao P, Rouse C, Chen Y, Dowling J, Wolinsky Y, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2007–2011. Neuro Oncol. 2014; 16:iv1–iv63. doi:10.1093/neuonc/nou223. [PubMed: 25304271]

18. Surveillance Epidemiology and End Results (SEER) Program. U. S. National Institutes of Health. National Cancer Institute; SEER Training Modules, Cancer Diagnosis. http://training.seer.cancer.gov/ [Accessed 20 June 2014]

19. Louis DN, Perry A, Burger P, Ellison DW, Reifenberger G, von Deimling A, Aldape K, Brat D, Collins VP, Eberhart C, Figarella-Branger D, Fuller GN, Giangaspero F, Giannini C, Hawkins C, Kleihues P, Korshunov A, Kros JM, Beatriz Lopes M, Ng HK, Ohgaki H, Paulus W, Pietsch T, Rosenblum M, Rushing E, Soylemezoglu F, Wiestler O, Wesseling P. International society of neuropathology-haarlem consensus guidelines for nervous system tumor classification and grading. Brain Pathol. 2014; 24:429–435. doi:10.1111/bpa.12171. [PubMed: 24990071]

20. Detti B, Scoccianti S, Di Cataldo V, Monteleone E, Cipressi S, Bordi L, Pellicano G, Gadda D, Saieva C, Greto D, Pecchioli G, Buccoliero A, Ceroti M, Ammannati F, Biti G. Atypical and

malignant meningioma: outcome and prognostic factors in 68 irradiated patients. J Neurooncol. 2013; 115:421–427. doi:10.1007/s11060-013-1239-7. [PubMed: 24045968]

21. Simon M, Bostrom J, Koch P, Schramm J. Interinstitutional variance of postoperative radiotherapy and follow up for meningiomas in Germany: impact of changes of the WHO classification. J Neurol Neurosurg Psychiatry. 2006; 77:767–773. doi:10.1136/jnnp.2005.077974. [PubMed: 16306156]

22. Yang SY, Park CK, Park SH, Kim DG, Chung YS, Jung HW. Atypical and anaplastic meningiomas: prognostic implications of clinicopathological features. J Neurol Neurosurg Psychiatry. 2007; 79:574–580. doi:10.1136/jnnp.2007.121582. [PubMed: 17766430]

23. Rosenberg LA, Prayson RA, Lee J, Reddy C, Chao ST, Barnett GH, Vogelbaum MA, Suh JH. Long-term experience with world health organization grade III (malignant) meningiomas at a single institution. Int J Radiat Oncol Biol Phys. 2009; 74:427–432. doi:10.1016/j.ijrobp.2008.08.018. [PubMed: 19427553]

Fig. 1.
Percentage of cases that are microscopically confirmed (MC)a, MC with documented WHO gradeb, and MC with documented WHO grade and graded concordantlyc per year for all selected CNS tumors between 2004 and 2011 (SEER 18 Registries Research Data)
[a]% MC: (APC, −1.6; 95% CI: −2.1, −1.1)
[b]% MC with documented WHO grade: (APC, 10.3; 95% CI: 9.0, 11.5)
[c]% MC with documented WHO grade and graded concordantly: (2004–2007; APC, 1.8; 95% CI: 1.0, 2.6), (2007–2011; APC, 0.2; 95% CI: −0.3, 0.7)
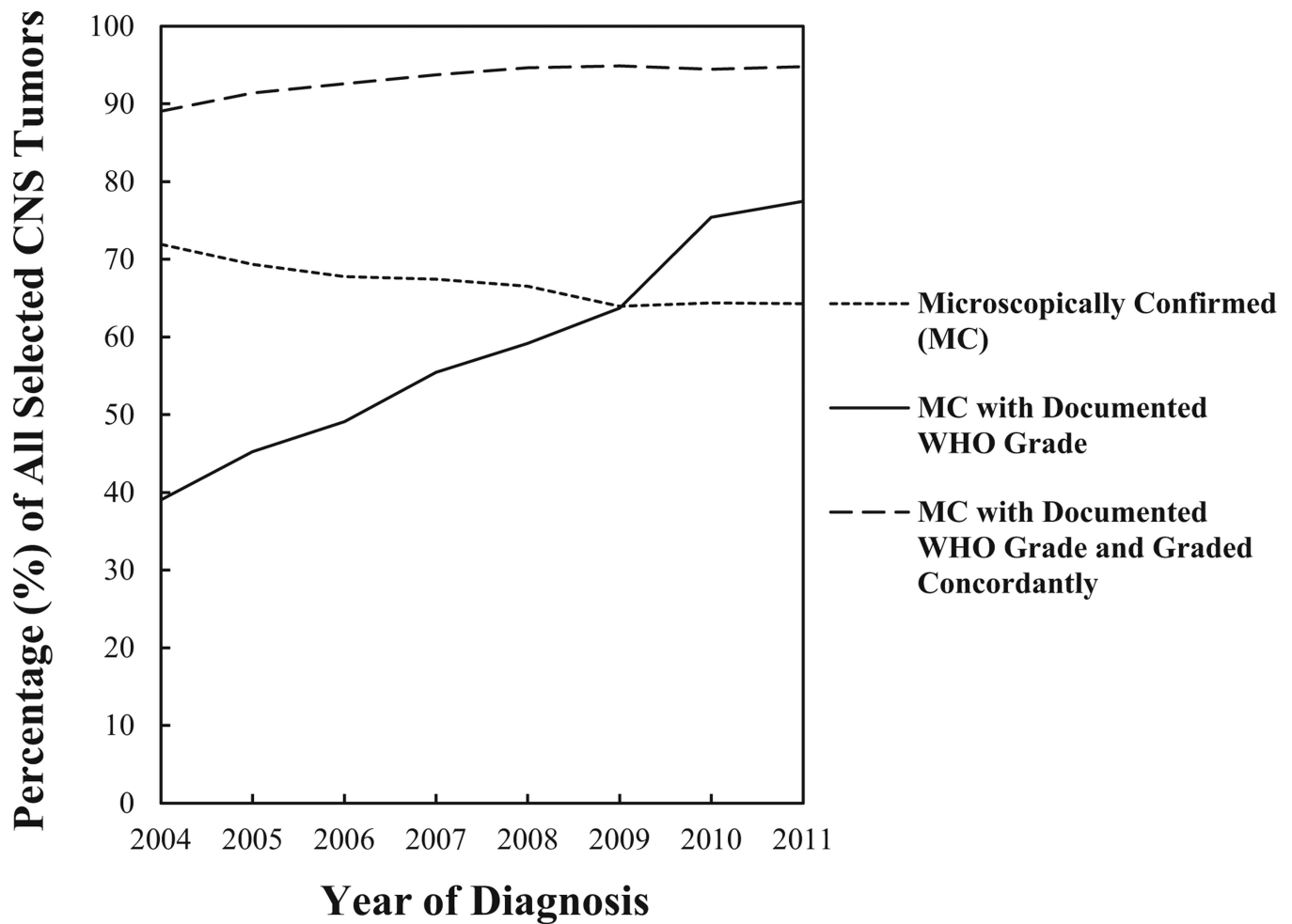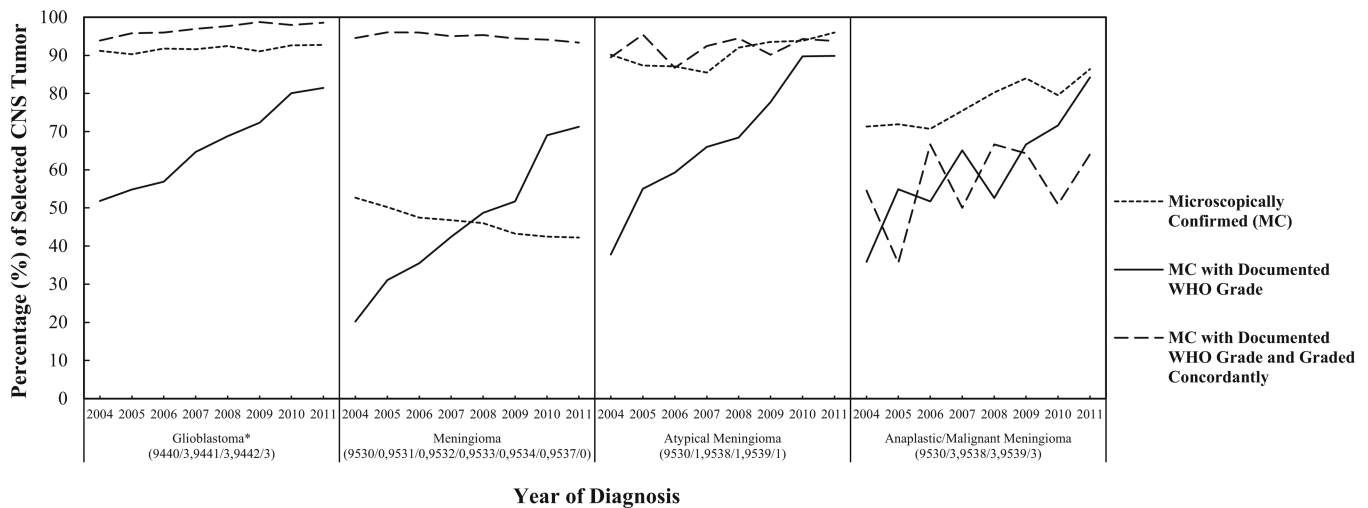
Fig. 2.

Percentage of cases that are microscopically confirmed (MC), MC with documented WHO grade, and MC with documented WHO grade and graded concordantly per year for selected CNS tumors between 2004 and 2011: Glioblastoma/Giant Cell Glioblastoma/Gliosarcomaa, Meningiomab, Atypical Meningiomac, Anaplastic/Malignant Meningiomad (SEER 18 Registries Research Data)

[a],*Glioblastoma (9440/3), Giant Cell Glioblastoma (9441/3), Gliosarcoma (9442/3): % MC: (APC, 0.3; 95% CI: 0.0, 0.5); % MC with documented WHO grade: (APC, 7.2; 95% CI: 6.2, 8.2); % MC with documented WHO grade and graded concordantly: (APC, 0.7; 95% CI: 0.4, 0.9)

[b]Meningioma: % MC: (APC, −3.1; 95% CI: −3.8, −2.5); % MC with documented WHO grade: (APC, 18.3; 95% CI: 13.8, 22.9); % MC with documented WHO grade and graded concordantly: (2004–2006; APC, 0.7; 95% CI: −1.0, 2.3), (2006–2011; APC, −0.6; 95% CI: −0.9, −0.2)

[c]Atypical Meningioma: % MC: (APC, 1.3; 95% CI: 0.2, 2.4); % MC with documented WHO grade: (APC, 11.8; 95% CI: 7.9, 15.8); % MC with documented WHO grade and graded concordantly: (APC, 0.5; 95% CI: −0.8, 1.8)

[d]Anaplastic/Malignant Meningioma: % MC: (APC, 2.9; 95% CI: 1.7, 4.2); % MC with documented WHO grade: (APC, 9.8; 95% CI: 4.5, 15.4); % MC with documented WHO grade and graded concordantly: (APC, 3.8; 95% CI: −4.2, 12.4)

Table 1

Aggregated percentages for all selected CNS tumors classified by WHO grade (Collaborative Site Specific Factor 1) and microscopically confirmed from 2004 to 2011 (SEER 18 registries research data)

	Total counts	Documented WHO grade (%)	Documented WHO grade and graded concordantly (%)
Microscopically confirmed	57,480	33,639 (58.5)	31,490 (93.6)
Not microscopically confirmed	28,600	555 (1.9)	532 (95.9)
Total	86,080	34,194 (39.7)	32,022 (93.6)

Table 2

Individual percentages for selected CNS tumors classified by WHO grade (Collaborative Stage Site Specific Factor 1) and microscopically confirmed (MC) from 2004 to 2011 (SEER 18 registries research data)

Histological type	ICD-O-3 histology and behavior code	WHO grade	Total count	Total MC	% MC	% MC with documented WHO grade	% MC with documented WHO grade and graded concordantly
Pilocytic astrocytoma	9421/1	I	2083	2009	96.4	61.0	92.3
Anaplastic astrocytoma	9401/3	III	2378	2360	99.2	85.7	85.6
Glioblastoma*	9440/3, 9441/3, 9442/3	IV	21,428	19,655	91.7	66.9	97.2
Oligodendroglioma	9450/3	II	1841	1774	96.4	83.2	84.8
Anaplastic oligodendroglioma	9451/3	III	766	761	99.3	86.7	80.0
Oligoastrocytoma/anaplastic Oligoastrocytoma	9382/3	II & III	1350	1343	99.5	86.7	90.3
Ependymoma	9391/3, 9393/3	II	1482	1402	94.6	46.5	90.5
Anaplastic ependymoma	9392/3	III	302	302	100.0	79.8	87.1
Medulloblastoma	9470/3, 9471/3, 9474/3	IV	1003	987	98.4	53.5	96.6
Craniopharyngioma	9350/1, 9351/1, 9352/1	I	1230	1092	88.8	19.3	100.0
Hemangioblastoma	9161/1	I	1196	1112	93.0	23.0	98.8
Meningioma	9530/0, 9531/0, 9532/0, 9533/0, 9534/0, 9537/0	I	48,106	22,141	46.0	46.7	94.6
Atypical meningioma	9530/1, 9538/1, 9539/1	II	2153	1957	90.9	70.0	92.5
Anaplastic/malignant meningioma	9530/3, 9538/3, 9539/3	III	762	585	76.8	60.0	55.8

*Glioblastoma (9440/3), Giant Cell Glioblastoma (9441/3), Gliosarcoma (9442/3)

Table 3

Annual percentage changes (APC) and 95 % confidence intervals (95 % CI) between 2004 and 2011: All selected histologies, Glioblastoma/Giant Cell Glioblastoma/Gliosarcoma[a], Meningioma[b], Atypical Meningioma[c], Anaplastic/Malignant Meningioma[d] (SEER 18 Registries Research Data)

	Total MC	% MC		% MC with documented WHO grade		% MC with documented WHO grade and graded concordantly	
		APC	95 % CI	APC	95 % CI	APC	95 % CI
All selected histologies	57,480	−1.6	−2.1, −1.1	10.3	9.0, 11.5	–	–
2004–2007		–	–	–	–	1.8	1.0, 2.6
2007–2011		–	–	–	–	0.2	−0.3, 0.7
Glioblastoma[*]	19,655	0.3	0.0, 0.5	7.2	6.2, 8.2	0.7	0.4, 0.9
Meningioma	22,141	−3.1	−3.8, −2.5	18.3	13.8, 22.9	–	–
2004–2006		–	–	–	–	0.7	−1.0, 2.3
2006–2011		–	–	–	–	−0.6	−0.9, −0.2
Atypical meningioma	1,957	1.3	0.2, 2.4	11.8	7.9, 15.8	0.5	−0.8, 1.8
Anaplastic/malignant meningioma	585	2.9	1.7, 4.2	9.8	4.5, 15.4	3.8	−4.2, 12.4

[a,*] Glioblastoma (9440/3), Giant Cell Glioblastoma (9441/3), Gliosarcoma (9442/3)

[b] Meningioma (9530/0, 9531/0, 9532/0, 9533/0, 9534/0, 9537/0)

[c] Atypical Meningioma (9530/1, 9538/1, 9539/1)

[d] Anaplastic/Malignant Meningioma (9530/3, 9538/3, 9539/3)