Review

Issues of Diagnostic Review in Brain Tumor Studies: From the Brain Tumor Epidemiology Consortium

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Abstract

Epidemiologists routinely conduct centralized single pathology reviews to minimize interobserver diagnostic variability, but this practice does not facilitate the combination of studies across geographic regions and institutions where diagnostic practices differ. A meeting of neuropathologists and epidemiologists focused on brain tumor classification issues in the context of protocol needs for consortial studies (http://epi.grants.cancer.gov/btec/). It resulted in recommendations relevant to brain tumors and possibly other rare disease studies. Two categories of brain tumors have enough general agreement over time, across regions, and between individual pathologists that one can consider using existing diagnostic data without further review: glioblastomas and meningiomas (as long as uniform guidelines such as those provided by the WHO are used). Prospective studies of these tumors benefit from collection of pathology reports, at a minimum recording the pathology department and classification system used in the diagnosis. Other brain tumors, such as oligodendroglioma, are less distinct and require careful histopathologic review for consistent classification across study centers. Epidemiologic study protocols must consider the study specific aims, diagnostic changes that have taken place over time, and other issues unique to the type(s) of tumor being studied. As diagnostic changes are being made rapidly, there are no readily available answers on disease classification issues. It is essential that epidemiologists and neuropathologists collaborate to develop appropriate study designs and protocols for specific hypothesis and populations. (Cancer Epidemiol Biomarkers Prev 2008;17(3):484–9)

Challenges to Epidemiologic Studies of Brain Tumors

The difficulty in making the correct diagnosis for certain subtypes of brain tumors has received considerable attention in the neuropathology community (1). Epidemiologists routinely work with centralized single pathology reviews for all study cases to minimize interobserver variability among different hospital pathologists in a region. This practice does not necessarily translate to accurate or consistent combination of study subjects across regions as diagnostic practices may differ substantially.

Aside from rare genetic syndromes, familial aggregation of brain tumors, and high doses of ionizing radiation, major risk factors for brain tumors have not been identified (2-4). Different histologic types have characteristic gender and ethnic distributions; for example, gliomas are more common in Whites and males and meningiomas are more common in females. If different subtypes of brain tumors also have different risk factors,
combining these subtypes in etiologic or clinical studies could obscure real differences. Thus, tumor classification and grouping issues may be limiting our ability to clarify the role of additional risk factors.

The etiology of brain tumors involves interactions of genes and environmental exposures. The sample sizes needed to elucidate such complex multifactorial etiologies can only be obtained via large collaborative research studies. Thus, there is a need to obtain adequate numbers of homogeneous types of brain tumors to test specific hypothesis. This is challenging for a rare tumor with >100 recognized subtypes (5). The accuracy of diagnosis and decision of what tumor subtypes to group together directly affect the feasibility of obtaining large study sizes with adequate biological commonality to allow identification of unique risk factors. Studies need to systematically address the issue of diagnostic accuracy while successfully recruiting numbers to achieve adequate statistical power and accumulating high-quality biological data.

To address these challenges, the Brain Tumor Epidemiology Consortium (http://epi.grants.cancer.gov/btec/) assembled an international panel of neuropathologists and brain tumor epidemiologists at a September 2005 meeting in Chicago. Issues, problems, and solutions associated with the process of obtaining accurate tumor groupings for the purpose of supporting collaborative epidemiologic research were reviewed. The agenda was to improve the precision of brain tumor epidemiology studies by better defining and classifying these diseases into homogeneous groups, particularly for multisite studies. Here, we present a synthesis of this discussion, which is not a comprehensive overview but rather our perspective on those diagnostic issues of most relevance to epidemiologists focused on learning more about the etiology of these tumors.

Histologic Classification of Brain Tumors

Most brain tumor research efforts have focused on the common adult (gliomas and meningiomas) and pediatric tumors. A complete array of relevant subgroups has been identified for surveillance purposes (Table 1), and reliable implementation of these broad groupings may be useful for etiologic purposes.

Previous studies have investigated misclassification of brain tumors. In a population-based study comparing clinical diagnoses to those from an expert panel of reviewers, there was good agreement (90-95%) for benign brain tumors but only 77% agreement for gliomas as a broad category (6). Agreement varied by specific histology, from 0% in the mixed glioma category to 58% in the medulloblastoma category. The agreement between a neuropathology review and the original clinical diagnosis has also been studied: 72% agreement for major groupings was seen in a referral series (7), 86% agreement for all brain tumors seen in a clinical series (1), and 77% agreement was seen in a population-based series of gliomas (8).

Patterns of agreement depend on several factors: type of tumors, composition of reviewers, how consensus is defined (e.g., an 85% concordance with registry diagnosis was observed with one reviewer versus a 59% concordance with the same surveillance diagnosis and three reviewers), and type of clinical facility (community versus academic clinical centers; ref. 6). Neuropathology is a dynamic discipline, and diagnostic quality will continue to evolve as the implications of increased tumor specificity for clinical management become apparent.

Gliomas

The challenge in classifying gliomas lies in fitting brain tumors, which are on an almost continuous spectrum of histology and malignancy, into distinct categories. Errors can be expected to occur in classifying tumors that have characteristics of two or more histologies, making some tumor subtypes particularly problematic to replicate (e.g., glioblastoma with oligodendrogial components, oligoastrocytoma, and oligodendroglioma). In addition, morphologically ambiguous tumors, for which no clear diagnostic consensus can be reached, are not infrequent. In contrast, progress has been made in that neuropathologists can now differentiate between glioblastoma and anaplastic oligodendrogliomas.

Before the early 1990s, glioblastomas were classified under poorly differentiated and embryonal tumors with unclear criteria. With the 1993 version of the WHO classification, glioblastomas were classified under astrocytic tumors, and the transition from anaplastic astrocytoma was better defined. Two pathways for the development of glioblastomas are now recognized primary (de novo) and secondary (9). This distinction arises at the molecular level, although empirical definitions are in use and some overlap in the molecular profile of each type are recognized. Approximately 95% of glioblastomas are primary; the remaining secondary

Table 1. Distribution and incidence rates of primary brain and central nervous system tumors by major histology groupings (Central Brain Tumor Registry of the United States, 1998-2002)

<table>
<thead>
<tr>
<th>Major histology groups</th>
<th>Total n</th>
<th>% of all reported brain tumors</th>
<th>Median age at diagnosis</th>
<th>Incidence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumors of neuroepithelial tissue</td>
<td>27,776</td>
<td>43.6</td>
<td>53</td>
<td>6.42</td>
</tr>
<tr>
<td>Tumors of cranial and spinal nerves</td>
<td>5,084</td>
<td>8.0</td>
<td>52</td>
<td>1.17</td>
</tr>
<tr>
<td>Tumors of meninges</td>
<td>19,980</td>
<td>31.4</td>
<td>63</td>
<td>4.70</td>
</tr>
<tr>
<td>Lymphomas and hemopoietic neoplasms</td>
<td>1,975</td>
<td>3.1</td>
<td>60</td>
<td>0.46</td>
</tr>
<tr>
<td>Germ cell tumors and cysts</td>
<td>397</td>
<td>0.6</td>
<td>16</td>
<td>0.09</td>
</tr>
<tr>
<td>Tumors of the sellar region</td>
<td>4,496</td>
<td>7.1</td>
<td>48</td>
<td>1.03</td>
</tr>
<tr>
<td>Local extensions from regional tumors</td>
<td>116</td>
<td>0.2</td>
<td>48</td>
<td>0.03</td>
</tr>
<tr>
<td>Unclassified tumors</td>
<td>3,864</td>
<td>6.1</td>
<td>68</td>
<td>0.91</td>
</tr>
<tr>
<td>Total</td>
<td>63,698</td>
<td>100.0</td>
<td>57</td>
<td>14.80</td>
</tr>
</tbody>
</table>

NOTE: Rates are per 100,000 person-years, age adjusted to the 2000 U.S. Standard Population. Details are available at www.cbtrus.org.
glioblastomas develop in patients with a previous histologically confirmed diagnosis of astrocytoma (9, 10). A practical clinical definition for a primary glioblastoma may be “any glioblastoma patient with <3 months history of clinical symptoms.” This definition, for which information is generally available in clinical records, may be adequate to distinguish glioblastoma subtypes in epidemiologic studies. A consensus was reached that glioblastoma can be pooled without additional pathology review, although this approach could result in the omission of some cases that were not originally labeled as glioblastoma, especially if current WHO guidelines are not uniformly applied.

The goal of molecular classification is to identify subgroups of tumors with distinct biological and clinical behavior. Work is ongoing that uses genome-wide gene expression data to associate specific changes in gene expression with differences in outcome; some of this work also shows different subtypes of glioblastomas. Using genome-wide scans and high-throughput arrays, a working model for subtypes of high-grade astrocytomas has been presented that involves DNA, RNA, and clinical features (11, 12). However, expression data may reflect immunohistochemical results, and studies are needed to confirm these results. This problem may be avoided by using multiple datasets from different institutions to provide a more robust molecular classification (12). Using the profile of overexpressed genes, cluster analyses have identified major subgroups, mesenchymal, proneural, and proliferative in nature. These molecular subtypes appear to confer different outcome probabilities and also differ in average age of onset. For example, the proneural class tends to occur at younger ages than the other two classes. Although follow-up studies are needed to confirm these results, it is possible that etiologic factors also will differ for these phenotypes. This example illustrates the types of new data that are emerging and need to be considered when developing case definitions for epidemiologic studies.

Adult low-grade gliomas include the grade 2 counterparts of those tumors with the same cell types having anaplastic or grade 3 features, astrocytomas, oligodendrogliomas, oligoastrocytomas, and ependymomas. Abnormalities of different chromosomes have been found in the different histologic tumor types. Diffuse astrocytomas have mutations in the TP53 gene (>60%) and trisomy chromosome 7 (20%), although many tumors show no copy number abnormalities (13). Oligodendrogliomas with classic features have losses in 1p (75%) and 19q (70%), and a potential mechanism for this combined loss has been proposed (14, 15). Alternatively, oligodendrogliomas with less classic (more “astrocytic”) tumors have a lower rate of combined 1p/19q loss. It is currently not clear whether oligoastrocytoma is a unique genetic entity as so far these tumors appear to be similar to either the astrocytomas or the oligodendrogliomas. Little is known about ependymomas at the molecular level, apart from the fact that chromosome 22 and the NF2 tumor suppressor gene have been implicated in adult spinal ependymomas.

The classification of oligodendrogliomas and astrocytomas did not change dramatically between 1930s and 1980s. Between 1990 and 1995, several new tumors were recognized that show similarities to oligodendrogliomas (that is, central neurocytoma, dysembryoplastic neuroepithelial tumor, and clear cell ependymoma), making diagnosis more difficult. In 1994, losses in 1p and 19q were recognized primarily in association with oligodendrogliomas, and by 1998, these genetic changes had been directly correlated with therapeutic response. As such, during the period of 1995 to 2000, large shifts in diagnosis were taking place, with increases in incidences of oligodendrogliomas and oligoastrocytomas and the recognition of the new entities listed above. As a consequence, there were large declines in astrocytoma numbers.

To advance our understanding of the etiology of oligodendrogliomas, Brain Tumor Epidemiology Consortium has embarked on an effort to pool data from several case-control studies of gliomas. Among the biggest obstacles to combining data from these studies is the variation in classification among neuropathologists and over time. As classic oligodendrogliomas are the simplest subtype to categorize into a homogenous group, it is proposed that classic oligodendrogliomas be identified by a single experienced neuropathologist reviewer followed by confirmation of 1p/19q loss. Given subjectivity in the application of diagnostic criteria for some of these complex brain tumors, central review by a single pathologist reviewer has significant limitations for epidemiologic studies. Mixed gliomas (oligoastrocytoma) are a recognized category of tumors but are ill-defined, prone to subjectivity, and based on an unproven concept of dual differentiation of astrocytoma and oligodendroglioma as neoplastic processes. Although we know there are widespread differences in the application of diagnostic criteria and known discordance between nosology coding and diagnosis (6), the mixed glioma category has been widely used in surveillance and epidemiologic studies.

Emerging data suggest a coming era in which the precision of diagnosis can be increased by a combination of immunohistochemical and molecular techniques, although there are currently no standardized immunohistochemistry or molecular panels. The use of classic features is defined by WHO criteria (5) and provides another tool to improve precision, but these details may or may not be present in descriptions on pathology reports. If details on classifications are present in a high proportion of reports, they could be used with some confidence for the purposes of case ascertainment and classification in population-based studies. Tumors with nonclassic features (labeled as mixed glioma) may need additional state-of-the-art molecular markers integrated into diagnostic protocols. For these, the only feasible way to accomplish a consensus is through a centralized pathology review including two to three experienced neuropathologists. In addition, as more diagnostic markers become available, the potential for assigning a probability score to a diagnosis may become a useful option to prevent forcing diagnoses that are really on a continuum into categories. Using ongoing clinical trials with mandated tissue and blood collection protocols may be a useful platform for etiologic studies, although there are difficulties in choosing appropriate control groups for such studies.

Gliomas present the most challenges with respect to classification and the above discussion highlights issues relevant to large population studies. A consensus was
reached among the neuropathologists and epidemiologists that glioblastomas, as reported in medical records, are likely to be correctly diagnosed and recorded. Although a few glioblastomas may be called anaplastic astrocytomas and missed, one can be reasonably confident that a glioblastoma is a glioblastoma. This single subset of tumors may not require further review in epidemiology studies and may be identified using the appropriate International Classification of Diseases for Oncology codes as routinely available in pathology departments. Other glioma tumor types face special challenges and protocols would need to be approached collaboratively.

Meningiomas

Meningiomas are predominantly benign brain tumors that are relatively noncontroversial with respect to diagnosis. The year 2000 WHO classification of this tumor type lists 16 variants of meningiomas divided into three grades. About 90% are grade 1, 8% are atypical, and 1% to 2% are anaplastic. Multiple meningiomas do occur particularly in familial cases with NF2. A high proportion (50-60%) of these tumors show deletion of chromosome 22q and these are typically grade 1 tumors. Multiple meningiomas are also more frequent as radiation-associated tumors (16). It is important to note that all types of meningiomas can invade the brain and that brain invasion increases the risk of recurrence and worsens the prognosis. Some reports have suggested an increase in the incidence of meningiomas over time, but this increase is thought to arise from incidental diagnosis (17-19). Some registry systems, such as those in Sweden, have routinely captured all intracranial tumors and therefore include all meningiomas. In the United States, it is only recently that benign tumors have been ascertained routinely. Meningiomas are not complex to classify; there is a 90% concordance for benign tumors (6). A consensus was reached that a central pathology review is not needed and that review by a single pathologist is adequate for studies of meningiomas.

Pediatric Brain Tumors

The current classification scheme for pediatric central nervous system tumors is based purely on morphologic criteria and the “cell of origin” paradigm, although neural stem cells may be an alternative or complementary paradigm in the future (20). Pediatric tumor classification has evolved through the definition of clinicopathologic entities that necessitate definition of the histologic type and grade of tumors. This schema has the advantages of providing independent prognostic factors that are informative in the choice of treatments. These diagnoses are largely, but not always, reproducible, easy to perform, affordable, and well accepted in the clinical community. Nevertheless, the quality of diagnosis is dependent on the experience and expertise of the pathologist. With the possible exceptions of medulloblastoma and atypical teratoid/rhabdoid tumor, the potential contribution of genetic information has been largely ignored for pediatric tumors.

There are broad categories of pediatric tumors that may be important to consider from an epidemiologic perspective: embryonal tumors, glioneuronal tumors, and others (including germ cell tumors, primitive neuroectodermal tumors, and craniopharyngiomas). Several issues need to be resolved with respect to the classification of pediatric gliomas: whether grading of ependymomas and medulloblastomas is clinically important and to what extent pediatric gliomas differ from those in adults. As the classification of these rare pediatric tumors is evolving, no single classification approach for epidemiology studies can be recommended for these tumors.

Central Review Strategies

Centralized pathology reviews fall into two general categories: uniform and consensus. A uniform individual review is useful to ensure consistency in diagnosis when cases of very similar types are coming from many institutions. However, in this situation with difficult diagnostic categories, it may be necessary to have several reviewers evaluate the case and develop a consensus diagnosis to ensure that a common standard is met and, in so doing, improve the overall quality (precision) of the diagnosis. For example, a prospective study of familial glioma (Gliogene) is implementing a pathology review of all brain tumor slides by several independent neuropathologists (21). Each study center is bringing study slides to annual project meetings where they will be reviewed onsite by a team of reviewers in the pathology department. If consensus cannot be reached with existing material by reviewers, new slides will be cut from the paraffin blocks for a similar second review. Other markers will be used as necessary to verify diagnosis. Pathology slides and other materials will be returned with collaborators to the originating institution at the end of this in person review. Methods for virtual microscopy diagnosis are being explored and, if widely accepted, may aid in centralized review processes in the future. A centralized review protocol needs to be a detailed multidisciplinary approach so that each step in this review is well understood and consistent. No minimal classification scheme will be perfect, but such a protocol will at least allow multicenter studies, such as those conducted by Brain Tumor Epidemiology Consortium (http://epi.grants.cancer.gov/btec/), to operate with some consistency. As these protocols are developed with collaborating neuropathologists, the goal of better identifying homogeneous case series for analysis of risk factors for brain tumors should be realized.

Because of changes in the WHO classification that took place in 1993 and 2000, comparisons of cases collected before and after these dates will be problematic and will require special consideration (22). A new classification has just been published with revisions that are unlikely to affect groupings used in epidemiologic studies (5). As some diagnoses are more prone to error than others, a standard centralized pathology review protocol does not seem appropriate for all brain tumor subtypes and there may be situations, such as for glioblastomas or meningiomas, when a consensus pathology review is not essential. The tools for diagnosis have also changed. Some of the variation in diagnostic practices lies in the various classification and coding schemes used and the changes in classification schemes over time (Table 2). Although histology has been the traditional “gold standard” in tumor diagnosis, new radiological and molecular
methods have added information to better characterize brain tumor types. The inclusion of genetic markers in the diagnostic process has been highly clinically relevant for other cancer sites, such as lymphoma and sarcoma. Relevant markers are being developed in the areas of brain tumor classification but have not yet been implemented in routine clinical practice but should help to move the discipline away from the commonly used crude low-grade and high-grade distinctions.

Neuropathology collaborators are essential in helping to identify tumors subtypes that can be considered a “homogeneous” entity for study purposes and to determine the extent of diagnostic review necessary for each study question or objective. In so doing, they will help define the quality and type of materials needed for diagnostic review, identify appropriate molecular studies, define the clinical information necessary to minimize error, standardize relevant immunohistochemistry, define what pathologic data are needed to help evaluate diagnostic variation, and help determine which study centers to include. A patient’s diagnosis is based on the most malignant section of the tumor; thus, an adequate sample of the tumor is needed for accurate diagnosis. One needs to be aware that stereotactic biopsy yields only small tumor samples, which can lead to an incorrect classification or malignancy grading, even when considering the clinical history and contrast enhancement of the tumors in magnetic resonance imaging and positron emission tomography scans (9). Because of heterogeneity both within and among tumors and the large number of histologic types of brain tumors, histopathologic diagnosis can be highly subjective. Additional information that may be relevant to collect is any treatment before specimen collection, whether diagnosis was in a community or academic center, history and timing of any preexisting low-grade astrocytoma (so the natural history of disease can be studied) and the history (and timing) of any watchful waiting period for benign tumors.

Tradeoffs between diagnostic precision and the practical constraints of large population studies often need to be made in multi-institutional studies. Feasibility and human subject issues were discussed. If pathology material is available, a central diagnostic review becomes feasible. However, the criteria for what constitutes the most informative brain tumor tissue needs to be carefully defined, and as standard procedures for other tumor types may not be adequate for brain tumors, this may limit the collaboration of hospital pathology groups for brain tumors. In the event that pathology material is unavailable for review, a central overview of the original written pathology report (which includes a more detailed description of the histology of the tumor) may help in the validation of the diagnosis.

If potentially eligible cases were originally misdiagnosed as having another type of brain tumor, they will be lost to the pool of eligible cases in any subsequent study, resulting in a loss of statistical power. The only way to identify these misclassified cases would be to conduct a review of all brain tumors, which would be extremely expensive and time consuming. The feasibility of obtaining retrospective pathology materials (tumor tissue and slides) on living and deceased cases is currently being tested in pilot studies, because different institutions have different requirements for releasing tumor material. The ability to obtain tissue for diagnosis will affect study power, as the sample size may be limited by the proportion of material that can be obtained.

With respect to epidemiologic studies, the age-old question of whether to group or split diagnostic subtypes remains. Because of the potential for developmental differences in tumor subtypes and because etiologic studies to date have not identified many risk factors for brain tumors, researchers are attempting to analyze the most homogenous groups possible. This then requires larger sample sizes and the inclusion of cases from more hospitals and information from more diagnosing pathologists. The approach towards greater specificity of tumor type has been successful in ovarian (23) and lung (24) cancer studies. In brain tumor studies, we may need to do both: group, to retain as much statistical power as possible, and then split to see if variation is present, which may trigger new hypotheses and help us to learn more. There is no reason, a priori, to believe the same environmental risk factors are not important for many subtypes of brain tumors, just as radiation is a rather general risk factor for many cancers. For example, with breast cancer, a well-studied common tumor, we know now that there are many subtypes involved, distinguished not only by histology but also with regard to receptor status (ER, PR, HER, etc.) and genetic profile (e.g., BRCA). However, we still do not know the implications of these subtypes with respect to known risk factors.

Central pathology review as part of pooling data from retrospective studies has human subject implications. One major barrier may be lack of a recent informed consent for use of slides or tissue that would be needed for such a review. Many subjects may have died by the time of the proposed analysis. Unless consent for future studies was built into the original study design and tissue was stored in a biorepository, the investigators may be required to get consent from next-of-kin to obtain materials from the institution where surgery was done. Without this, one

Table 2. Different grading systems in place for glial tumors

<table>
<thead>
<tr>
<th>WHO grade</th>
<th>WHO designation</th>
<th>St. Anne’s Mayo System*</th>
<th>Common terms</th>
<th>Glioblastoma multiforme subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Pilocytic astrocytoma</td>
<td></td>
<td>Low-grade glioma</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Diffuse astrocytoma</td>
<td>Astrocytoma grade 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Anaplastic astrocytoma</td>
<td>Astrocytoma grade 3</td>
<td>High-grade glioma</td>
<td>Primary glioblastoma</td>
</tr>
<tr>
<td>IV</td>
<td>Glioblastoma</td>
<td>Astrocytoma grade 4</td>
<td></td>
<td>Secondary glioblastoma</td>
</tr>
</tbody>
</table>

*Developed for infiltrating astrocytomas only and does not include pilocytic tumors.

1Common terms are not recommended due their imprecision and they are included only for the sake of completeness.
must rely on the clinical (local) diagnosis to identify cases. Some, but not all, institutional review boards will provide waivers for review of materials from deceased subjects if vital status is well documented.

All prospective studies need to obtain consent for use of tissue/pathology slides and use of blood samples for future studies. Pathology slides are often required to be returned to the originating institution, so some effort may need to be made to get approval to retain some representative tissue at a central facility to avoid the expensive process of having to go back and recollect material as new hypotheses emerge. Investigators also need to obtain approval of ongoing studies to share de-identified data for collaborative studies. It is important to build the potential for future studies into protocols of ongoing studies.

Finally, etiologic research studies of concern to Brain Tumor Epidemiology Consortium and other disease-specific consortia often take many years to conduct, and even after completion, the clinical or intervention implications of results require extensive further research. Given this, it is not advisable to promise individual-level results to participants, because the clinical implications of such results usually will be unknown. Furthermore, although pathology review may identify a diagnostic error during the course of a study, research studies are not equipped to provide such information in a timely fashion to patients or their physicians. Thus, wording of consent forms should clearly specify that diagnostic reviews are not for clinical purposes and that individual results will not be provided to the participant.

Recommendations

A consensus was reached for two categories of brain tumors for which there is enough general agreement over time, across regions, and among pathologists that one can consider using existing data without a further central pathology review: glioblastoma and meningiomas. Therefore, prospective studies for these tumor sites do not need the traditional centralized consensus review. It is recommended that a minimum data set, including diagnosis and diagnostic information, such as pathology department and type of classification system used in diagnosis, be maintained when using existing data.

Consent forms should optimally include consent for future uses of data and specimens, including tissue for re-review, as diagnostic practices may change over time. Forms should also recognize that the diagnosis review is for research purposes and that it would generally not be of clinical relevance nor would it be appropriate to give this information to study subjects.

Because classification issues are tumor specific, each epidemiologic study, in conjunction with a collaborating neuropathologist coinvestigator, must consider the specific aims of the study, changes that have taken place over time, and the many issues unique to the type(s) of tumor being studied. There is no simple general answer on classification issues as changes are being made rapidly; epidemiologists, clinicians, and neuropathologists must work in close collaboration to know the details of the hypotheses and protocols and develop the most appropriate study designs to answer current and future questions.

Acknowledgments

We thank the scientists who attended the Brain Tumor Epidemiology Consortium Meeting in Chicago, September 2005, and who participated in the discussions that led to this work.

References

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