The 2016 WHO Classification of Tumours of the Central Nervous System: The Major Points of Revision

Takashi KOMORI¹

¹*Department of Laboratory Medicine and Pathology (Neuropathology),
Tokyo Metropolitan Neurological Hospital, Tokyo, Japan*

Abstract

The updated 2016 edition of the World Health Organization (WHO) Classification of Tumours of the Central Nervous System (CNS) uses molecular parameters and the histology to define the main tumor categories for the first time. This represents a shift from the traditional principle of using neuropathological diagnoses, which are primarily based on the microscopic features, to using molecularly-oriented diagnoses. Major restructuring was made with regard to diffuse gliomas, medulloblastomas and other embryonal tumors. New entities that are defined by both the histological and molecular features include glioblastoma, isocitrate dehydrogenase (IDH)-wildtype and glioblastoma, IDH-mutant; diffuse midline glioma, H3 K27M-mutant; *RELA* fusion-positive ependymoma; medulloblastoma, wingless (WNT)-activated and medulloblastoma, sonic hedgehog (SHH)-activated; and embryonal tumor with multilayered rosettes, C19MC-altered. In addition, some entities that are no longer diagnostically relevant—such as CNS-primitive neuroectodermal tumor—have been deleted from this updated edition. The WHO2016 certainly facilitates clinical and basic research to improve the diagnosis of brain tumors and patient care.

Key words: World Health Organization (WHO), classification, histology, genetics, new entities

Introduction

In the past decades, the traditional approach to the diagnosis of tumors of the central nervous system, which was primarily based on the microscopic features, has shifted to a molecularly-oriented approach. This change has been driven by genetic as well as epigenetic discoveries.¹⁾ The updated 4th edition of the World Health Organization (WHO) Classification of Tumours of the Central Nervous System (WHO2016) has opened the door to a molecular era that the neuropathology/neuro-oncology community has never faced.^{2–4)}

Since Bailey & Cushing introduced the histogenetic classification of the tumors of the central nervous system in 1926,⁵⁾ the basic concept of classification has remained essentially unchanged, regardless of developments in the methods that are applied to the analysis of human tissue. Tumors are classified according to their similarity to the constituent cells of the central nervous system, such as astrocytes, oligodendrocytes and ependymal cells and are further sub-classified according to the presumed level of differentiation, which is determined based on morphological irregularities in comparison to their normal counterpart.

Such similarities have been depicted by microscopic features on hematoxylin and eosin-stained sections, immunohistochemistry corresponding to lineage-specific proteins such as glial fibrillary acidic protein for the astrocytic lineage and ultrastructural findings that characterize histogenetic differentiation. Mitosis and cell cycle-specific antigens are used as markers to evaluate the proliferation activity and biological behavior (the WHO grading system).⁶⁾

These histogenetic classification and grading systems have been valid for near a century because they were roughly correlated with the prognosis and have remained beneficial to determining treatment strategies, including adjuvant therapies. Nonetheless, for the past 2 decades, these classification and grading systems have been challenged by genetic/epigenetic discoveries in at least three areas. First, histogenetic classification is no longer valid since it is clear that various differentiations can co-exist within the tissue of a single tumor. For example, astrocytic,⁷⁾ oligodendroglial⁸⁾ and ependymal tumors^{9–13)} can co-exist with mature neurons and ependymal differentiation can be found across many different lineages beyond ependymomas. Second, the prognoses are less correlated with the WHO grade than the major molecular profiles.^{14–21)} Third, when making a pathological diagnosis, inter-observer

differences are no longer acceptable since molecular testing offers better objectivity and reproducibility than subjective microscopic observation.^{22–24)}

One of the first genetic alterations that led to the transformation of the diagnostic approach was a codeletion of chromosome 1p and 19q in oligodendroglioma.^{14,25,26)} The term of oligodendroglioma was coined in remembrance of normal oligodendroglia, as defined by Baily & Cushing in the 1920s.⁵⁾ Nonetheless, true oligodendroglial differentiation, such as myelin formation, has never been identified in ultrastructural studies and neither myelin-related protein nor messenger RNA has been consistently demonstrated in oligodendroglioma. Instead, oligodendroglia-like cells are often found in various neuroepithelial tumors with diverse differentiation and biological behavior—a situation that has caused significant diagnostic difficulties.^{27–31)} On the other hand, the 1p/19q codeletion is well-correlated with both classic oligodendroglioma morphology and its clinical, radiological and biological characteristics,^{17,18,32,33)} all of which indicate that gliomas harboring 1p/19q fall into a single entity.

Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2, respectively) mutations are another type of genetic alteration that has had an impact on tumor classification.^{16–18,21,34)} These mutations are found exclusively in infiltrating astrocytomas and oligodendrogliomas but not in circumscribed astrocytomas or ependymomas.^{34–36)} A number of studies have shown that these mutations are strong prognostic makers and that they may well be the most upstream genetic event in the tumorigenesis of infiltrating astrocytomas and oligodendrogliomas.³⁷⁾ The discovery of *IDH1/2* mutations is significant because it provides further evidence to rebut the traditional histogenetic classification systems and because it provides a common frame for two different entities beyond presumed lineages.

The incorporation of the sonic hedgehog (SHH) and wingless (WNT) pathways in medulloblastomas also has prognostic and predictive implications.^{38,39)} Medulloblastoma with alterations in the WNT pathways is associated with a significantly indolent prognosis while medulloblastoma with group 3 and 4 has the worst prognosis. Most WNT-activated tumors exhibit classic medulloblastoma morphology but not all tumors with classic medulloblastoma morphology show WNT activation. Thus, medulloblastomas are classified according to their genetic and histological features.

The basic principles of the revision of WHO2016 The Haarlem consensus guidelines

Before the consensus meeting for WHO2016 in Heidelberg, a meeting was held in Haarlem, the

Netherlands, to discuss how non-histological data such as molecular information could be incorporated into the next WHO classification of brain tumors. A consensus was reached that molecular information should be incorporated into the next WHO classification in accordance with a set of guidelines provided by the “International Society of Neuropathology-Haarlem meeting”.⁴⁰⁾ The main recommendations were that (i) diagnostic entities should be defined as narrowly as possible in order to optimize inter-observer reproducibility, the clinicopathological predictions and therapeutic planning; (ii) diagnoses should be “layered” with a histological classification, the WHO grade and molecular information should be listed below an “integrated diagnosis” (Table 1); and (iii) determinations should be made for each tumor entity as to whether molecular information is required, suggested, or not needed for its definition.

Histology-based molecular classification

In WHO2016, the conventional histological results obtained using H&E-stained sections remain the initial stratifier. After determining the major category (such as infiltrating glioma, neuronal tumor or embryonal tumor) based on the histology, a subset is applied based on the results of molecular testing (Table 2).^{40,41)}

Table 1 Reporting format

	Nomenclature	Example
Layer 1	Integrated diagnosis (incorporating all tissue-based information)	Astrocytoma, IDHmt
Layer 2	Histological classification	Oligoastrocytoma
Layer 3	WHO grade (reflecting natural history)	II
Layer 4	Molecular information	IDH1R132H+, 1p/19q non-deleted, p53+, ATRX loss

IDH: isocitrate dehydrogenase, mt: mutant.

Table 2 Tumor categories requiring molecular information for classification

	Adults or supratentorial location	Child and adolescence or infratentorial location
Diffuse astrocytic and oligodendroglial tumors	<i>IDH1/2</i> 1p19q codeletion	H3 K27M
Ependymal tumors	<i>RELA</i> fusion	
Embryonal tumors		WNT/SHH <i>INI-1</i> , C19MC

IDH: isocitrate dehydrogenase.

In terms of discordant results such as “a diffuse glioma that histologically appears astrocytic but proves to have IDH mutation and 1p/19q codeletion” or “a tumor that resembles oligodendroglioma by light microscopy but has IDH, *ATRX* and *TP53* mutations in the setting of intact 1p and 19q”, it is clearly stated in the review article written by the senior editors of the WHO2016 that the genotype trumps the histological phenotype.³⁾ Nevertheless, it remains possible that ‘not otherwise specified (NOS)’ designations can be applied to discordant examples since the WHO2016 is predicated on the basis of combined phenotypic and genotypic classification and on the generation of “integrated” diagnoses.⁴⁰⁾

The ‘not otherwise specified’ (NOS) status

In accordance with the Haarlem guidelines, the NOS status was introduced in WHO2016 to define entities as narrowly as possible. NOS is applied when (i) genetic testing is not available, (ii) genetic testing does not show diagnostic genetic alterations that are compatible with the histological findings or (iii) when there is uncertainty about a tumor’s architectural or cytological features due to insufficient tissue sampling or the presence of tissue artifacts.^{2,3)}

The Major Points of Revision

The revised entities and variants are listed in Table 3.

Oligodendrogliomas: The histology of oligodendroglioma has to be ‘classic’, since this nomenclature is intended to define 1p19q codeleted glioma. More than 90% of classic oligodendrogliomas show IDH mutation and 1p19q codeletion; which is now considered a genetic signature of oligodendroglioma.³⁾ Given the high frequency of R132H mutations in *IDH1* that are detectable by immunohistochemistry,^{42,43)} molecular testing for another locus in *IDH1/2* may be required in less than 10% of classic oligodendrogliomas.⁴⁴⁾ If it becomes anaplastic, the classic histology will be unclear and genetic testing for codeletion will be mandatory in that setting. When a classic oligodendroglioma is classified as IDH wildtype, the final diagnosis is oligodendroglioma, NOS, after other mimicking entities are excluded (Table 4).³⁾

Diffuse astrocytomas (Fig. 1)

After the histological confirmation of astrocytoma, the second stratifier for adult patients is the presence or absence of *IDH1* or *IDH2* mutations. If *TP53* as well as *ATRX* mutations (both of which are mutually exclusive to 1p19q codeletion) are present in IDH-mutant gliomas, the diagnosis of oligodendroglioma is immediately excluded.^{41,45–47)} Either *TP53* or *ATRX*

mutations can be detected by immunohistochemistry (Table 5). If the tumor is located in the thalamus or pons, an H3 K27M mutation,^{48–50)} which is mutually exclusive of *IDH1/2* mutations, should be considered. When a 1p19q codeletion is present, the tumor is further classified as oligodendroglioma, regardless of the histology. All *IDH1/2*-mutant gliomas without codeletions are now classified as astrocytoma. Oligoastrocytoma, anaplastic oligoastrocytoma and glioblastoma with an oligodendroglial component were deleted from the classification, since they are no longer genetically relevant.³¹⁾ Gliomas in pediatric patients, particularly patients under ten years of age, are unlikely to possess *IDH1/2* mutations or 1p19q codeletions^{51–53)} and generally fall into the category of diffuse or anaplastic astrocytoma, IDH wildtype. The nosological positions of pediatric- and adult-type IDH-wildtype gliomas are currently ambiguous; most of the latter behave like glioblastoma,⁵⁴⁾ and are transcribed in italics. Although some data suggest that the prognosis of WHO grade II IDH-mutant glioma does not differ from that of WHO grade III IDH-mutant glioma,²⁰⁾ the grading scheme was not changed in this revision. Nonetheless some amendments will be required in the next revision.

Glioblastomas

The definition of this nomenclature remains histological rather than genetic, i.e. a high-grade glioma with predominantly astrocytic differentiation, featuring nuclear atypia, cellular pleomorphism as well as microvascular proliferation and/or necrosis.²⁾ Depending on the absence or presence of *IDH1/2* mutations, glioblastomas are divided into glioblastoma, IDH-wildtype, which corresponds to clinically-defined primary or *de novo* glioblastoma, and glioblastoma, IDH-mutant, which corresponds to so-called secondary glioblastoma.⁵⁵⁾ It was decided that the terms, primary and secondary, would not be used in WHO2016, since they are clinically defined. Glioblastomas with negative R132H *IDH1* immunohistochemistry are quite important clinically and are considered to be equivalent to glioblastoma, IDH-wildtype in patients older than 55 years of age, since no mutations other than *IDH1* R132H have been reported in glioblastomas in that age group.³⁾

One new glioblastoma variant is epithelioid glioblastoma, which has been designated as rhabdoid or epithelioid/rhabdoid.^{56,57)} To avoid confusion with true rhabdoid tumors such as atypical teratoid/rhabdoid tumor (AT/RT), which harbors *INI1* or *BRG1* mutations, the term ‘rhabdoid’ is abandoned to describe this variant; in approximately half of the cases, it lacks either mutation but harbors a *BRAF* V600E mutation.⁵⁷⁾

Table 3 Major points of revision

Diffuse astrocytic and oligodendroglial tumours	Embryonal tumours
Diffuse astrocytoma, IDH mutant	Medulloblastoma, genetically defined
Gemistocytic astrocytoma, IDH mutant	Medulloblastoma, WNT activated
<i>Diffuse astrocytoma IDH wildtype</i>	Medulloblastoma, SHH activated, <i>TP53 mutated</i>
Diffuse astrocytoma, NOS	Medulloblastoma, SHH activated, <i>TP53 wildtype</i>
	Medulloblastoma, non-WNT/non-SHH
Anaplastic astrocytoma, IDH mutant	<i>Medulloblastoma, group 3</i>
<i>Anaplastic astrocytoma, IDH wildtype</i>	<i>Medulloblastoma, group 4</i>
Anaplastic astrocytoma, NOS	
	Medulloblastoma, histologically defined
Glioblastoma, IDH wildtype	Medulloblastoma, classic
Giant cell glioblastoma	Medulloblastoma, desmoplastic/nodular
Gliosarcoma	Medulloblastoma with extensive nodularity
Epithelioid glioblastoma	Medulloblastoma, large cell/anaplastic
Glioblastoma, IDH mutant	
Glioblastoma, NOS	Medulloblastoma, NOS
Diffuse midline glioma, H3-K27M mutant	<i>Embryonal tumour with multilayered rosettes, C19MC altered</i>
Oligodendroglioma, IDH mutant and 1p/19q codeleted	Embryonal tumour with multilayered rosettes, NOS
Oligodendroglioma, NOS	Medulloepithelioma
Anaplastic oligodendroglioma, IDH mutant and 1p/19q codeleted	CNS neuroblastoma
Anaplastic oligodendroglioma, NOS	CNS ganglioneuroblastoma
	CNS embryonal tumour, NOS
<i>Oligoastrocytoma, NOS</i>	Atypical teratoid/rhabdoid tumour
<i>Anaplastic oligoastrocytoma, NOS</i>	<i>CNS embryonal tumour with rhabdoid features</i>
Other astrocytic tumours	
Pilocytic astrocytoma	
Pilomyxoid astrocytoma	
Subependymal giant cell astrocytoma	
Pleomorphic xanthoastrocytoma	
Anaplastic pleomorphic xanthoastrocytoma	

Table 4 WHO grade II adult diffuse gliomas

	Astrocytoma histology	Oligodendroglioma histology	Oligoastrocytoma or ambiguous histology
IDHmt, 1p19q-nondel, ATRX loss	Diffuse astrocytoma, IDHmt	Diffuse astrocytoma, IDHmt	Diffuse astrocytoma, IDHmt
IDHmt, 1p19q-codel, ATRX intact	Oligodendroglioma, IDHmt & 1p19q codel	Oligodendroglioma, IDHmt & 1p19q codel	Oligodendroglioma, IDHmt & 1p19q codel
IDHwt	Diffuse astrocytoma, IDHwt	Oligodendroglioma, NOS	Diffuse astrocytoma, IDHwt

IDH: isocitrate dehydrogenase.

Fig. 1 Anaplastic astrocytoma, WHO2016. (a) Relatively uniform oval to elongated nuclei are evident in microcystic background. (b) In a higher-powered view, some nuclei are naked without apparent cytoplasmic processes while some pose fibrillary processes, nuclei showing irregularity and hyperchromasia. Such features correspond to anaplastic oligoastrocytoma in the previous WHO classification. (c) IDH1R132H immunohistochemistry is negative. (d) p53 is diffusely positive, suggesting *TP53* mutation. (e) ATRX immunoreactivity is lost in tumor cells but intact in endothelial cells. (f) Positive p53 and negative ATRX suggest the presence of IDH mutation. Sanger sequence reveals a R132L mutation in *IDH1*.

Table 5 Immunohistochemical surrogates for molecular alterations required in WHO2016

Antibody	Clone	Molecular alterations	Positive pattern
<i>IDH1</i> R132H	H09	Arg to His at 132 in <i>IDH1</i>	Cytoplasmic staining
<i>ATRX</i>	HPA001906	<i>ATRX</i> mutations	Loss of nuclear expression
p53	DO-7	<i>TP53</i> mutations	More than 10% of nuclear expression
<i>BRAF</i> V600E	VE1	Val to Glu at 600 in <i>BRAF</i>	Cytoplasmic staining
H3 K27M	ABE419	Lys to Met at 27 in H3.1 or H3.3	Nuclear staining
L1CAM	OTI2C7	Correlation with C11orf95- <i>RELA</i> fusion and NF-Kappa B activation	Diffuse cytoplasmic staining
β -catenin	Ab610154	Medulloblastoma, WNT-activated	Diffuse nuclear staining
GAB1	Ab133486	Medulloblastoma, SHH-activated	Cytoplasmic staining
LIN28A	A177, #3978	ETMR	Diffuse cytoplasmic staining

IDH: isocitrate dehydrogenase.

Pediatric diffuse astrocytomas and oligodendrogliomas

These tumors, which share a common histology, are grouped with their adult counterparts in WHO2016, despite the clear difference in clinical behavior between the tumors in pediatric and adult patients.

This is partly because WHO2016 is an upgrade of the previous edition, which did not allow the coining of a new framework, such as pediatric glioma subgroup within the classification but also because no single genetic alteration is sufficient to create a new entity in these pediatric gliomas.^{51,52} The only

Fig. 2 Diffuse midline glioma, H3 K27M-mutant. (a) Axial FLAIR MRI shows an ill-defined high intensity area in the left thalamus. (b) Thalamic tumor shows diffuse astrocytic morphology with anaplasia. (c) The tumor cells show strong GFAP expression. (d) Sagittal FLAIR MRI shows a diffusely infiltrating pontine glioma expanding the pons. (e) *IDH1* R132H immunohistochemistry is negative. (f) Strong nuclear staining for K27M-mutant H3 is present.

exception is a newly defined entity, diffuse midline glioma, H3 K27M-mutant.²⁾

Diffuse midline glioma, H3 K27M-mutant (Fig. 2)

This is an infiltrative, high-grade glioma with predominately astrocytic differentiation that occurs in a midline location, i.e., the thalamus, brainstem or spinal cord, harboring a K27M mutation in either *H3F3A* or *HIST1H3B/C*.^{48,50)} This tumor predominately affects children but can also be seen in adults. It is classified as WHO grade IV regardless of the presence or absence of anaplastic features.²⁾

Ependymomas

There have been few changes in the nomenclature related to ependymomas in this revision, since the recently proposed molecular classification of

ependymomas is based on DNA methylation profiling, which is only available in restricted institutions.⁵⁸⁾ One genetically-defined ependymoma subtype, ependymoma, *RELA* fusion-positive, has been accepted. The genetic alteration of this subtype is detectable by fluorescence *in situ* hybridization (FISH).^{59,60)} This variant accounts for the majority of supratentorial examples. The expression of L1 cell adhesion molecule (CAM) is well correlated with the presence of a *RELA* fusion in supratentorial ependymomas but this is also expressed by other tumors.⁵⁹⁾

Neuronal and mixed neuronal-glial tumors (Fig. 3)

Two lesions, diffuse leptomeningeal glioneuronal tumor (DLGNT)^{61–63)} and multinodular and vacuolating neuronal tumor (MVNT),^{64–66)} both of which are considered to be unique lesions, have been described by various similar

Fig. 3 Diffuse leptomeningeal glioneuronal tumor (DLGNT) (a–d) and vacuolating neuronal tumor (MVNT) (e–j). (a) Expansion by tumor tissue of the cerebellar leptomeninges without apparent intraparenchymal masses (Klüver-Barrera staining). (b) Showing the mixture of small, round oligodendroglia-like cells and irregularly oriented neuronal cells. (c) Occasionally tumor tissue shows mucin-rich microcystic background. (d) Neuronal cells as well as the neoplastic stroma show positive synaptophysin immunoreactivity. (e, f) Axial FLAIR MRIs show a irregular cortical lesion in the right medial temporal lobe. (g) Multiple nodular or patchy lesions in the subcortical white matter are evident in Klüver-Barrera staining. (h) Dysplastic cells having an abundant amphiphilic to eosinophilic cytoplasm with peripheral Nissl substance showed focal clustering. (i). Tumor cells are strongly positive for α -internexin on the cell membranes. (j) The dysplastic neurons were intensely stained by HuC/Hu.

terms in the literature. DLGNT is characterized by the diffuse involvement of the leptomeninges, particularly those of the spinal cord, with or without recognizable parenchymal components. The major constituent of DLGNT is oligodendroglia-like cells with variable neuronal components (from neurocytes to ganglioid cells). DLGNT often poses *BRAF* fusions as well as chromosome 1p deletions.⁶³⁾ MVNT is a quasi-tumor that is characterized by multiple nodules composed of vacuolating dysplastic neurons in the subcortical white matter. A relatively restrictive—either nodular or ribbon-like—growth pattern suggests that MVNT has a hamartomatous nature.⁶⁶⁾

Embryonal tumors

The main changes in this category included the addition of medulloblastomas, which are genetically defined, and embryonal tumor with multilayered rosettes (ETMR), C19MC-altered. Central Nervous System (CNS)-primitive neuroectodermal tumor (PNET) was eliminated. For medulloblastoma, the most popular 4-type classification was not adopted in this revision;^{38,67)} however, WNT-activated, SHH-activated and non-WNT/SHH have been accepted instead. The SHH-activated tumors were divided into those with and without *TP53* mutations that can be detected by immunohistochemistry.⁶⁸⁾ Multilayered rosettes are characterized by a pseudostratified neuroepithelium with a central lumen covered by a defined apical surface with an internal limiting membrane; rosettes of this type always lack a defined outer membrane.^{69,70)} Multilayered rosettes are not always present in ETMR, C19MC-altered but medulloepithelioma-type rosettes may be present. Of note, a small portion of medulloepithelioma may harbor C19MC-alteration.⁷¹⁾ If no diagnostic genetic alteration is identified, the tumor is classified as plain “medulloepithelioma”.

DNA methylation profiling has revealed that majority of CNS-PNETs display molecular profiles indistinguishable from those of various other well-defined CNS tumor entities, which strongly suggests that CNS-PNETs are not an entity.⁷²⁾ In the remaining fractions, in which well-defined entities were excluded, some unknown tumors, one of which resembles CNS neuroblastoma, have been reported, the details of those unknown tumors remain unclear.⁷²⁾

Immunohistochemical surrogates in a clinical setting

Although WHO2016 does not allow the use of surrogate markers to detect molecular alterations, some hospitals/medical centers, particularly those located in areas other than Europe and North America, do not have full access to methods to detect the signature molecular alterations.⁷³⁾ In the clinical setting, the use of immunohistochemical

surrogates is necessary.⁷⁴⁾ Since Sanger sequencing, the most standard method to detect point mutations on *IDH1/2*, requires at least 20% of mutant alleles for identifying mutations,⁷⁵⁾ immunohistochemistry can be more sensitive than genetic testings. Nonetheless, it is important to bear in mind that no surrogate markers can be used as a substitute for an official WHO diagnosis and we have to facilitate departmental and institutional molecular testing to improve the diagnosis of brain tumors. The immunohistochemical surrogates that fulfill the WHO2016 diagnoses are shown in Table 5.

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Conflicts of Interest Disclosure

The author declares no conflicts of interest.

References

- 1) Louis DN: The next step in brain tumor classification: “Let us now praise famous men”... or molecules? *Acta Neuropathol* 124: 761–762, 2012
- 2) Louis DN, Ohgaki H, Wiestler OD, Cavenee WK: WHO classification of tumours of the central nervous system. Revise 4th edition. Lyon: IARC Press, 2016
- 3) Louis DN, Perry A, Reifenberger G, et al.: The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol* 131: 803–820, 2016
- 4) Perry A: WHO's arrived in 2016! An updated weather forecast for integrated brain tumor diagnosis. *Brain Tumor Pathol* 33: 157–160, 2016
- 5) Bailey P, Cushing H: A classification of tumors of the glioma group on a histogenetic basis with a correlated study of prognosis. Philadelphia: JB Lippincott, 1926
- 6) Louis DN, Ohgaki H, Wiestler OD, Cavenee WK: WHO Classification of Tumours of the Central Nervous System. 4th edition. Lyon: IARC Press, 2007
- 7) Teo JG, Gultekin SH, Bilsky M, Gutin P, Rosenblum MK: A distinctive glioneuronal tumor of the adult cerebrum with neuropil-like (including “rosetted”)

- islands: report of 4 cases. *Am J Surg Pathol* 23: 502–510, 1999
- 8) Perry A, Burton SS, Fuller GN, et al.: Oligodendroglial neoplasms with ganglioglioma-like maturation: a diagnostic pitfall. *Acta Neuropathol* 120: 237–252, 2010
 - 9) Rodriguez FJ, Scheithauer BW, Robbins PD, et al.: Ependymomas with neuronal differentiation: a morphologic and immunohistochemical spectrum. *Acta Neuropathol* 113: 313–324, 2007
 - 10) Brat DJ, Hirose Y, Cohen KJ, Feuerstein BG, Burger PC: Astroblastoma: clinicopathologic features and chromosomal abnormalities defined by comparative genomic hybridization. *Brain Pathol* 10: 342–352, 2000
 - 11) Pasquier B, Pécot M, Morrison AL, et al.: Chordoid glioma of the third ventricle: a report of two new cases, with further evidence supporting an ependymal differentiation, and review of the literature. *Am J Surg Pathol* 26: 1330–1342, 2002
 - 12) Jouvét A, Fauchon F, Liberski P, et al.: Papillary tumor of the pineal region. *Am J Surg Pathol* 27: 505–512, 2003
 - 13) Wang M, Tihan T, Rojiani AM, et al.: Monomorphous angiocentric glioma: a distinctive epileptogenic neoplasm with features of infiltrating astrocytoma and ependymoma. *J Neuropathol Exp Neurol* 64: 875–881, 2005
 - 14) Cairncross JG, Ueki K, Zlatescu MC, et al.: Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *J Natl Cancer Inst* 90: 1473–1479, 1998
 - 15) Ohgaki H, Kleihues P: Population-based studies on incidence, survival rates, and genetic alterations in astrocytic and oligodendroglial gliomas. *J Neuropathol Exp Neurol* 64: 479–489, 2005
 - 16) Hartmann C, Hentschel B, Wick W, et al.: Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas. *Acta Neuropathol* 120: 707–718, 2010
 - 17) Cancer Genome Atlas Research Network, Brat DJ, Verhaak RG, Aldape KD, et al.: Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. *N Engl J Med* 372: 2481–2498, 2015
 - 18) Eckel-Passow JE, Lachance DH, Molinaro AM, et al.: Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. *N Engl J Med* 372: 2499–2508, 2015
 - 19) Mur P, Mollejo M, Hernández-Iglesias T, et al.: Molecular classification defines 4 prognostically distinct glioma groups irrespective of diagnosis and grade. *J Neuropathol Exp Neurol* 74: 241–249, 2015
 - 20) Reuss DE, Mamatjan Y, Schrimpf D, et al.: IDH mutant diffuse and anaplastic astrocytomas have similar age at presentation and little difference in survival: a grading problem for WHO. *Acta Neuropathol* 129: 867–73, 2015
 - 21) Olar A, Wani KM, Alfaro-Munoz KD, et al.: IDH mutation status and role of WHO grade and mitotic index in overall survival in grade II-III diffuse gliomas. *Acta Neuropathol* 129: 585–596, 2015
 - 22) Kros JM, Gorlia T, Kouwenhoven MC, et al.: Panel review of anaplastic oligodendroglioma from European Organization For Research and Treatment of Cancer Trial 26951: assessment of consensus in diagnosis, influence of 1p/19q loss, and correlations with outcome. *J Neuropathol Exp Neurol* 66: 545–551, 2007
 - 23) Giannini C, Burger PC, Berkey BA, et al.: Anaplastic oligodendroglial tumors: refining the correlation among histopathology, 1p 19q deletion and clinical outcome in Intergroup Radiation Therapy Oncology Group Trial 9402. *Brain Pathol* 18: 360–369, 2008
 - 24) van den Bent MJ: Interobserver variation of the histopathological diagnosis in clinical trials on glioma: a clinician's perspective. *Acta Neuropathol* 120: 297–304, 2010
 - 25) Reifenberger J, Reifenberger G, Liu L, James CD, Wechsler W, Collins VP: Molecular genetic analysis of oligodendroglial tumors shows preferential allelic deletions on 19q and 1p. *Am J Pathol* 145: 1175–1190, 1994
 - 26) Ueki K, Nishikawa R, Nakazato Y, et al.: Correlation of histology and molecular genetic analysis of 1p, 19q, 10q, TP53, EGFR, CDK4, and CDKN2A in 91 astrocytic and oligodendroglial tumors. *Clin Cancer Res* 8: 196–201, 2002
 - 27) Giannini C, Scheithauer BW, Weaver AL, et al.: Oligodendrogliomas: reproducibility and prognostic value of histologic diagnosis and grading. *J Neuropathol Exp Neurol* 60: 248–262, 2001
 - 28) Miller CR, Dunham CP, Scheithauer BW, Perry A: Significance of necrosis in grading of oligodendroglial neoplasms: a clinicopathologic and genetic study of newly diagnosed high-grade gliomas. *J Clin Oncol* 24: 5419–5426, 2006
 - 29) Komori T, Hirose T, Shibuya M, Suzuki H, Tanaka S, Sasaki A: Controversies over the diagnosis of oligodendroglioma: a report from the satellite workshop at the 4th international symposium of brain tumor pathology, Nagoya Congress Center, May 23, 2012. *Brain Tumor Pathol* 30: 253–261, 2013
 - 30) Takahashi K, Tsuda M, Kanno H, et al.: Differential diagnosis of small cell glioblastoma and anaplastic oligodendroglioma: a case report of an elderly man. *Brain Tumor Pathol* 31: 118–123, 2014
 - 31) Sahm F, Reuss D, Koelsche C, et al.: Farewell to oligoastrocytoma: in situ molecular genetics favor classification as either oligodendroglioma or astrocytoma. *Acta Neuropathol* 128: 551–559, 2014
 - 32) Cairncross G, Wang M, Shaw E, et al.: Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. *J Clin Oncol* 31: 337–343, 2013
 - 33) van den Bent MJ, Brandes AA, Taphoorn MJ, et al.: Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic

- oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol* 31: 344–350, 2013
- 34) Yan H, Parsons DW, Jin G, et al.: IDH1 and IDH2 mutations in gliomas. *N Engl J Med* 360: 765–773, 2009
 - 35) Hartmann C, Meyer J, Balss J, et al.: Type and frequency of IDH1 and IDH2 mutations are Related to astrocytic and oligodendroglial differentiation and age: a study of 1,010 diffuse gliomas. *Acta Neuropathol* 2009
 - 36) Balss J, Meyer J, Mueller W, Korshunov A, Hartmann C, von Deimling A: Analysis of the IDH1 codon 132 mutation in brain tumors. *Acta Neuropathol* 116: 597–602, 2008
 - 37) Suzuki H, Aoki K, Chiba K, et al.: Mutational landscape and clonal architecture in grade II and III gliomas. *Nat Genet* 47: 458–468, 2015
 - 38) Taylor MD, Northcott PA, Korshunov A, et al.: Molecular subgroups of medulloblastoma: the current consensus. *Acta Neuropathol* 123: 465–472, 2012
 - 39) Kool M, Jones DT, Jäger N, et al.: ICGC PedBrain Tumor Project: Genome sequencing of SHH medulloblastoma predicts genotype-related response to smoothened inhibition. *Cancer Cell* 25: 393–405, 2014
 - 40) Louis DN, Perry A, Burger P, et al.; International Society of Neuropathology—Haarlem: International Society of Neuropathology—Haarlem consensus guidelines for nervous system tumor classification and grading. *Brain Pathol* 24: 429–435, 2014
 - 41) Reuss DE, Sahm F, Schrimpf D, et al.: ATRX and IDH1-R132H immunohistochemistry with subsequent copy number analysis and IDH sequencing as a basis for an “integrated” diagnostic approach for adult astrocytoma, oligodendroglioma and glioblastoma. *Acta Neuropathol* 129: 133–146, 2015
 - 42) Capper D, Berghoff AS, Magerle M, et al.: Immunohistochemical testing of BRAF V600E status in 1,120 tumor tissue samples of patients with brain metastases. *Acta Neuropathol* 123: 223–233, 2012
 - 43) Kato Y: Specific monoclonal antibodies against IDH1/2 mutations as diagnostic tools for gliomas. *Brain Tumor Pathol* 32: 3–11, 2015
 - 44) Arita H, Narita Y, Yoshida A, Hashimoto N, Yoshimine T, Ichimura K: IDH1/2 mutation detection in gliomas. *Brain Tumor Pathol* 32: 79–89, 2015
 - 45) Nguyen DN, Heaphy CM, de Wilde RF, et al.: Molecular and morphologic correlates of the alternative lengthening of telomeres phenotype in high-grade astrocytomas. *Brain Pathol* 23: 237–243, 2013
 - 46) Abedalthagafi M, Phillips JJ, Kim GE, et al.: The alternative lengthening of telomere phenotype is significantly associated with loss of ATRX expression in high-grade pediatric and adult astrocytomas: a multi-institutional study of 214 astrocytomas. *Mod Pathol* 26: 1425–1432, 2013
 - 47) Takami H, Yoshida A, Fukushima S, et al.: Revisiting TP53 mutations and immunohistochemistry—a comparative study in 157 diffuse gliomas. *Brain Pathol* 25: 256–265, 2015
 - 48) Khuong-Quang DA, Buczkowicz P, Rakopoulos P, et al.: K27M mutation in histone H3.3 defines clinically and biologically distinct subgroups of pediatric diffuse intrinsic pontine gliomas. *Acta Neuropathol* 124: 439–447, 2012
 - 49) Wu G, Broniscer A, McEachron TA, et al.; St. Jude Children’s Research Hospital–Washington University Pediatric Cancer Genome Project: Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. *Nat Genet* 44: 251–253, 2012
 - 50) Castel D, Grill J, Debily MA: Histone H3 genotyping refines clinico-radiological diagnostic and prognostic criteria in DIPG. *Acta Neuropathol* 131: 795–796, 2016
 - 51) Zhang J, Wu G, Miller CP, et al.; St. Jude Children’s Research Hospital–Washington University Pediatric Cancer Genome Project: Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas. *Nat Genet* 45: 602–612, 2013
 - 52) Wu G, Diaz AK, Paugh BS, et al.; St. Jude Children’s Research Hospital–Washington University Pediatric Cancer Genome Project: The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. *Nat Genet* 46: 444–450, 2014
 - 53) Rodriguez FJ, Tihan T, Lin D, et al.: Clinicopathologic features of pediatric oligodendrogliomas: a series of 50 patients. *Am J Surg Pathol* 38: 1058–1070, 2014
 - 54) Reuss DE, Kratz A, Sahm F, et al.: Adult IDH wild type astrocytomas biologically and clinically resolve into other tumor entities. *Acta Neuropathol* 130: 407–417, 2015
 - 55) Ohgaki H, Kleihues P: The definition of primary and secondary glioblastoma. *Clin Cancer Res* 19: 764–772, 2013
 - 56) Kleinschmidt-DeMasters BK, Alassiri AH, Birks DK, Newell KL, Moore W, Lillehei KO: Epithelioid versus rhabdoid glioblastomas are distinguished by monosomy 22 and immunohistochemical expression of INI-1 but not claudin 6. *Am J Surg Pathol* 34: 341–354, 2010
 - 57) Kleinschmidt-DeMasters BK, Aisner DL, Birks DK, Foreman NK: Epithelioid GBMs show a high percentage of BRAF V600E mutation. *Am J Surg Pathol* 37: 685–698, 2013
 - 58) Pajtler KW, Pfister SM, Kool M: Molecular dissection of ependymomas. *Oncoscience* 2: 827–828, 2015
 - 59) Parker M, Mohankumar KM, Punchihewa C, et al.: C11orf95-RELA fusions drive oncogenic NF- κ B signaling in ependymoma. *Nature* 506: 451–455, 2014
 - 60) Pietsch T, Wohlers I, Goschzik T, et al.: Supratentorial ependymomas of childhood carry C11orf95-RELA fusions leading to pathological activation of the NF- κ B signaling pathway. *Acta Neuropathol* 127: 609–611, 2014

- 61) Yamamoto T, Komori T, Shibata N, Toyoda C, Kobayashi M: Multifocal neurocytoma/gangliocytoma with extensive leptomeningeal dissemination in the brain and spinal cord. *Am J Surg Pathol* 20: 363–370, 1996
- 62) Rodriguez FJ, Perry A, Rosenblum MK, et al.: Disseminated oligodendroglial-like leptomeningeal tumor of childhood: a distinctive clinicopathologic entity. *Acta Neuropathol* 124: 627–641, 2012
- 63) Rodriguez FJ, Schniederjan MJ, Nicolaides T, Tihan T, Burger PC, Perry A: High rate of concurrent BRAF-KIAA1549 gene fusion and 1p deletion in disseminated oligodendroglioma-like leptomeningeal neoplasms (DOLN). *Acta Neuropathol* 129: 609–610, 2015
- 64) Huse JT, Edgar M, Halliday J, Mikolaenko I, Lavi E, Rosenblum MK: Multinodular and vacuolating neuronal tumors of the cerebrum: 10 cases of a distinctive seizure-associated lesion. *Brain Pathol* 23: 515–524, 2013
- 65) Nagaishi M, Yokoo H, Nobusawa S, et al.: Localized overexpression of alpha-internexin within nodules in multinodular and vacuolating neuronal tumors. *Neuropathology* 35: 561–568, 2015
- 66) Yamaguchi M, Komori T, Nakata Y, Yagishita A, Morino M, Isozaki E: Multinodular and vacuolating neuronal tumor affecting amygdala and hippocampus: A quasi-tumor? *Pathol Int* 66: 34–41, 2016
- 67) Ramaswamy V, Remke M, Bouffet E, et al.: Risk stratification of childhood medulloblastoma in the molecular era: the current consensus. *Acta Neuropathol* 131: 821–831, 2016
- 68) Zhukova N, Ramaswamy V, Remke M, et al.: Subgroup-specific prognostic implications of TP53 mutation in medulloblastoma. *J Clin Oncol* 31: 2927–2935, 2013
- 69) Judkins AR, Ellison DW: Ependymoblastoma: Dear, Damned, Distracting Diagnosis, Farewell!*. *Brain Pathol* 20: 133–139, 2008
- 70) Korshunov A, Remke M, Gessi M, et al.: Focal genomic amplification at 19q13.42 comprises a powerful diagnostic marker for embryonal tumors with ependymoblastic rosettes. *Acta Neuropathol* 120: 253–260, 2010
- 71) Spence T, Sin-Chan P, Picard D, et al.: CNS-PNETs with C19MC amplification and/or LIN28 expression comprise a distinct histogenetic diagnostic and therapeutic entity. *Acta Neuropathol* 128: 291–303, 2014
- 72) Sturm D, Orr BA, Toprak UH, et al.: New brain tumor entities emerge from molecular classification of CNS-PNETs. *Cell* 164: 1060–1072, 2016
- 73) Anderton JA, Lindsey JC, Lusher ME, et al.: Global analysis of the medulloblastoma epigenome identifies disease-subgroup-specific inactivation of COL1A2. *Neuro-oncology* 10: 981–994, 2008
- 74) Tanboon J, Williams EA, Louis DN: The Diagnostic Use of Immunohistochemical Surrogates for Signature Molecular Genetic Alterations in Gliomas. *J Neuropathol Exp Neurol* 75: 4–18, 2016
- 75) Arita H, Narita Y, Matsushita Y, et al.: Development of a robust and sensitive pyrosequencing assay for the detection of IDH1/2 mutations in gliomas. *Brain Tumor Pathol* 32: 22–30, 2015

Address reprint requests to: Takashi Komori, MD, PhD,
Department of Laboratory Medicine and Pathology
(Neuropathology), Tokyo Metropolitan Neurological
Hospital, 2-6-1 Musashidai, Fuchu, Tokyo 183-0042,
Japan.
e-mail: komori-tk@igakuken.or.jp