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The fifth edition of the World Health Organization Classification of Tumors of the Central Nervous System: Implications for cancer registries

Raoull Hoogendijk, Jasper van der Lugt, Eelco Hoving, Leontien Kremer, Otto Visser, Pieter Wesseling, Dannis van Vuurden†, and Henrike Karim-Kos†

Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands (R.H., J.v.d.L., E.H., L.K., P.W., D.v.V., H.K.-K.); Department of Neurosurgery, University Medical Center Utrecht, Utrecht, The Netherlands (E.H.); Department of Pediatrics, Emma Children's Hospital/ Amsterdam University Medical Center/AMC, Amsterdam, The Netherlands (L.K.); Department of Research, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, The Netherlands (O.V., H.K.-K.); Department of Pathology, Amsterdam University Medical Centers/VUmc, Amsterdam, The Netherlands (P.W.)

Corresponding Authors: Henrike E. Karim-Kos, PhD, Princess Máxima Center for Pediatric Oncology, Heidelberglaan 25, 3584 CS Utrecht, The Netherlands (h.e.karim-kos@prinsesmaximacentrum.nl); Raoull Hoogendijk, MSc, Princess Máxima Center for Pediatric Oncology, Heidelberglaan 25, 3584 CS Utrecht, The Netherlands (r.hoogendijk@prinsesmaximacentrum.nl)

†These authors contributed equally.

The fifth version of the World Health Organization Classification of Tumors of the Central Nervous System (WHO CNS5) that was published in 2021 represents a major revision of the recognized histo-molecular tumor types.[1] The impact was especially notable for glial tumors. Diffuse gliomas are now grouped according to adult type or pediatric type, the latter further differentiated into 2 families, low-grade and high-grade tumors, each encompassing 4 different tumor types.

Clinical implications of the WHO CNS5 were discussed in a previous editorial.[2] However, to date, the impact on cancer registries has been underexposed. The final WHO CNS5 Blue Book provided insight into which International Classification of Diseases for Oncology (ICD-O) morphology codes were assigned to the different tumor types. Unfortunately, ICD-O morphology codes from the third edition of the ICD-O (ICD-O-3) have not been updated and do not reflect all WHO CNS5 tumor entities accurately (Table 1).[3] For example, all pediatric-type diffuse high-grade gliomas (eg, diffuse midline glioma H3 K27–altered, diffuse hemispheric glioma H3 G34–mutant, and infant-type hemispheric glioma) are now grouped under the ICD-O morphology code 9385/3, not reflecting that these tumors differ in clinical outcomes. For research utilizing cancer registries, it will therefore impossible to differentiate these tumor entities and accurately reflect the clinical situation.

The clustering of different tumor entities to the same morphology code was driven by the fact that there is no plan to publish another version of the ICD-O-3. It is expected that a fifth digit will be added to the morphology code in the fourth edition of the ICD-O (ICD-O-4).[4] However, as the completion of the last blue book is planned for mid-2023, and ICD-O-4 will follow thereafter, the impact of clustering tumor entities has major consequences for cancer registry research in the coming years.

The WHO CNS classifications are primarily set up to support pathologists and oncologists to make an accurate diagnosis by means of international standardization of diagnostic criteria. However, the classification system is also used to facilitate comparability in (inter)national cancer research. Population-based studies have the potential to deliver a large sample size and there is limited to no selection bias. It also provides the possibility to study rare exposure and outcome measures, which can be used as mirror information in clinical practice and for novel research directions.[5] It is, therefore, of importance to overcome the limitations of clustering tumor entities.

Some interesting initiatives have already been taken by cancer registries after the publication of the 2016 WHO CNS classification system.[6] For example, from 2018 onwards, the North American Association of Central Cancer Registries includes the 2016 WHO CNS-defined molecular markers in their Uniform Data Standards. Consequently, since 2021, the Central Brain Tumor Registry of the United States reports the distribution of these markers for selected tumor entities in their annual statistical report.[7] However, for most countries including molecular markers will not be feasible due to costs and time restrictions, limiting its use.

Table 1 Tumors within the of the fifth edition of WHO CNS5 which were assigned the same ICD-O morphology code with their ICD-11 extension codes and molecular profile.

ICD-O-M	ICD-11 Extension Code	Tumor Type According to WHO CNS 5	Genes/ Molecular Profile
9421/1	Not yet available	Diffuse astrocytoma, MYB- or MYBL1-altered	MYB,MYBL1
9421/1	XH17F8	Diffuse low-grade glioma, MAPK pathway–altered	FGFR1, BRAF
9421/1	XH12D2	Pilocytic astrocytoma	KIAA1549-BRAF, BRAF, NF1
9385/3	XH7692[a] XH9YU2[b]	Diffuse midline glioma, H3 K27–altered	H3 K27,TP53, ACVR1, PDGFRA, EGFR, EZHIP
9385/3	XH2SS9	Diffuse hemispheric glioma, H3 G34–mutant	H3 G34,TP53, ATRX
9385/3	XH4Q01	Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype	IDH-wildtype, H3-wildtype, PDGFRA, MYCN, EGFR (methylome)
9385/3	XH4ZM8	Infant-type hemispheric glioma	NTRK family, ALK, ROS, MET
9412/1	XH6TQ7	Desmoplastic infantile ganglioglioma	
9412/1	XH7M44	Desmoplastic infantile astrocytoma	
9413/0	Not yet available	Polymorphous low-grade neuroepithelial tumor of the young	BRAF, FGFR family
9413/0	XH0H76	Dysembryoplastic neuroepithelial tumor	FGFR1
9509/1	XH3XU4	Papillary glioneuronal tumor	PRKCA
9509/1	XH2JU8	Rosette-forming glioneuronal tumor	FGFR1, PIK3CA, NF1
9509/1	Not yet available	Myxoid glioneuronal tumor	PDFGRA
9506/1	XH0C11	Central neurocytoma	
9506/1	XH2HS1	Extraventricular neurocytoma	
9506/1	XH2GB0	Cerebellar liponeurocytoma	
9391/3	Not yet available	Supratentorial ependymoma, NOS	
9391/3	Not yet available	Posterior fossa ependymoma, NOS	
9391/3	Not yet available	Spinal ependymoma, NOS	
9396/3	Not yet available	Supratentorial ependymoma, ZFTA fusion–positive	ZFTA, RELA, YAP1, MAML2
9396/3	Not yet available	Supratentorial ependymoma, YAP1 fusion–positive	ZFTA, RELA, YAP1, MAML2
9396/3	Not yet available	Posterior fossa group A (PFA) ependymoma	H3K27me3, EZHIP (methylome)
9396/3	Not yet available	Posterior fossa group B (PFB) ependymoma	H3K27me3, EZHIP (methylome)
9396/3	Not yet available	Spinal ependymoma, MYCN-amplified	NF2, MYCN
9471/3	XH7PN5	Desmoplastic nodular medulloblastoma	
9471/3	XH6JN6	Medulloblastoma with extensive nodularity	
9471/3	XH9M38	Medulloblastoma, SHH-activated and TP53-wildtype	TP53, PTCH1, SUFU, SMO, MYCN, GLI2 (methylome)
9474/3	XH5PR7	Large cell medulloblastoma	
9474/3	XH0H95	Anaplastic medulloblastoma	
9500/3	XH85Z0	CNS neuroblastoma, FOXR2-activated	FOXR2
9500/3	XH85Z0	CNS tumor with BCOR internal tandem duplication	BCOR
9362/3	XH1S48	Pineal parenchymal tumor of intermediate differentiation	
9362/3	XH1ZH1	Pineoblastoma	
9540/3	XH5C30	Malignant melanotic nerve sheath tumor	
9540/3	XH2XP8	Malignant peripheral nerve sheath tumor	
9766/1	XH4P09	Lymphomatoid granulomatosis	
9766/1	XH4F97	Lymphomatoid granulomatosis, grade 1	
9766/1	XH7BG6	Lymphomatoid granulomatosis, grade 2	
9749/3	XH1VJ3	Erdheim–Chester disease	
9749/3	EK92	Rosai–Dorfman disease	

[a] Diffuse midline glioma, H3 K27M-mutant.
[b] Diffuse intrinsic pontine glioma, H3 K27M-mutant.

A more feasible long-term solution appears to be the utilization of the 11th revision of the International Classification of Diseases and Related Health Problems (ICD-11), which has several advantages compared to the ICD-O coding system.[8] ICD-11 is the international standard for systematic recording, reporting, analysis, interpretation, and comparison of mortality and morbidity data. ICD-11 uses a hierarchical structure and has the possibility to assign specific extension codes for most pathological confirmed CNS tumor entities. In addition, recognized clinical entities without pathological confirmation like diffuse midline gliomas located in the pons, formerly diffuse intrinsic pontine glioma, are lacking a formal ICD-O morphology code but are recognized in ICD-11. This provides the opportunity to further differentiate tumors than, for example, the commonly used ICD-O denominator malignant Glioma, NOS (ICD-O-M 9380/3).

By means of extension codes for anatomy and topography, ICD-11 has the possibility to include detailed information on tumor location. Tumor location, according to ICD-O, is currently collected as a standard practice in most cancer registrations. However, the use of ICD-O topography codes for detailed differentiation is limited as these codes are an umbrella concept covering multiple locations in one code. For example, topography code *C71.7 Brain stem* can contain tumors located at the pons, medulla oblongata, but also the fourth ventricle. As no further details on tumor location are specified, it is impossible to further differentiate the tumor location leading to outcomes difficult to interpret at a clinical level. For example, when classifying pediatric high-grade gliomas for patients below 18 years in the Netherlands for the period 2003–2017 to their ICD-O topography codes *Brain Stem* (*C71.7, n* = 166) and Non-Brain Stem (*C71-C72* excl. *C71.7, n* = 106). Comparable survival outcomes are found with a median survival of 9.7 and 9.8 months ($P = 0.6$), respectively. When reclassifying these patients based on additionally gathered tumor location information to more clinically relevant groups, that is, midline ($n = 217$) and hemispheric ($n = 55$) tumors. Median survival for midline tumors was 9 months and differed significantly from hemispheric tumors (14 months, $P = 0.01$), showing the importance and difference detailed tumor location information can have on survival outcomes (R. Hoogendijk, unpublished data).

In contrast with the ICD-O-3, ICD-11 has abandoned the behavior code (fifth digit in ICD-O morphology code). This will facilitate a more accurate comparison between countries as grouping tumors to their behavior code can lead to biased estimates of incidence and survival.[9]

As estimation of time trends is a critical public health use of cancer registries, it is important when implementing ICD-11 to perform dual coding studies. These studies can help establish comparability factors for time trend analyses and provide an indication of the effect a newly implemented coding system has on incidence, survival and mortality outcomes.

A limitation of ICD-11 is that due to the recent publication of the final WHO CNS5 Blue Book, not all new CNS tumor entities are yet recognized by (eg, ependymomas), or differentiated to (ie, CNS neuroblastoma, FOXR2-activated, and CNS tumor with BCOR internal tandem duplication, Table 1), a unique extension code. However, the classification system is updated annually making this limitation temporary.

Lastly, implementing ICD-11 in cancer registries, many of which are under-resourced, will not be without challenges as it comes with additional costs and retraining of cancer registrars.

In conclusion, assigning multiple tumor entities to a single ICD-O morphology code can have major consequences for cancer registry research. Innovative measures and a fast response are needed from cancer registries and their stakeholders to prevent that they will lag behind in the continuously evolving field of CNS tumor classification. Using the ICD-11 extension and topography codes for the classification of CNS tumors will increase the clinical relevance of cancer registry data, facilitate a more clinically relevant comparison between countries, and make cancer registries future proof.

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