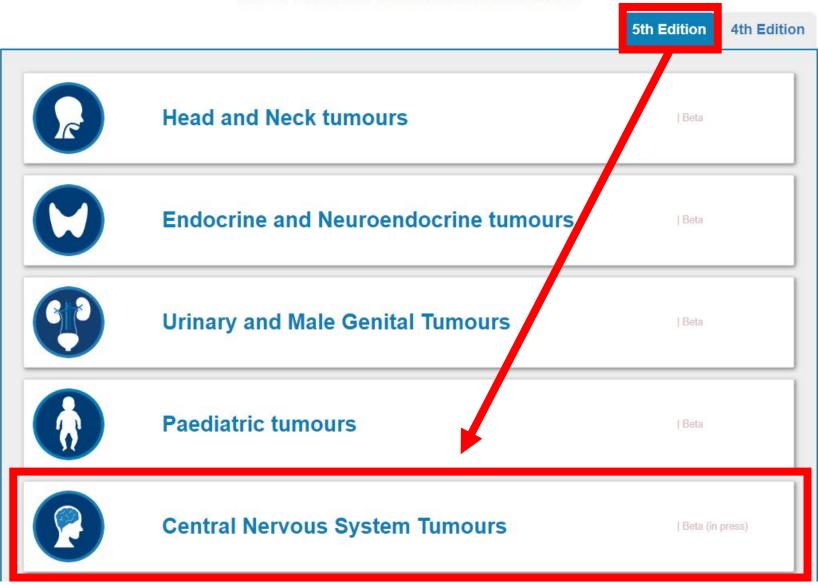
The BIGNEWS

for 2022

WHO Tumour classification series

WHO CNS 5E 2021!





WHO Classification of Tumours

Central Nervous System Tumours

- // Gliomas, glioneuronal tumours, and neuronal tumours
- // Gliomas, glioneuronal tumours, and neuronal tumours
- // Adult-type diffuse gliomas ✓

Epidermal growth factor receptor

 $\triangle A A$

Definition
ICD-O coding
ICD-11 coding
Related terminology
Subtype(s)
Localization
Clinical features
Epidemiology
Etiology

The receptor tyrosine kinase (RTK) EGFR (HER1) is frequently altered in IDH-wildtype glioblastoma. Overall, about 60% of tumours show evidence of *EGFR* amplification, mutation, rearrangement, or altered splicing { 24120142 }. The most frequent of these alterations is *EGFR* amplification { 1374522 }, which occurs in about 40% of all IDH-wildtype glioblastomas { 24120142 ; 30187121 } and in as many as 60% of glioblastomas in the DNA methylation group RTK2, but only in about 25% of RTK1 and mesenchymal glioblastomas { 23079654 ; 30187121 }. In the majority of cases, *EGFR* amplifications are associated with a second *EGFR* alteration, such as extracellular domain mutations or in-frame intragenic deletions encoding either *EGFRvIII* or other alternative transcripts { 24120142 ; 7622287 ; 2236070 }. *EGFR* gene fusions are discussed below.



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Review > Mutat Res. 1992 May;276(3):299-306. doi: 10.1016/0165-1110(92)90016-3.

Amplified cellular oncogenes in neoplasms of the human central nervous system

Affiliations + expand

PMID: 1374522 DOI: 10.1016/0165-1110(92)90016-3

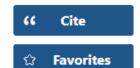
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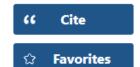
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G N Fuller ¹, S H Bigner

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Abstract

Similar articles

Mutation Research, 276 (1992) 299-306

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MUTREV 00323

Amplified cellular oncogenes in neoplasms of the human central nervous system

Gregory N. Fuller and Sandra H. Bigner

Department of Pathology, Duke University Medical Center, Durham, NC 27710 (U.S.A.)

(Accepted 12 December 1991)

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(protooncogene/c-erbB/peptide immunization/brain tumor)

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Head and Neck tumours

Small Stuff



WHO Grade vs <u>CNS</u> WHO Grade

WHO Grade vs CNS WHO Grade

WHO Grade vs CNS WHO Grade

• I, II, III, IV vs 1, 2, 3, 4

WHO Grade vs CNS WHO Grade

• 1, 11, 111, 11V vs 1, 2, 3, 4

WHO Grade vs CNS WHO Grade

• 1, 11, 111, 1V vs 1, 2, 3, 4

Pit Adenoma vs PitNET

WHO Grade vs CNS WHO Grade

• 1, 11, 111, 1V vs 1, 2, 3, 4

Pit Adenoma vs PitNET



WHO Classification of Tumours online

Central Nervous System Tumours // Tumours of the sellar region

// Pituitary adenoma / pituitary neuroendocrine tumour ❤



Definition

ICD-O coding

ICD-11 coding

Related terminology

Subtype(s)

Localization

Clinical features

Epidemiology

Etiology

Pathogenesis

Macroscopic appearance

Histopathology

Cytology

Diagnostic molecular pathology

Pituitary adenoma / pituitary neuroendocrine tumour 🗐

Definition

Pituitary adenoma / pituitary neuroendocrine tumour (PitNET) is a clonal neoplastic proliferation of anterior pituitary hormone–producing cells.

ICD-O coding

8272/3 Pituitary adenoma / pituitary neuroendocrine tumour (PitNET)

ICD-11 coding

2F37.Y & XH94U0 Other specified benign neoplasm of endocrine glands & Pituitary adenoma, NOS

2F9A & XH94U0 Neoplasms of unknown behaviour of endocrine glands & Pituitary adenoma, NOS

Related terminology

Acceptable: PitNET; pituitary adenoma.

NOS Not Otherwise Specified

NEC Not Elsewhere Classified









4th Edition



Head and Neck tumours

Biggest Change?



Paediatric tumours





WHO Tumour classification series

5th Edition

4th Edition

Dramatic expansion of newly codified tumors!





Newly RecognizedTumorTypes

Diffuse astrocytoma, MYB- or MYBL1-altered

Polymorphous low-grade neuroepithelial tumor of the young

Diffuse low-grade glioma, MAPK pathway-altered

Diffuse hemispheric glioma, H3 G34-mutant

Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype

Infant-type hemispheric glioma

High-grade astrocytoma with piloid features

 $Diffuse\ glioneuronal\ tumor\ with\ oligodendrog liom a-like\ features\ and\ nuclear\ clusters\ (provisional\ type)$

Myxoid glioneuronal tumor

Multinodular and vacuolating neuronal tumor

Supratentorial ependymoma, YAP1 fusion-positive

Posterior fossa ependymoma, group PFA

Posterior fossa ependymoma, group PFB

Spinal ependymoma, MYCN-amplified

Cribriform neuroepithelial tumor (provisional type)

CNS neuroblastoma, FOXR2-activated

CNS tumor with BCOR internal tandem duplication

Desmoplastic myxoid tumor of the pineal region, SMARCB1-mutant

Intracranial mesenchymal tumor, FET-CREB fusion positive (provisional type)

CIC-rearranged sarcoma

Primary intracranial sarcoma, DICER1-mutant

Pituitary blastoma

WHO 5E

22 NEW CNS TUMOR TYPES

Neuro-Oncology 2021 PMID 34185076

Table 7 Newly Recognized Tumor Types in the 2021 WHO Classification of Tumors of the Central Nervous System

Newly RecognizedTumorTypes

Diffuse astrocytoma, MYB- or MYBL1-altered

Polymorphous low-grade neuroepithelial tumor of the young

Diffuse low-grade glioma, MAPK pathway-altered

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Infant-type hemispheric glioma

High-grade astrocytoma with piloid features

Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (provisional type)

Myxoid glioneuronal tumor

Multinodular and vacuolating neuronal tumor

Supratentorial ependymoma, YAP1 fusion-positive

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Primary intracranial sarcoma, DICER1-mutant

Pituitary blastoma

WHO 5E

12 NEW

Molecular

Signature-Defined CNS TUMOR TYPES

Neuro-Oncology 2021 PMID 34185076

12 NEW

Molecular Signature-Defined **CNS Tumors**

TumorType	Genes/Molecular Profiles Characteristically Altered
Astrocytoma, IDH-mutant	IDH1, IDH2, ATRX, TP53, CDKN2A/B
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	IDH1, IDH2, 1p/19q, TERT promoter, CIC, FUBP1, NOTCH
Glioblastoma, IDH-wildtype	IDH-wildtype, TERT promoter, chromosomes 7/10, EGFR
Diffuse astrocytoma, MYB- or MYBL1-altered	MYB, MYBL1
Angiocentric glioma	MYB
Polymorphous low-grade neuroepithelial tumor of the young	BRAF, FGFR family
Diffuse low-grade glioma, MAPK pathway-altered	FGFR1, BRAF
Diffuse midline glioma, H3 K27-altered	H3 K27, TP53, ACVR1, PDGFRA, EGFR, EZHIP
Diffuse hemispheric glioma, H3 G34-mutant	H3 G34, TP53, ATRX
Diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype	IDH-wildtype, H3-wildtype, PDGFRA, MYCN, EGFR (methylome)
Infant-type hemispheric glioma	NTRK family, ALK, ROS, MET
Pilocytic astrocytoma	KIAA1549-BRAF, BRAF, NF1
High-grade astrocytoma with piloid features	BRAF, NF1, ATRX, CDKN2A/B (methylome)
Pleomorphic xanthoastrocytoma	BRAF, CDKN2A/B
Subependymal giant cell astrocytoma	TSC1, TSC2
Chordoid glioma	PRKCA
Astroblastoma, MN1-altered	MN1
Ganglion cell tumors	BRAF
Dysembryoplastic neuroepithelial tumor	FGFR1
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters	Chromosome 14, (methylome)
Papillary glioneuronal tumor	PRKCA
Rosette-forming glioneuronal tumor	FGFR1, PIK3CA, NF1
Myxoid glioneuronal tumor	PDFGRA
Diffuse leptomeningeal glioneuronal tumor	KIAA1549-BRAF fusion, 1p (methylome)
Multinodular and vacuolating neuronal tumor	MAPK pathway
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	PTEN
Extraventricular neurocytoma	FGFR (FGFR1-TACC1 fusion), IDH-wildtype
Supratentorial ependymomas	ZFTA, RELA, YAP1, MAML2
Posterior fossa ependymomas	H3 K27me3, EZHIP (methylome)
Spinal ependymomas	NF2, MYCN
Medulloblastoma, WNT-activated	CTNNB1, APC
Medulloblastoma, SHH-activated	TP53, PTCH1, SUFU, SMO, MYCN, GLI2 (methylome)
Medulloblastoma, non-WNT/non-SHH	MYC, MYCN, PRDM6, KDM6A (methylome)
Atypical teratoid/rhabdoid turnor	SMARCB1, SMARCA4
Embryonal tumor with multilayered rosettes	C19MC, DICER1
CNS neuroblastoma, FOXR2-activated	FOXR2
CNS tumor with BCOR internal tandem duplication	BCOR
Desmoplastic myxoid tumor of the pineal region, SMARCB1-mutant	SMARCB1
Meningiomas	NF2, AKT1, TRAF7, SMO, PIK3CA; KLF4, SMARCE1, BAP1 in subtypes; H3K27me3; TERT promoter, CDKN2A CNSWHO grade 3
Solitary fibrous tumor	NAB2-STAT6
Meningeal melanocytic tumors	NRAS (diffuse); GNAQ, GNA11, PLCB4, CYSLTR2 (circum scribed)
Adamantinomatous craniopharyngioma	CTNNB1
Papillary craniopharyngioma	BRAF

WHO 5E

43 Tumor Types with *critical* molecular signature determinants

WHO CNS 5 (WHO 2021) Major Changes in the Most Common CNS Tumor Types

Major Changes in the Most Common CNS Tumor Types

- Adult-type Diffuse Gliomas
- Pediatric-type Diffuse Gliomas
- Ependymomas
- Meningiomas

2. Gliomas, glioneuronal tumours, and neuronal tumours

Gliomas, glioneuronal tumours, and neuronal tumours: Introduction Gliomas, glioneuronal tumours, and neuronal tumours

Adult-type diffuse gliomas

Astrocytoma, IDH-mutant

Oligodendroglioma, IDH-mutant and 1p/19q-codeleted

Glioblastoma, IDH-wildtype

Paediatric-type diffuse low-grade gliomas

Diffuse astrocytoma, MYB- or MYBL1-altered

Angiocentric glioma

Polymorphous low-grade neuroepithelial tumour of the young

Diffuse low-grade glioma, MAPK pathway-altered

Paediatric-type diffuse high-grade gliomas

Diffuse midline glioma, H3 K27-altered

Diffuse hemispheric glioma, H3 G34-mutant

Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype

Infant-type hemispheric glioma

Circumscribed astrocytic gliomas

Pilocytic astrocytoma

High-grade astrocytoma with piloid features

Pleomorphic xanthoastrocytoma

Subependymal giant cell astrocytoma

Chordoid glioma

Astroblastoma, MN1-altered

Adult-type diffuse gliomas

Astrocytoma, IDH-mutant

Oligodendroglioma, IDH-mutant and 1p/19q-codeleted

Glioblastoma, IDH-wildtype

Paediatric-type diffuse low-grade gliomas

Diffuse astrocytoma, MYB- or MYBL1-altered

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Infant-type hemispheric glioma

Adult-Type Diffuse Gliomas (WHO 2000/2016) 10 entities!

Adult-Type Diffuse Gliomas (WHO 2000/2016) 10 entities!

- Diffuse Astrocytoma, IDH-Mutant, WHO Grade II
- Diffuse Astrocytoma, IDH-Wildtype, WHO Grade II
- Anaplastic Astrocytoma, IDH-Mutant, WHO Grade III
- Anaplastic Astrocytoma, IDH-Wildtype, WHO Grade III
- Glioblastoma, IDH-Mutant, WHO Grade IV
- Glioblastoma, IDH-Wildtype, WHO Grade IV
- Oligodendroglioma, IDH-Mutant, 1p/19q-Codeleted, WHO Grade II
- Anaplastic Oligodendroglioma, IDH-Mutant, 1p/19q-Codeleted, WHO Grade III
- Oligoastrocytoma, WHO Grade II
- Anaplastic Oligoastrocytoma, WHO Grade III

Adult-Type Diffuse Gliomas (WHO 2021)

Only 3 Distinct Diseases!

- Astrocytoma, IDH-Mutant
- Glioblastoma, IDH-Wildtype
- Oligodendroglioma, IDH-Mutant, 1p/19q-Codeleted

International Agency for Research on Cancer



WHO Classification of Tumours online

Central Nervous System Tumours

- // Gliomas, glioneuronal tumours, and neuronal tumours
- // Gliomas, glioneuronal tumours, and neuronal tumours
- // Adult-type diffuse gliomas // Astrocytoma, IDH-mutant ➤



Definition

ICD-O coding

ICD-11 coding

Related terminology

Subtype(s)

Localization

Clinical features

Epidemiology

Etiology

Pathogenesis

Macroscopic appearance

Histopathology

Cytology

Diagnostic molecular pathology

Essential and desirable diagnostic criteria

Staging

Prognosis and prediction

Astrocytoma, IDH-mutant 힌

Definition

Astrocytoma, IDH-mutant, is a diffusely infiltrating *IDH1*- or *IDH2*-mutant glioma with frequent *ATRX* and/or *TP53* mutation and absence of 1p/19q codeletion (CNS WHO grade 2, 3, or 4).

ICD-O coding

9400/3 Astrocytoma, IDH-mutant, grade 2

9401/3 Astrocytoma, IDH-mutant, grade 3

9445/3 Astrocytoma, IDH-mutant, grade 4

ICD-11 coding

2A00.0Y & XH6PH6 Other specified gliomas of brain & Astrocytoma, NOS 2A00.0Y & XH2HK4 Other specified gliomas of brain & Diffuse astrocytoma, IDH-mutant

Related terminology

Not recommended: diffuse astrocytoma, IDH-mutant; anaplastic astrocytoma, IDH-mutant; glioblastoma, IDH-mutant; low-grade astrocytoma; lower-grade astrocytoma; high-grade astrocytoma; infiltrating astrocytoma; diffuse

IDH-Mutant Astrocytoma

Astrocytoma, IDH-Mutant, CNS WHO Grade 2

Astrocytoma, IDH-Mutant, CNS WHO Grade 3

Astrocytoma, IDH-Mutant, CNS WHO Grade 4

IDH-Mutant Astrocytoma

Astrocytoma, IDH-Mutant, CNS WHO Grade 2

- Mitotic activity absent or very low
- NO microvascular proliferation
- NO necrosis
- NO CDKN2A/B homozygous deletion

Astrocytoma, IDH-Mutant, CNS WHO Grade 3

- Mitotic activity elevated
- NO microvascular proliferation
- NO necrosis
- NO CDKN2A/B homozygous deletion

Astrocytoma, IDH-Mutant, CNS WHO Grade 4

At least one of the following must be present:

- Microvascular proliferation, or
- Necrosis, or
- CDKN2A/B homozygous deletion

Glioblastoma, IDH-Wildtype, CNS WHO Grade 4

At least one of the following must be present:

- Microvascular proliferation, or
- Necrosis, or
- TERT promoter mutation, or
- EGFR gene amplification, or
- Combined gain of chr 7 with loss of chr 10 (+7/-10)

? IDH-Wildtype Astrocytoma, Grade 2, Grade 3?

Diffuse Astrocytoma, IDH-Wildtype, WHO Grade 2

- Mitotic activity absent or very low
- NO microvascular proliferation
- NO necrosis
- NO TERTp mutation, EGFR amplification, or +7/-10

Anaplastic Astrocytoma, IDH-Wildtype, WHO Grade 3

- Mitotic activity elevated
- NO microvascular proliferation
- NO necrosis
- NO TERTp mutation, EGFR amplification, or +7/-10

? IDH-Wildtype Astrocytoma, Grade 2, Grade 3?

Diffuse Astrocytoma, IDH-Wildtype, WHO Grade 2

- Mitotic activity absent or very low
- NO microvascular proliferation
- NO necrosis
- NO TERTp mutation, EGFR amplification, or +7/-10

Anaplastic Astrocytoma, IDH-Wildtype, WHO Grade 3

- Mitotic activity elevated
- NO microvascular proliferation
- NO necrosis
- NO TERTp mutation, EGFR amplification, or +7/-10

Adult-type diffuse gliomas

Astrocytoma, IDH-mutant

Oligodendroglioma, IDH-mutant and 1p/19q-codeleted

Glioblastoma, IDH-wildtype

Paediatric-type diffuse low-grade gliomas

Diffuse astrocytoma, MYB- or MYBL1-altered

Angiocentric glioma

Polymorphous low-grade neuroepithelial tumour of the young

Diffuse low-grade glioma, MAPK pathway-altered

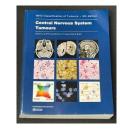
Paediatric-type diffuse high-grade gliomas

Diffuse midline glioma, H3 K27-altered

Diffuse hemispheric glioma, H3 G34-mutant

Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype

Infant-type hemispheric glioma



? IDH-Wildtype Astrocytoma, Grade 2, Grade 3?

Diffuse Astrocytoma, IDH-Wildtype NOS WHO Histologic Grade 2

- Mitotic activity absent or very low
- NO microvascular proliferation
- **NO** necrosis
- **NO** *TERT*p mutation, *EGFR* amplification, or +7/-10

Anaplastic Astrocytoma, IDH-Wildtype NOS WHO Histologic Grade 3

- Mitotic activity elevated
- NO microvascular proliferation
- NO necrosis
- **NO** *TERT*p mutation, *EGFR* amplification, or +7/-10

Oligodendroglioma

 Oligodendroglioma, IDH-Mutant and 1p/19q-Codeleted, CNS WHO Grade 2

 Oligodendroglioma, IDH-Mutant and 1p/19q-Codeleted, CNS WHO Grade 3

Oligodendroglioma

Oligodendroglioma, NOS
 CNS WHO Grade 2

Oligodendroglioma, NOS
 CNS WHO Grade 3

Pediatric-Type Diffuse Gliomas

Adult-type diffuse gliomas

Astrocytoma, IDH-mutant

Oligodendroglioma, IDH-mutant and 1p/19q-codeleted

Glioblastoma, IDH-wildtype

Paediatric-type diffuse low-grade gliomas

Diffuse astrocytoma, MYB- or MYBL1-altered

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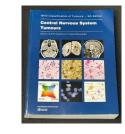
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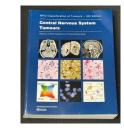
Paediatric-type diffuse high-grade gliomas

Diffuse midline glioma, H3 K27-altered

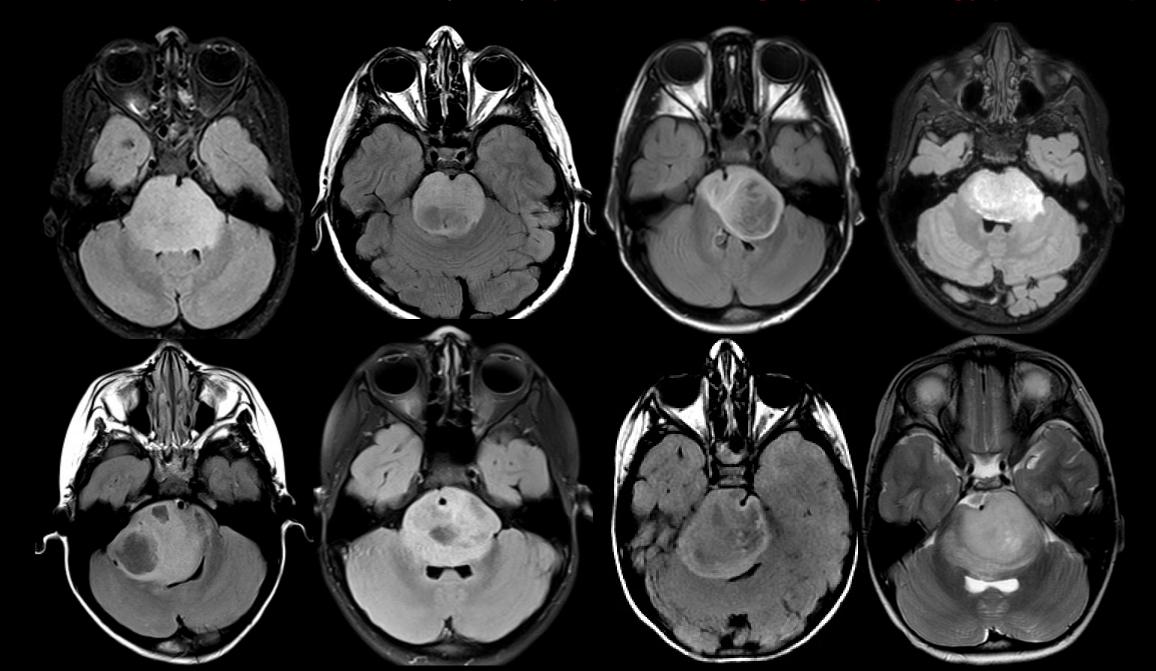
Diffuse hemispheric glioma, H3 G34-mutant

Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype

Infant-type hemispheric glioma

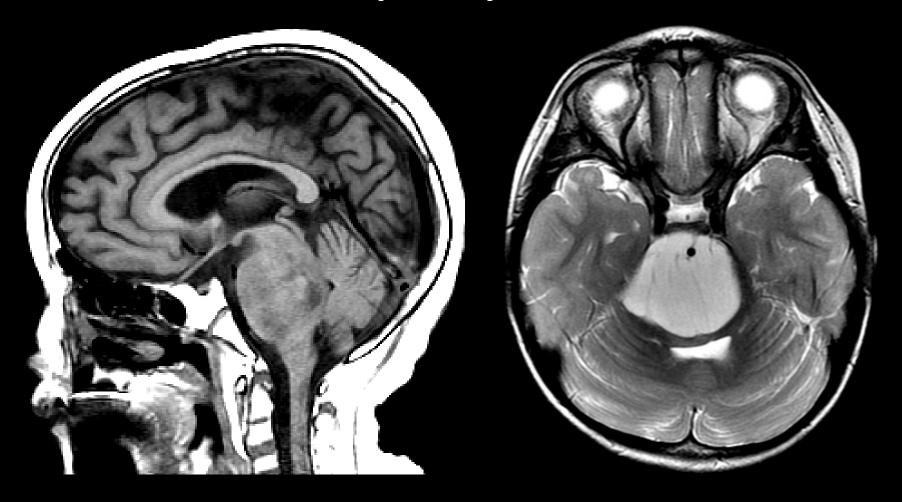


Diffuse Intrinsic Pontine Glioma (DIPG) Spectrum of Imaging Morphology (8 Patients)



Diffuse Midline Glioma, H3 K27-Altered

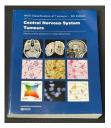
Classical Pontine Glioma (DIPG) 80% are H3 K27-Alt DMG



Diffuse midline glioma, H3 K27-altered

Definition

Diffuse midline glioma, H3 K27—altered, is an infiltrative midline glioma with loss of H3 p.K28me3 (K27me3) and usually either an H3 c.83A>T p.K28M (K27M) substitution in one of the histone H3 isoforms, aberrant overexpression of EZHIP, or an *EGFR* mutation (CNS WHO grade 4).



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ICD-O coding

9385/3 Diffuse midline glioma, H3 K27-altered

ICD-11 coding

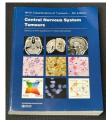
2A00.0Y & XH7692 Other specified gliomas of brain & Diffuse midline glioma, H3 K27M-mutant

Related terminology

Acceptable: diffuse intrinsic pontine glioma.

Subtype(s)

Diffuse midline glioma, H3.3 K27-mutant; diffuse midline glioma, H3.1 or H3.2 K27-mutant; diffuse midline glioma, H3-wildtype with EZHIP overexpression; diffuse midline glioma, EGFR-mutant



Pediatric Diffuse Gliomas Histone H3 Mutation

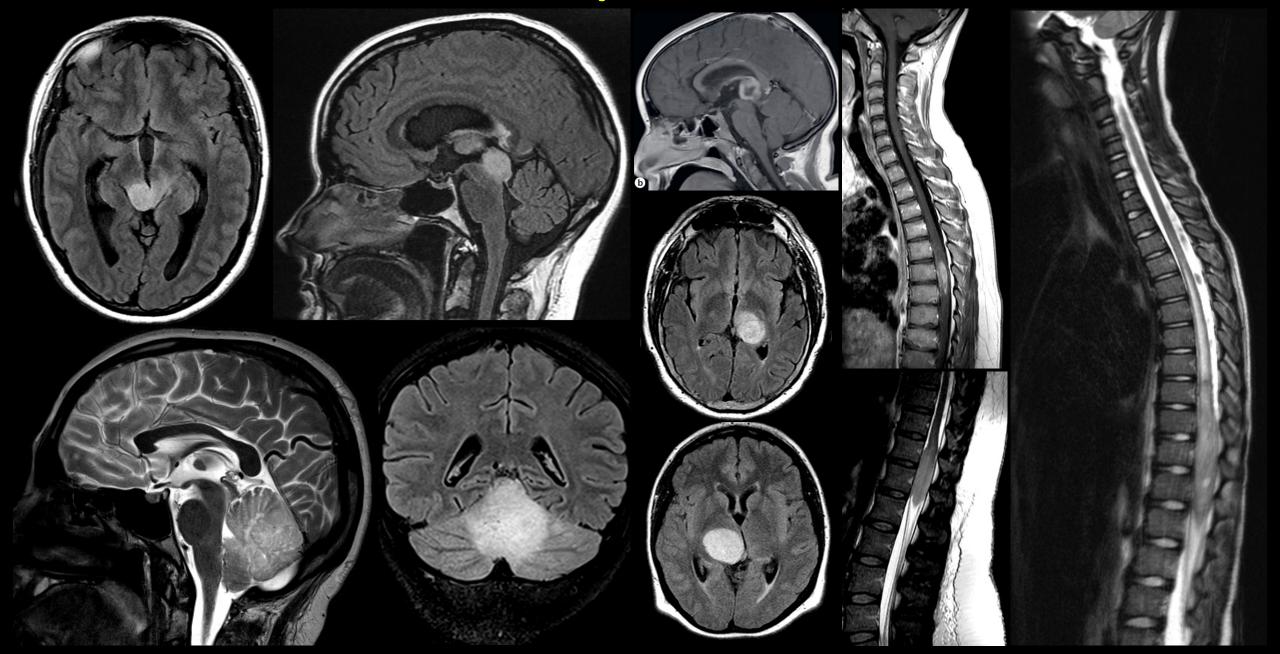
- H3 K27-Altered in the MIDLINE
 Diffuse Midline Glioma, H3 K27-Altered
- H3 G34-Mutant in the Cerebral Hemisphere
 Diffuse Hemispheric Glioma, G34-Mutant

Histone H3 Mutation Nomenclature

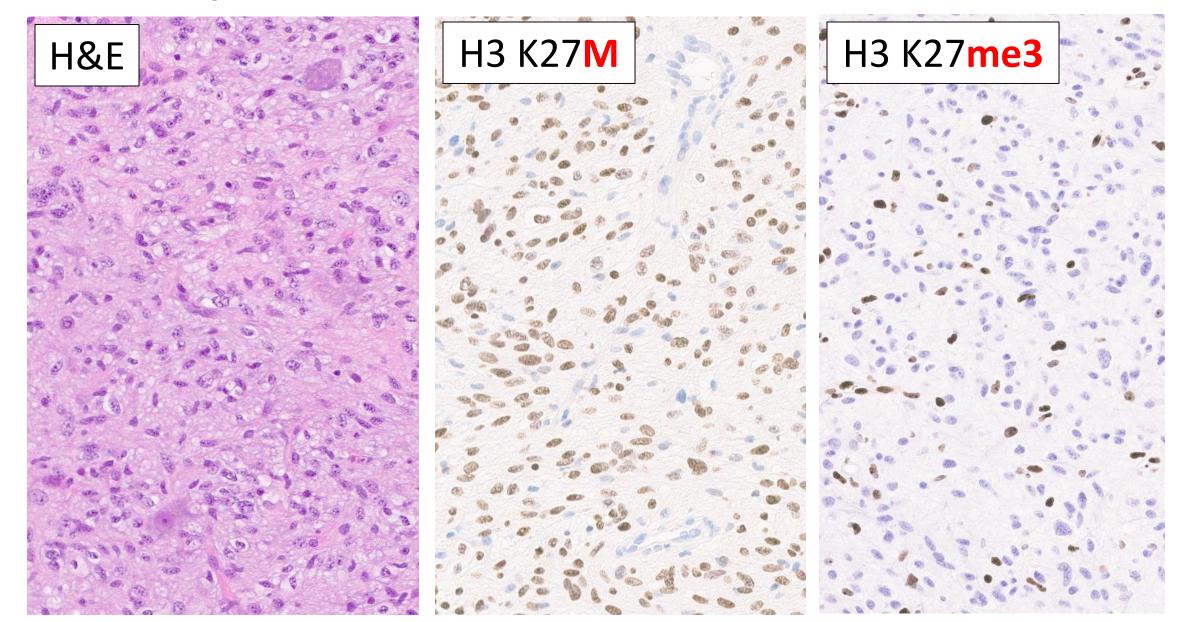
Histone H3 nomenclature can be based on either on the amino acid numbering of the mature processed protein (K27 / G34) or on the DNA codon numbering (K28 / G35)

- H3 K27 and H3 G34 are entrenched in the neuro-oncologic literature
- H3 K28 and H3 G35 are favored by most (if not all) Next Generation Sequencing (NGS) reference laboratories
- In this context, H3 K27 = H3 K28, and H3 G34 = H3 G35

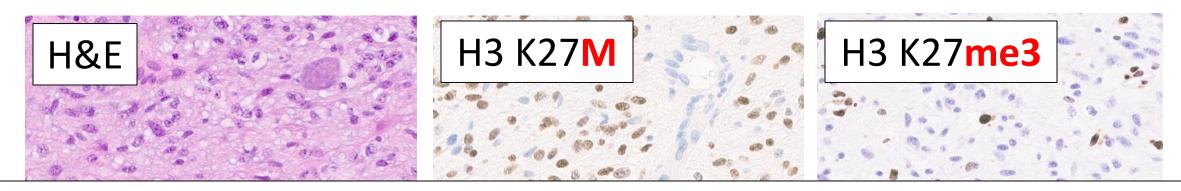
DMG, H3 K27-Altered Spectrum of Anatomic Locations



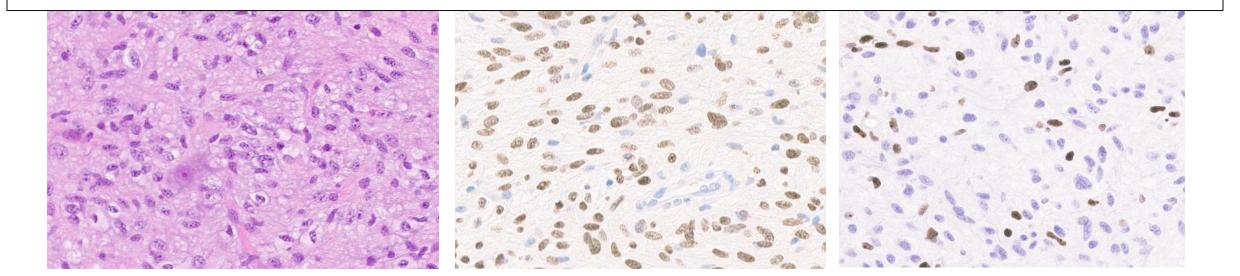
DMG, H3 K27-Altered HISTOLOGY



DMG, H3 K27-Altered HISTOLOGY



Diffuse Midline Glioma, H3 K27-Altered CNS WHO Grade 4



- Supratentorial Ependymoma
- Posterior Fossa Ependymoma
- Spinal Cord Ependymoma

- RELA Fusion-Positive (poor prognosis)
- YAP1 Fusion-Positive
- NOS / NEC

- RELA Fusion-Positive (poor prognosis)
- YAP1 Fusion-Positive
- NOS / NEC

- C11orf95 Fusion-Positive (poor prognosis)
- YAP1 Fusion-Positive
- NOS / NEC

- C11orf95 Fusion-Positive (poor prognosis)
- YAP1 Fusion-Positive
- NOS / NEC

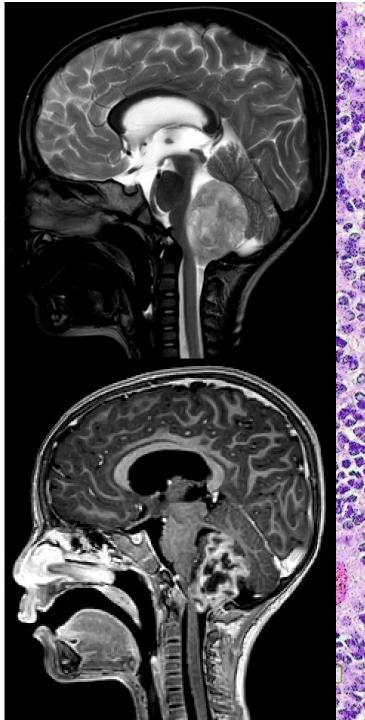
- **ZFTA** Fusion-Positive (poor prognosis)
- YAP1 Fusion-Positive
- NOS / NEC

Posterior Fossa Ependymoma

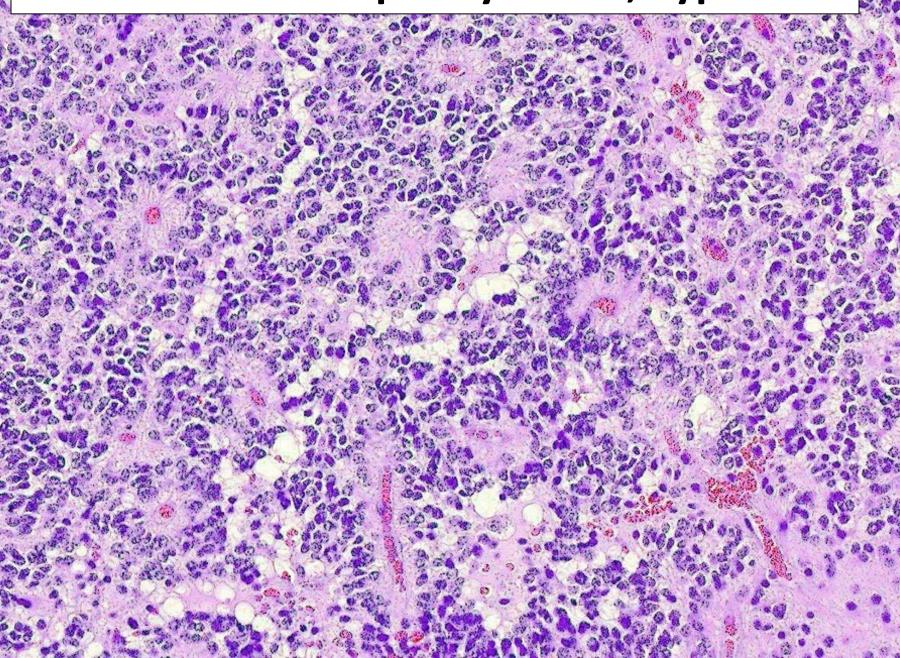
- Pediatric-Type (PFA) (poor prognosis)
- Adult-Type (PFB)
- NOS / NEC

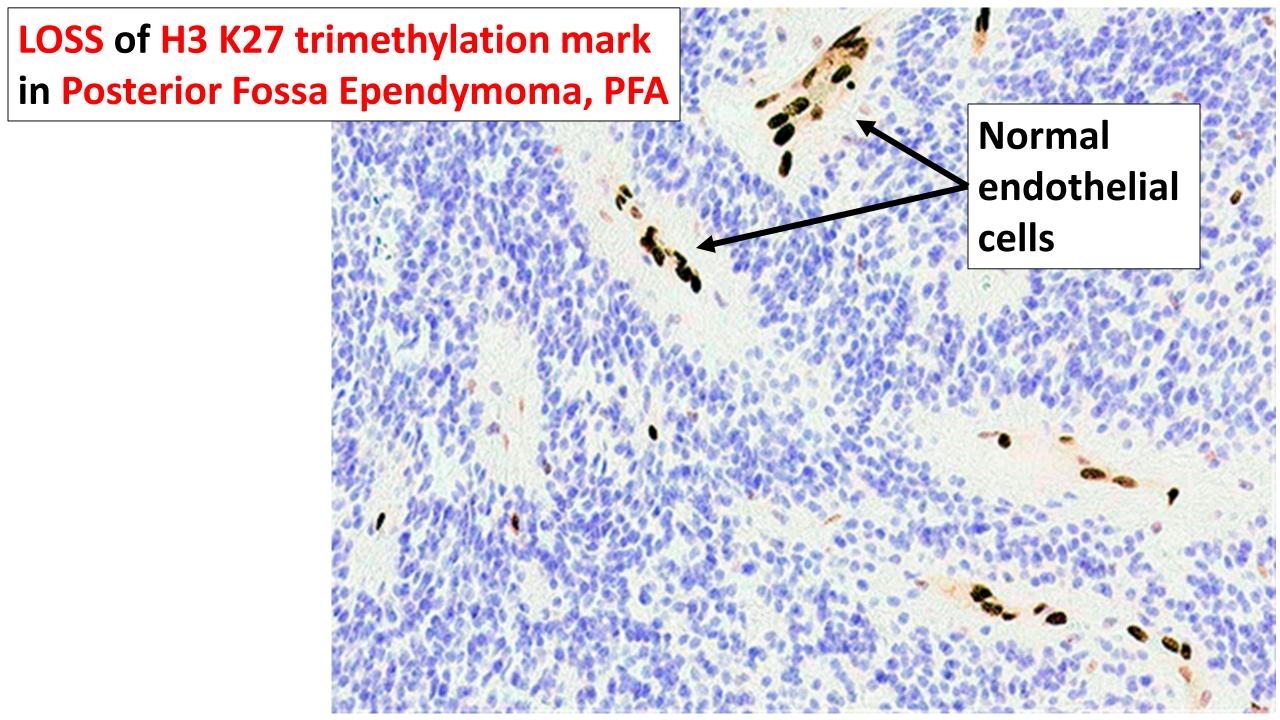
Spinal Ependymoma

- MYCN-Amplified
- NOS / NEC



Posterior Fossa Ependymoma, Type PFA





Meningiomas

International Agency for Research on Cancer



WHO Classification of Tumours

Central Nervous System Tumours// Embryonal tumours // Medulloblastoma// Medulloblastomas, histologically defined >

AAA Meningioma 🔄

Definition

ICD-O coding

ICD-11 coding

Related terminology

Subtype(s)

Localization

Clinical features

Epidemiology

Etiology

Pathogenesis

Macroscopic appearance

Histopathology

Cytology

Diagnostic molecular

pathology

Essential and desirable diagnostic criteria

Staging

Definition

Meningiomas comprise a family of neoplasms that are most likely derived from the meningothelial cells of the arachnoid mater (CNS WHO grade 1, 2, or 3).

ICD-O coding

9530/0 Meningioma

ICD-11 coding

2A01.0Z Meningiomas, unspecified

Related terminology

None

Subtype(s)

See #19607Box 7.01.

Localization

However, some genetic changes (e.g.

TERT promoter mutation or homozygous CDKN2A and/or CDKN2B deletion) are evidence for diagnosing CNS WHO grade 3 meningioma

However, some genetic changes (e.g.

TERT promoter mutation or homozygous CDKN2A and/or CDKN2B deletion) are evidence for diagnosing CNS WHO grade 3 meningioma (see below), so consideration should be given to TERT, CDKN2A, and CDKN2B analysis in clinically aggressive atypical meningiomas or those with borderline CNS WHO grade 2/3 features.

Anaplastic (malignant) meningioma

Anaplastic (malignant) meningioma is a high-grade meningioma with overtly malignant cytomorphology (anaplasia) that can (1) resemble carcinoma, high-grade sarcoma, or melanoma; (2) display markedly elevated mitotic activity;

Anaplastic (malignant) meningioma

Anaplastic (malignant) meningioma is a high-grade meningioma with overtly malignant cytomorphology (anaplasia) that can (1) resemble carcinoma, high-grade sarcoma, or melanoma; (2) display markedly elevated mitotic activity; (3) harbour a *TERT* promoter mutation; and/or (4) have a homozygous *CDKN2A* and/or *CDKN2B* deletion.

Anaplastic (malignant) meningioma

(3) harbour a TERT promoter mutation; and/or (4) have a homozygous CDKN2A and/or CDKN2B

2022 Update

One Caveat!

ADULT Diffuse Astrocytic Disease -WHO 2021

Glioblastoma, IDH-Wildtype, CNS WHO Grade 4

At least one of the following must be present:

- Microvascular proliferation, or
- Necrosis, or
- TERT promoter mutation, or
- EGFR gene amplification, or
- Combined gain of chr 7 with loss of chr 10 (+7/-10)

Isolated *TERT* promoter mutation as the *Sole molecular criterion* for upgrading Histologic Grade 2 IDH-WT Diffuse Astrocytoma to GLIOBLASTOMA, IDH-WT, CNS WHO GRADE 4

Neuro-Oncology

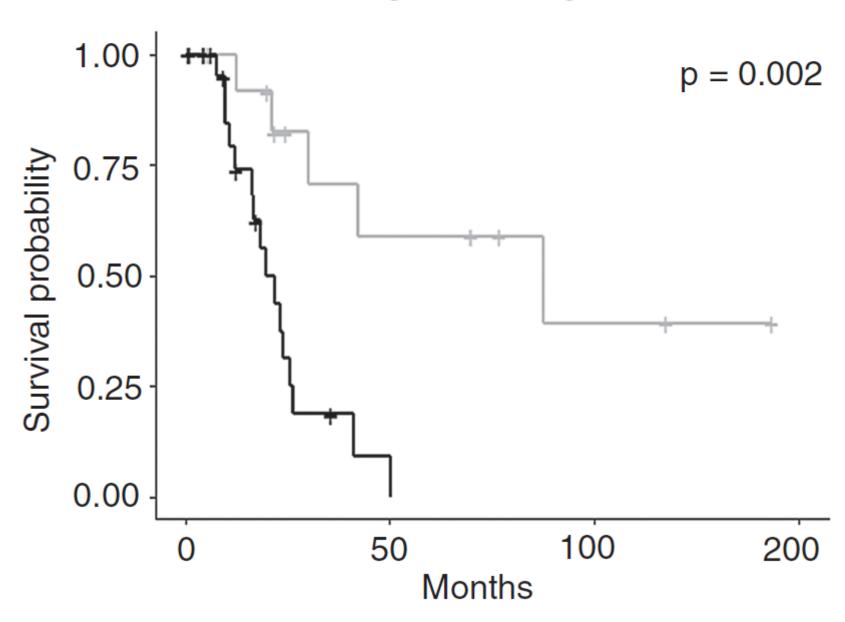
23(6), 955–966, 2021 | doi:10.1093/neuonc/noaa258 | Advance Access date 11 November 2020

IDH-wildtype lower-grade diffuse gliomas: the importance of histological grade and molecular assessment for prognostic stratification

Giulia Berzero, Anna Luisa Di Stefano[®], Susanna Ronchi, Franck Bielle[®], Chiara Villa, Erell Guillerm, Laurent Capelle, Bertrand Mathon[®], Alice Laurenge, Marine Giry, Yohann Schmitt, Yannick Marie, Ahmed Idbaih, Khe Hoang-Xuan, Jean-Yves Delattre, Karima Mokhtari, and Marc Sanson

Isolated *TERT* promoter mutations: I*DH*wt grade II vs. grade III

PMID 33173941



PMID 33173941

Key Points

- 1. *IDH*-wildtype diffuse grade II gliomas should be distinguished from grade III because of a lower burden of genetic alterations (including *EGFR* amplifications, whole chromosome 7 gain/whole chromosome 10 loss, *TERT* promoter mutations, *TP53* mutations, deletions of cyclin-dependent kinase inhibitor 2A, and chromosome 9p loss) and a much better outcome.
- 2. With a median overall survival of 88 months, *IDH*-wildtype grade II gliomas with isolated *TERT* promoter mutations should not be assimilated to molecular glioblastomas.

PMID 33173941

Importance of the Study

The cIMPACT-NOW update 3 has recently established that *IDH*wt histological grade II and III diffuse gliomas with *EGFR* amplifications, and/or combined whole chromosome 7 gain and whole chromosome 10 loss, and/or *TERT* promoter mutations should be considered as bona fide glioblastomas. Our data suggest that, while true for histological grade III gliomas, these considerations do not fit a subset of grade II gliomas, and namely

those with isolated *TERT* promoter mutations (median overall survival: 88 mo). These findings highlight the importance of histological grade, in parallel to molecular profile, for the prognostic stratification of *IDH*wt lowergrade gliomas and suggest that *IDH*wt gliomas with grade II histology (<2 mitosis per 10 high power fields) and isolated *TERT* promoter mutations should not be assimilated to molecular glioblastomas.

Neuro-Oncology

PMID 33660766

23(6), 865–866, 2021 | doi:10.1093/neuonc/noab052 | Advance Access date 28 February 2021

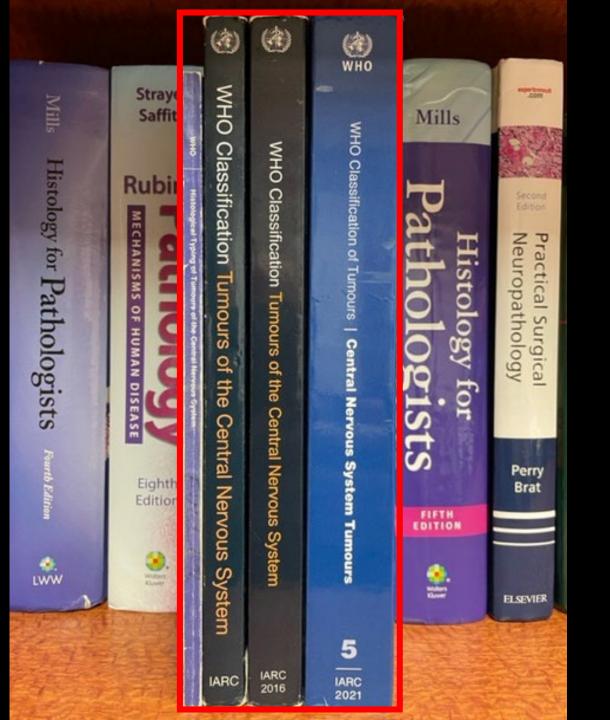
TERT promoter mutation: is it enough to call a WHO grade II astrocytoma IDH wild-type glioblastoma?

Caterina Giannini[®] and Felice Giangaspero

While it may be too late for the results of this paper to be incorporated in the upcoming 2021 WHO classification for CNS Tumor, clinicians and pathologists should be aware of its conclusions. Histological grade is still useful for prognostic stratification of *IDH*-wt gliomas and *pTERTmut* in isolation in strictly defined grade II astrocytoma does not appear to be sufficient to assume that the tumor will behave as glioblastoma, wild-type (WHO CNS grade 4) as proposed in cIMPACT-NOW update 6.4

A Brief History of the World Health Organization Classification of Tumours of the

Central Nervous System



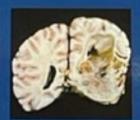
WHO CNS "Blue Books"

WHO Classification of Tumours • 5th Edition

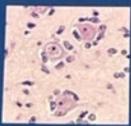
Central Nervous System Tumours

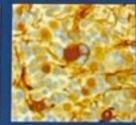
Edited by the WHO Classification of Tumours Editorial Board

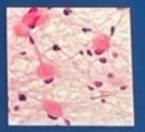






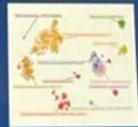












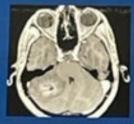
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WHO Classification of Tumours • 5th Edition

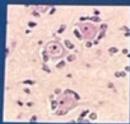
Central Nervous System Tumours

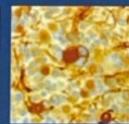
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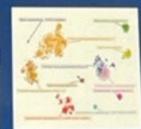












International Agency for Research on Concar



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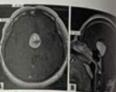
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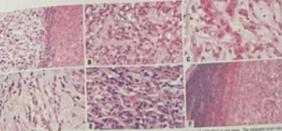
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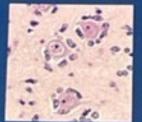


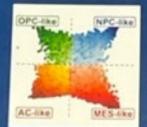
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Central Nervous System Tumours

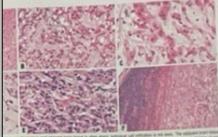
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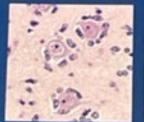
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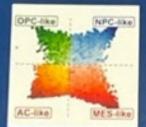


Central Nervous System Tumours

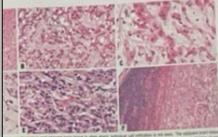
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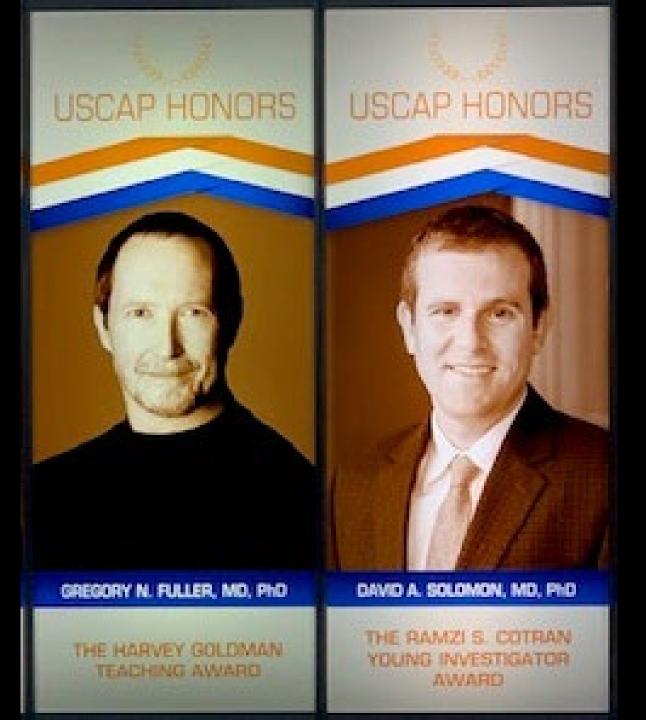


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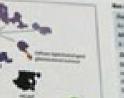


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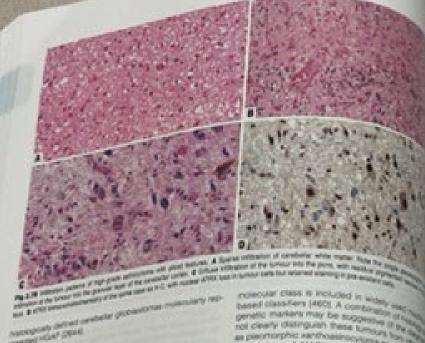
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Progressic data on patients diagnosed with HGAP are, to date, only evaluate from a single retrispective study (364%, to the study the 5-year overall survival rate of patients diagnosed with HGAP was approximately 50%. Quest survival was shorter then that of patients with conventional phocytic astropytoma. (CNS WHO grade T) and CH-mutant satistiyona (CNS WHO grade 3s longer than that of patients with 10th wildtype globinstome, and approximately comparable to that of patients with OH mutare astrocytoma (CNS-WHO grade 4) (MAS), Associafore of prognoss and histological features were not identified. rundon, but MAPK pathway gane mutations otherwise occur. Secred hecrose of of 28 patients deal entry 2 years of diagnoskill or lacked misses (3 of 15 patients ded within 2 years). A mempiesed MGMT promoter was reported in 46% of HGMPs. who, it is statistical association with patient outcome, however, information on treatment of the patients by alkylating agent shemotherapy was not available (2643). More data are required In one study of 74 cases, homogypous deleton by, very for esegment of a delinque CNS WHO grade, but current data. suggest a circuit behaviour roughly corresponding to CNS



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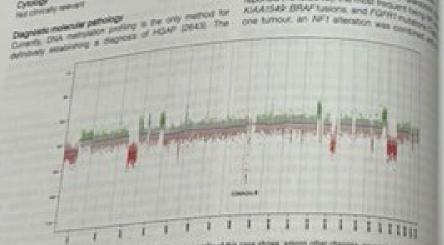


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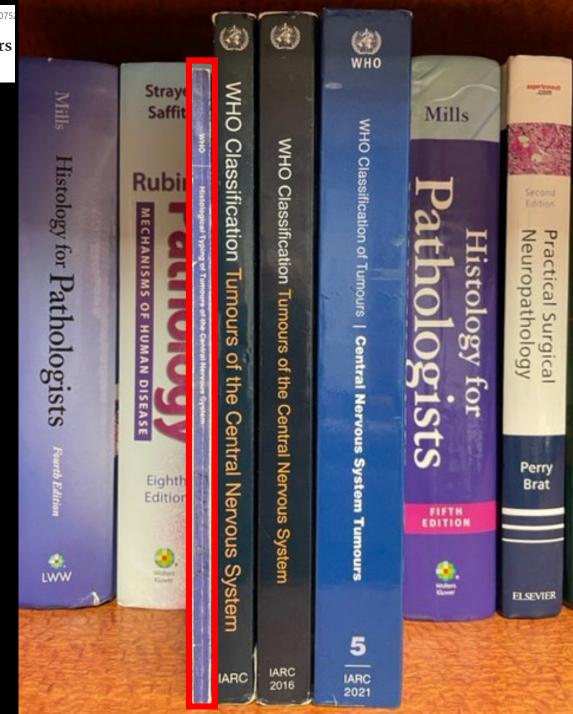
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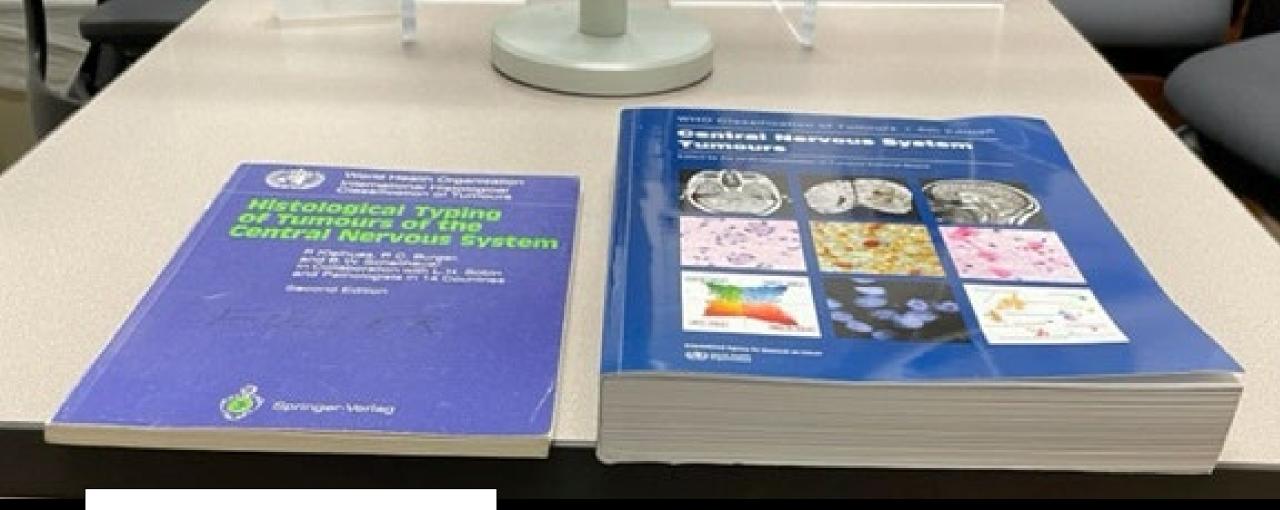
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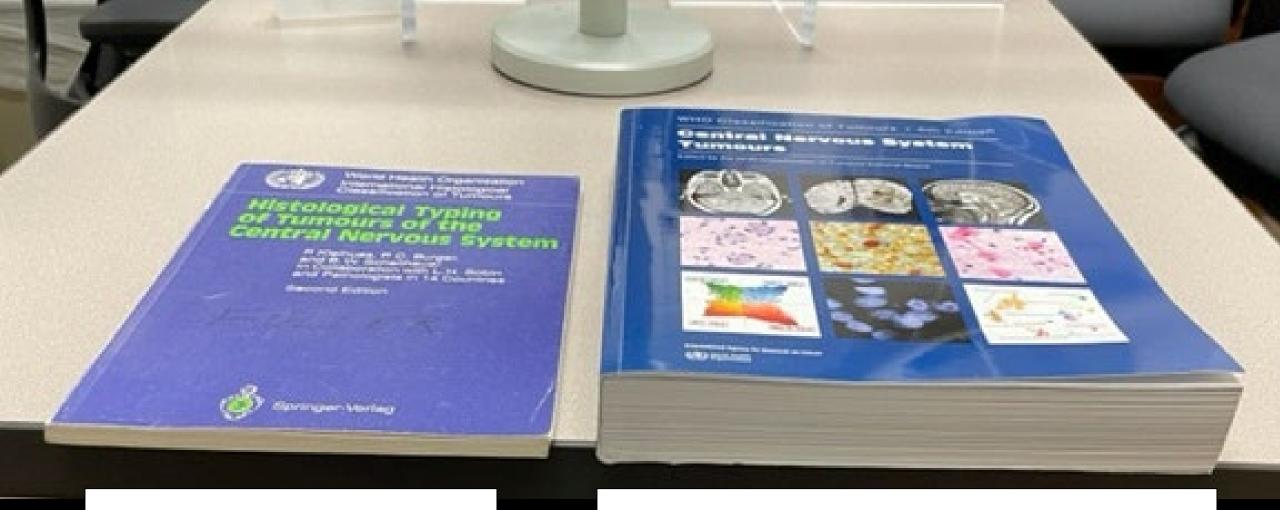
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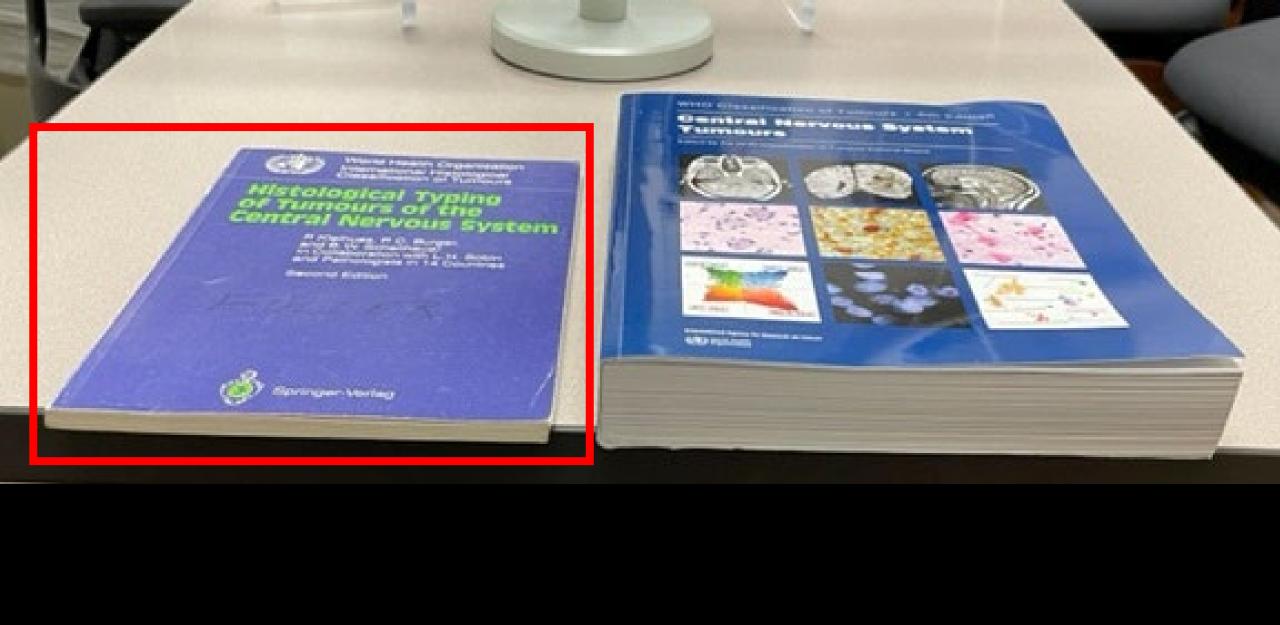


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14 Definitions and Explanatory Notes 14 Denominary of the Property to Grade IV.

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1.1.4 Pilocytic Astrocytoma (Figs. 13-16)

A circumscribed astrocytoma composed, at least in part, of bipoles A circumscribed area with dense fibrillation. Turnour cells tend to fusion or parallel bundles. Particularly common is a biphasie form compact parallel bundles. Particularly common is a biphasie form compact or pilocytic areas are intimately associated with a pattern in which a microcystic component consisting of protoplasmipoorly fibrillated neoplastic astrocytes.

Hyperchromatic, bizarre nuclei may be present and are not in the absence of significant mitotic activity, associated with a poor prognosis. GFAP expression is always demonstrable a poor programme and process apparently coalesce to larger cysts which may, when situated in the posterior forest displace the vermis or large parts of the cerebellar hemisphere The stroma consists of irregularly disposed blood vessels which may be hyalinized. Glomeruloid capillary or even endothelial proliferation is not uncommon, both within the tumour and in the wall of cysts, but does not signify malignancy. Elongated eosinophilic, club-shaped structures (Rosenthal fibres) and eosinophilic intracytoplasmic protein droplets ("granular bodies") ate histopathological hallmarks of this neoplasm. Calcification may also be seen but is usually inconspicuous. Local invasion of the subarachnoid space is frequent and may be accompanied by

Neuroepithelial Tumours 15

a desmoplastic leptomeningeal reaction, but does not indicate malignancy.

In contrast to the above mentioned diffuse astrocytic tumours, the pilocytic astrocytoma is more circumscribed, expands into the surrounding brain only slowly, and very rarely shows a tendency for progression to anaplasia. This tumour occurs mainly in children, with a peak incidence around the age 10 years, and in young adults. Pilocytic astrocytomas are typically located in midline structures, e.g. optic nerve (optic nerve glioma), third ventricle, thalamus, median temporal lobe, brain stem and in the cerebellum ('cystic and solid cerebellar astrocytoma"). The cerebral hemispheres are affected less frequently. Biological behaviour: This slowly growing tumour corresponds histologically to Grade I. Malignant transformation occurs very rarely, in which case the tumour is categorized as an anapiastic (pilocytic) astrocytoma (Grade III).

1.1.5 Pleomorphic Xanthoastrocytoma (Figs. 17-19)

An astrocytoma with a mixture of pleomorphic tumour cells, ranging from ordinary fibrillary astrocytes to giant, multinucleated forms. The latter typically contain lipid vacuoles; thus they are xanthomatous, but express GFAP.

The superficial, in particular the leptomeningeal, portions of these tumours, exhibit a dense intercellular reticulin network due to the presence of pericellular basement membranes. Mitoses are rare and necrosis as well as vascular proliferation are absent. This rare variant of astrocytoma often occurs in children or young adults and affects the cerebral hemispheres, particularly the temporal lobe. It is typically superficial in location, shows an intimate relation to the meninges and may be associated with an underlying cyst.

Biological behaviour: Despite its pleomorphic appearance, this neoplasm is usually rather well-demarcated. A generally favourable prognosis justifies its inclusion in Grade II gliomas. A minority of pleomorphic xanthoastrocytomas do, however, progress to anaplastic astrocytoma (Grade III) or glioblastoma (Grade IV).

1.1.6 Subependymal Giant Cell Astrocytoma (Tuberous Sclerosis) (Figs. 20, 21)

A circumscribed, usually calcified intraventricular tumour arising from the walls of the lateral ventricles. It is composed mainly of large plump cells resembling astrocytes.

14 Definitions and Explanatory Notes 14 Dental Peluriour: Gliobiastomas correspond histologicals geological Peluriour: to Grade IV.

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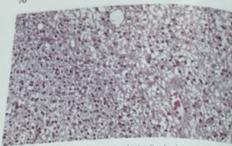


Fig. 35. Oligo-astrocytoma. Focus of neoplastic oligodendrocytes (left) next so a less cellular area with astrocytic differentiation

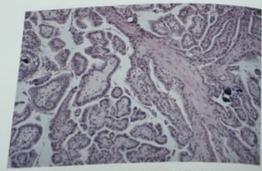
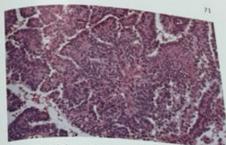


Fig.36. Choroid plexus papilloma. Highly differentiated cuboidal cells cover papillary connective tissue cores. Occasional calcifications are typical



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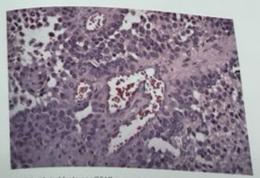


Fig.38. Astroblastoma. GFAP expressing neoplastic astrocytes with broad processes radiating towards central blood vessels

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INTERNATIONAL HISTOLOGICAL CLASSIFICATION OF TUMOURS No. 21

Histological
Typing of Tumours
of the Central
Nervous System



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OF TUMOURS OF THE CENTRAL NERVOUS SYSTEM

K. J. ZÜLCH

Head, WHO Collaborating Centre for the Histological Classification of Tumours of the Central Nervous System, Max-Planck Institute for Brain Research, Cologne, Federal Republic of Germany

in collaboration with pathologists in 14 countries



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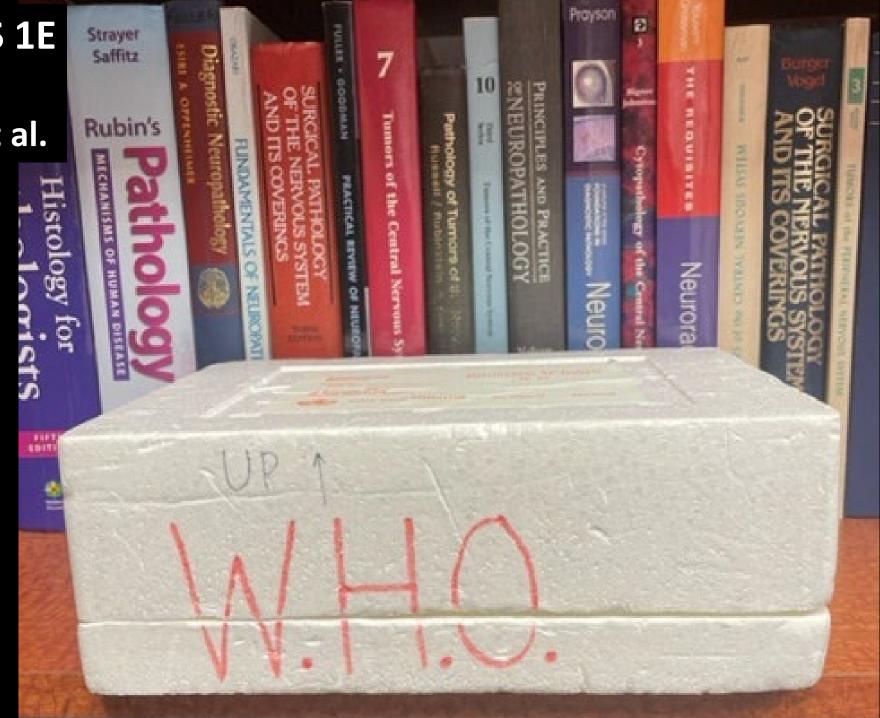
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Book Reviews

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This is No. 21 of the volumes of the WHO International Histological Classification of Tumours. Previous volumes have been reviewed in this journal, and interested readers will be familiar with the aims and achievements of this valuable series.

Tumours of the central nervous system have always formed a difficult field of study, divorced from the main corpus of tumour pathology, and shrouded in a mystique which neuropathologists have not always seemed eager to dissipate. But the general principles of tumour classification are as applicable within the CNS as elsewhere, and in recent years less intimidating classifications of CNS tumours have appeared. The present volume follows this more down to-earth trend, and offers a relatively simple scheme. Each tumour type is briefly described, and illustrated by excellent and apposite colour photomicrographs. The dedicated neuropathologist may find points to criticise, but the "occasional" histopathologist, faced with an intracranial neoplasm, will not go far wrong if he follows this guide. It can also be recommended as a reference book for neurosurgeons and oncologists.

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Fast Forward 4 Decades

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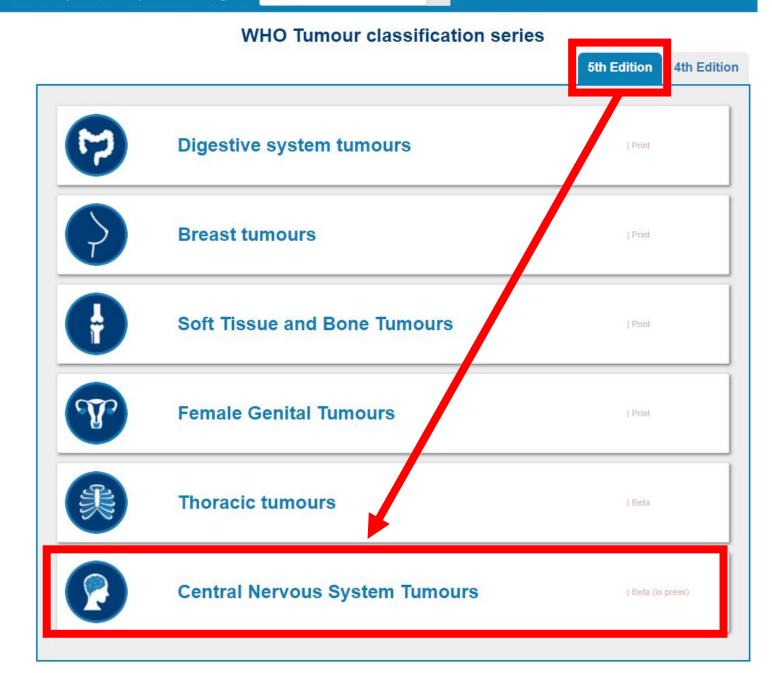
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WHO

CNS 5E

2021



Newly RecognizedTumorTypes

Diffuse astrocytoma, MYB- or MYBL1-altered

Polymorphous low-grade neuroepithelial tumor of the young

Diffuse low-grade glioma, MAPK pathway-altered

Diffuse hemispheric glioma, H3 G34-mutant

Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype

Infant-type hemispheric glioma

High-grade astrocytoma with piloid features

Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (provisional type)

Myxoid glioneuronal tumor

Multinodular and vacuolating neuronal tumor

Supratentorial ependymoma, YAP1 fusion-positive

Posterior fossa ependymoma, group PFA

Posterior fossa ependymoma, group PFB

Spinal ependymoma, MYCN-amplified

Cribriform neuroepithelial tumor (provisional type)

CNS neuroblastoma, FOXR2-activated

CNS tumor with BCOR internal tandem duplication

Desmoplastic myxoid tumor of the pineal region, SMARCB1-mutant

Intracranial mesenchymal tumor, FET-CREB fusion positive (provisional type)

CIC-rearranged sarcoma

Primary intracranial sarcoma, DICER1-mutant

Pituitary blastoma

WHO 5E

22 NEW CNS TUMOR TYPES

Neuro-Oncology 2021 PMID 34185076

Table 7 Newly Recognized Tumor Types in the 2021 WHO Classification of Tumors of the Central Nervous System

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WHO 5E

12 NEW

Molecular

Signature-Defined CNS TUMOR TYPES

Neuro-Oncology 2021 PMID 34185076

Tumor Type	Genes/Molecular Profiles Characteristically Altered*
Astrocytoma, IDH-mutant	IDH1, IDH2, ATRX, TP53, CDKN2A/B
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	IDH1, IDH2, 1p/19q, TERT promoter, CIC, FUBP1, NOTCH
Glioblastoma, IDH-wildtype	IDH-wildtype, TERT promoter, chromosomes 7/10, EGFR
Diffuse astrocytoma, MYB- or MYBL1-altered	MYB, MYBL1
Angiocentric glioma	MYB
Polymorphous low-grade neuroepithelial tumor of the young	BRAF, FGFR family
Diffuse low-grade glioma, MAPK pathway-altered	FGFR1, BRAF
Diffuse midline glioma, H3 K27-altered	H3 K27, TP53, ACVR1, PDGFRA, EGFR, EZHIP
Diffuse hemispheric glioma, H3 G34-mutant	H3 G34, TP53, ATRX
Diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype	IDH-wildtype, H3-wildtype, PDGFRA, MYCN, EGFR (methylome)
Infant-type hemispheric glioma	NTRK family, ALK, ROS, MET
Pilocytic astrocytoma	KIAA1549-BRAF, BRAF, NF1
High-grade astrocytoma with piloid features	BRAF, NF1, ATRX, CDKN2A/B (methylome)
Pleomorphic xanthoastrocytoma	BRAF, CDKN2A/B
Subependymal giant cell astrocytoma	TSC1, TSC2
Chordoid glioma	PRKCA
Astroblastoma, MN1-altered	MN1
Ganglion cell tumors	BRAF
Dysembryoplastic neuroepithelial tumor	FGFR1
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters	Chromosome 14, (methylome)
Papillary glioneuronal tumor	PRKCA
Rosette-forming glioneuronal tumor	FGFR1, PIK3CA, NF1
Myxoid glioneuronal tumor	PDFGRA
Diffuse leptomeningeal glioneuronal tumor	KIAA1549-BRAF fusion, 1p (methylome)
Multinodular and vacuolating neuronal tumor	MAPK pathway
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	PTEN
Extraventricular neurocytoma	FGFR (FGFR1-TACC1 fusion), IDH-wildtype
Supratentorial ependymomas	ZFTA, RELA, YAP1, MAML2
Posterior fossa ependymomas	H3 K27me3, EZHIP (methylome)
Spinal ependymomas	NF2, MYCN
Medulloblastoma, WNT-activated	CTNNB1, APC
Medulloblastoma, SHH-activated	TP53, PTCH1, SUFU, SMO, MYCN, GLI2 (methylome)
Medulloblastoma, non-WNT/non-SHH	MYC, MYCN, PRDM6, KDM6A (methylome)
Atypical teratoid/rhabdoid tumor	SMARCB1, SMARCA4
Embryonal tumor with multilayered rosettes	C19MC, DICER1
CNS neuroblastoma, FOXR2-activated	FOXR2
CNS tumor with BCOR internal tandem duplication	BCOR
Desmoplastic myxoid tumor of the pineal region, SMARCB1-mutant	SMARCB1
Meningiomas	NF2, AKT1, TRAF7, SMO, PIK3CA; KLF4, SMARCE1, BAP1 in subtypes; H3K27me3; TERT promoter, CDKN2A; CNSWHO grade 3
Solitary fibrous tumor	NAB2-STAT6
Meningeal melanocytic tumors	NRAS (diffuse); GNAQ, GNA11, PLCB4, CYSLTR2 (circum scribed)
Adamantinomatous craniopharyngioma	CTNNB1

WHO 5E

43 Tumor Types with *critical* molecular signature determinants

Tumor Typ Astrocyto Oligodend Glioblasto Diffuse ast Angiocent Polymorp Diffuse lov Diffuse pe and IDH-w Chordoid Astroblast Ganglion (Dysembry Diffuse gli nuclear clu Papillary p Posterior

Dysplastic

Spinal epe Medullobl

Medullobl

Atypical te

Embryona CNS neuro

CNS tumo

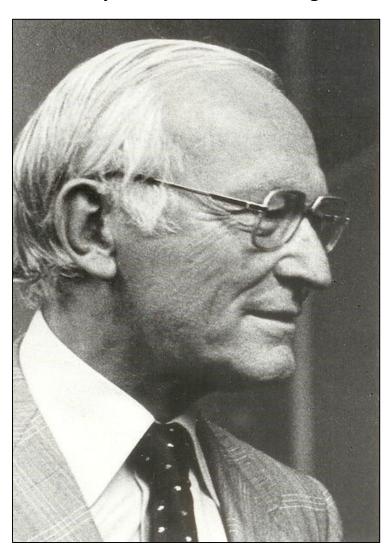
Solitary fib Meningea

Adamantii Papillary o

THE

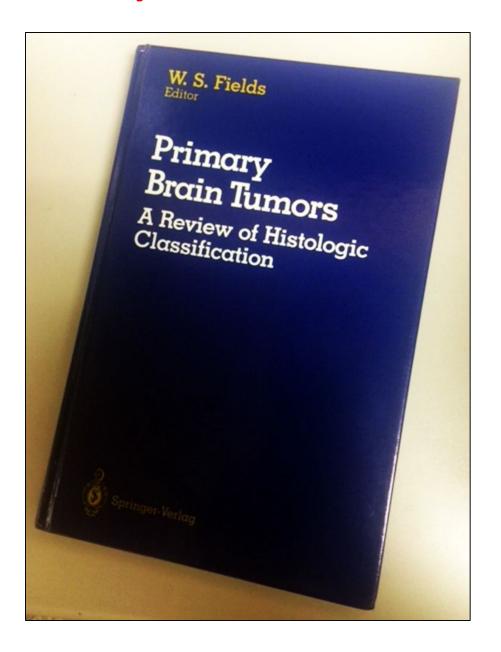
NTIMIDATINGs CLASSIFICATION IS BACK BABY!

• 1979 1st Edition. Zulch KJ, et al. Histological Typing of Tumours of the Central Nervous System. World Health Organization, Geneva.



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- 2000 3rd Edition. Kleihues, Cavenee. Classification of Tumours: Pathology and Genetics of Tumours of the Nervous System. IARC Press, Lyon. (First volume of the 3rd Edition of the WHO Series)
- 2007 4th Edition. Louis, Ohgaki, Wiestler, Cavenee. WHO Classification of Tumours of the Central Nervous System. (First volume of the 4TH Edition of the WHO Series)
- **2016** Revised 4th Edition. Louis, Ohgaki, Wiestler, Cavenee, Ellison, Figarella-Branger, Perry, Reifenberger, von Deimling. WHO Classification of Tumours of the Central Nervous System.

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History of WHO Classification of CNS Tumors Planning Colloquia and Consensus Conferences

1988

1990

• 2006

• 2014

2015





The new WHO classification of brain tumours

P Kleihues ¹, P C Burger, B W Scheithauer

The New WHO Classification of Brain Tumours

PMID 8293185

Paul Kleihues ¹, Peter C. Burger ² and Bernd W. Scheithauer ³

- ¹ Institute of Neuropathology, Department of Pathology, University Hospital, CH-8091 Zurich, Switzerland
- ² Department of Pathology, The Johns Hopkins Hospital, Baltimore, MD 21287, U.S.A.
- ³ Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN 55905, U.S.A.

The new edition of the World Health Organization (WHO) book on 'Histological Typing of Tumours of the Central Nervous System' reflects the progress in brain tumour classification which has been achieved since publication of the first edition in 1979. Several new tumour entities have been added, including the pleomorphic xanthoastrocytoma, central neurocytoma, the infantile desmoplastic astrocytoma / ganglioglioma, and the dysembryoplastic neuro-

(CNS) neoplasms and, particularly, their histogenesis. Considering that immunohistochemistry was not yet available, the task was enormous. However, the result of the collaborative effort was quite successful as the "Blue Book" rapidly gained popularity world-

Preparation of the second edition, just published, was initiated during a consensus meeting held in Houston, Texas, in 1988 (2).

nomenclature for CNS neoplasms that can be used internationally and which serves as a reliable guideline in day-to-day surgical pathology and as a unifying basis for the evaluation of brain tumour therapy trials. In this article, the major alterations and amendments are briefly reviewed, some with comments on the opinions expressed by participants of the WHO working group.

Astrocytic Tumours and Glioma Progression

The working group unanimously proposed that a

History of WHO Classification of CNS Tumors Planning Colloquia and Consensus Conferences

- 1988 Houston M D ANDERSON Cancer Center
- 1990 Geneva
- 2006 Heidelberg

2014 Haarlem

2015 Heidelberg

1988 Planning Colloquia and Consensus Conference

- Dawna **Armstrong**
- Robin Barnard
- Laurence Becker
- Darell **Bigner**
- Jean-Marie Brucher
- Janet Bruner
- Peter **Burger**
- Catherine Daumas-Duport
- Richard Davis
- Kenneth Earle
- William Fields
- Floyd **Gilles**
- Jacques **Hassoun**

- Yoichi Yashida
- Werner Janisch
- Kurt Jellinger
- John Kepes
- Joel Kirkpatrick
- Paul Kleihues
- Lucy Rorke
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- Alfred Yung
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History of WHO Classification of CNS Tumors 1988 Planning Conference Houston M D Anderson Cancer Center



History of WHO Classification of CNS Tumors Planning Colloquia and Consensus Conferences

1988 Houston M D ANDERSON

Why Houston?

History of WHO Classification of CNS Tumors Planning Colloquia and Consensus Conferences

1988 Houston M D ANDERSON

• W. S. Fields



History of WHO Classification of CNS Tumors Planning Colloquia and Consensus Conferences

1988 Houston M D ANDERSON

• W. S. Fields

"The Zulch-Texas Connection"

What is the Connection between Klaus Zulch and Texas?

What is the Connection between Klaus Zulch and Texas?

North Zulch, Texas

Where and What is North Zulch, Texas?

North Zulch Texas



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North Zulch, Texas

From Wikipedia, the free encyclopedia

North Zulch is an unincorporated community in Madison County, Texas, United States at the intersection of U.S. Highway 190 and State Highway 21 and is six miles from the Navasota River and thirteen miles west of Madisonville in west central Madison County.

Education [edit]

The North Zulch Independent School District has served the community for over 100 years and is home to the North Zulch High School Bulldogs. The 2A school is rich in tradition and history.

External links [edit]

- North Zulch, Texas & (and Zulch, Texas &) from the Handbook of Texas Online
- U.S. Geological Survey Geographic Names Information System: North Zulch, Texas 🗗

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Coordinates: 30°55′04″N 96°06′30″W

North Zulch, Texas

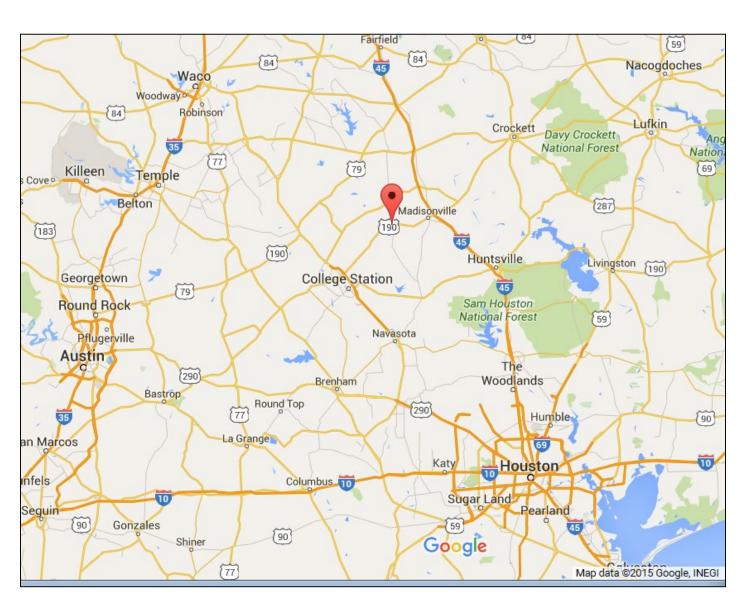
Unincorporated community



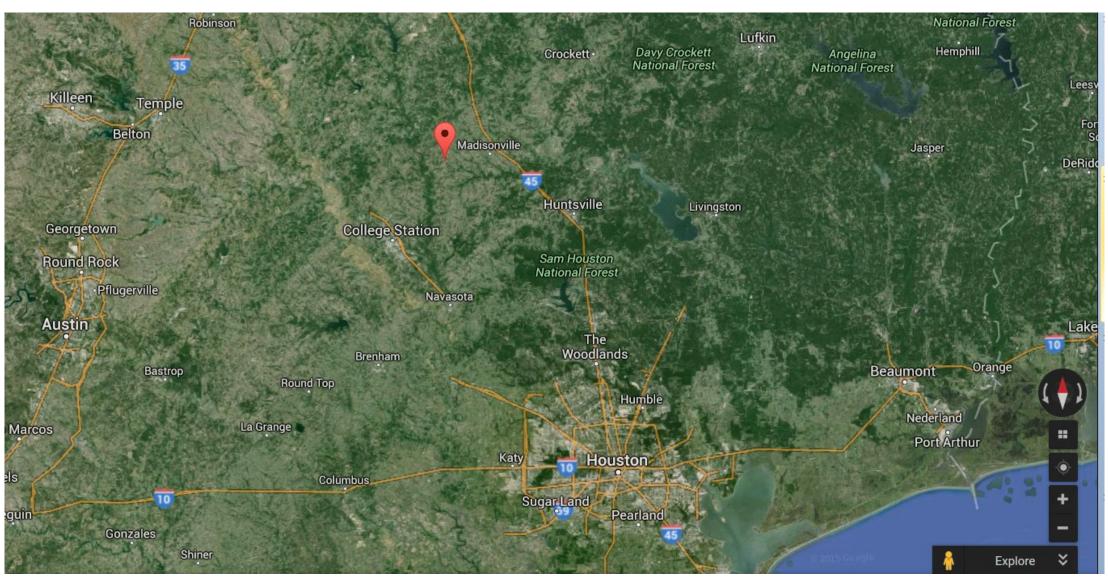
Old Coca Cola Sign at North Zulch Grocery

United States Country Texas State Madison County Elevation 318 ft (97 m) **Population** Estimated Total 100 Central (CST) Time zone (UTC-6) Summer (DST) CDT (UTC-5) Area code(s) 936

North Zulch Texas

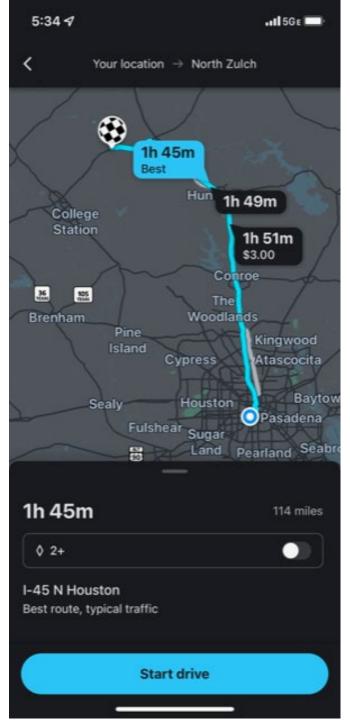


North Zulch Texas

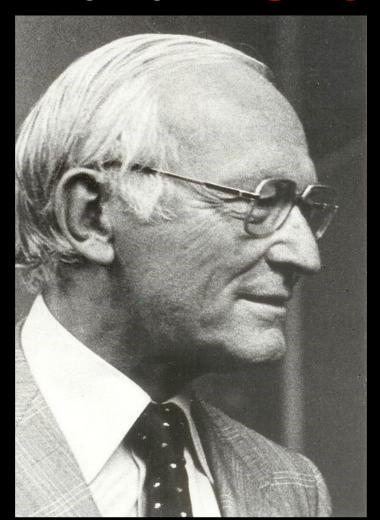


How far is North Zulch, Texas from my office at MDACC?

TMC to North Zulch Texas



What is the Connection between Klaus Zulch and North Zulch TX?



The Zulch-Texas Connection

Julius Zulch

The Zulch-Texas Connection

Julius Zulch

Klaus Zulch's Grandfather's Brother

• 1850 Julius Zulch, Brother of Klaus Zulch's Grandfather immigrated to Texas, arriving in the United States by ship in

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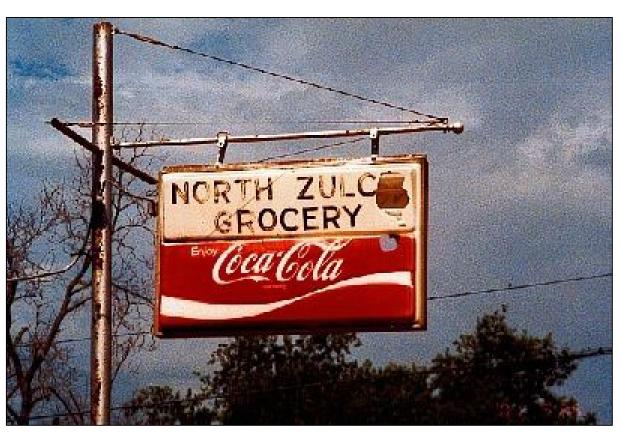
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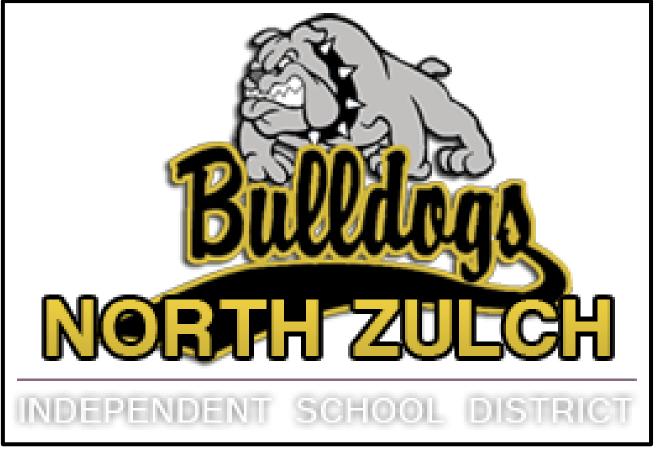
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- 1906 Willow Hole renamed Zulch
- 1906 The Houston and Texas Central Railroad built a line from Houston to Navasota that passed 2 miles north of Zulch
- 1907 The Trinity and Brazos Railway built a spur adjacent to the HTC spur
- The Zulch population began migrating north to be closer to the railway – and thus North Zulch was established!
 Zulch proper slowly shrank away...

The WHO-Zulch-Texas Connection Julius Zulch and his legacy, North Zulch





This was a Brief History of the WHO CNS Classification according to Fuller...

But there is a Better History

of the

WHO CNS Classification

Scheithauer

HISTORICAL PERSPECTIVE

Development of the WHO Classification of Tumors of the Central Nervous System: A Historical Perspective

Bernd W. Scheithauer, MD

Department of Pathology and Laboratory Medicine, Mayo Clinic, Rochester, Mi.

Brain Pathology 2009

PMID 18771526

Keywords

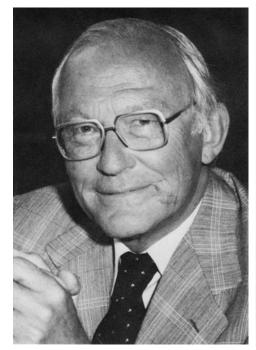
brain tumors, classification, historical development, World Health Organization.

Corresponding author:

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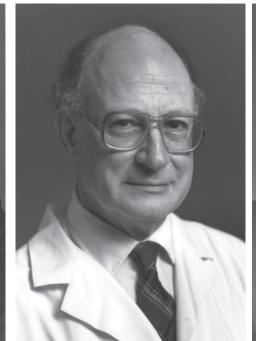
Abstract

The classification of brain tumors has undergone numerous changes over the past half century. The World Health Organization has played a key role in the effort. Four versions of its *Classification of Tumours of the Central Nervous System* have been published. The present work chronicles their progress, placing emphasis on the historical context of the earliest effort.



















THE Pathology of
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NERVOUS SYSTEM

DOROTHY S. RUSSELL

and

L. J. RUBINSTEIN

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