

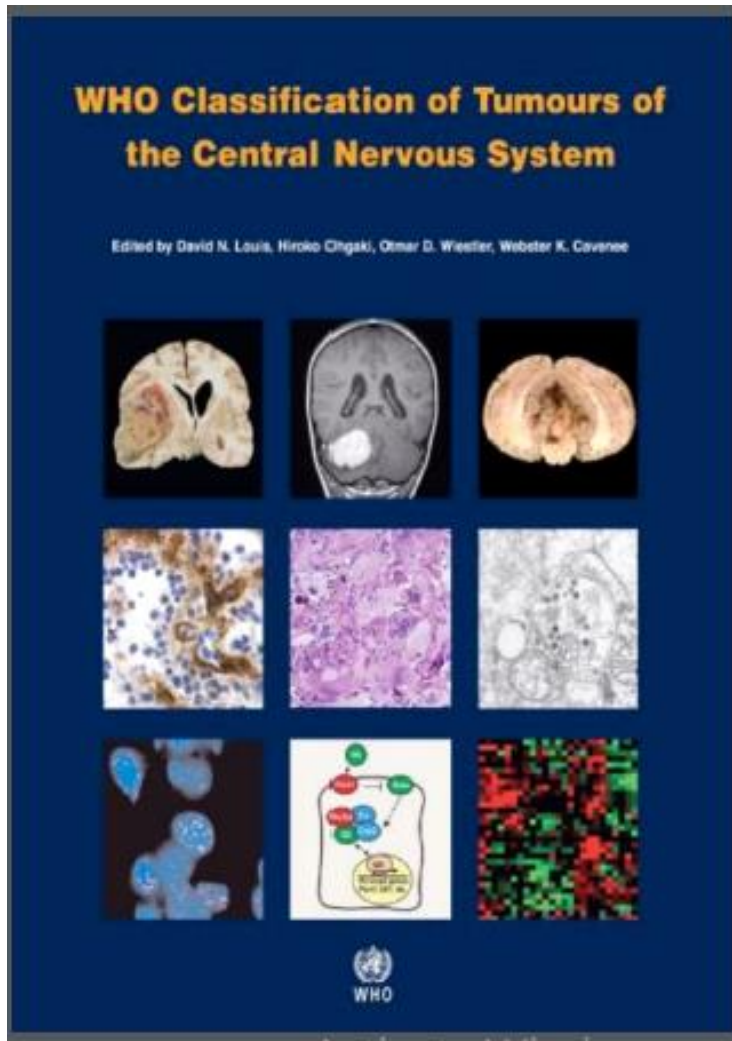
WHO CLASSIFICATION OF BRAIN TUMOR- CHANGES MADE FOR FUTURE INCLUDING MOLECULAR BIOLOGY

PRITI TRIVEDI

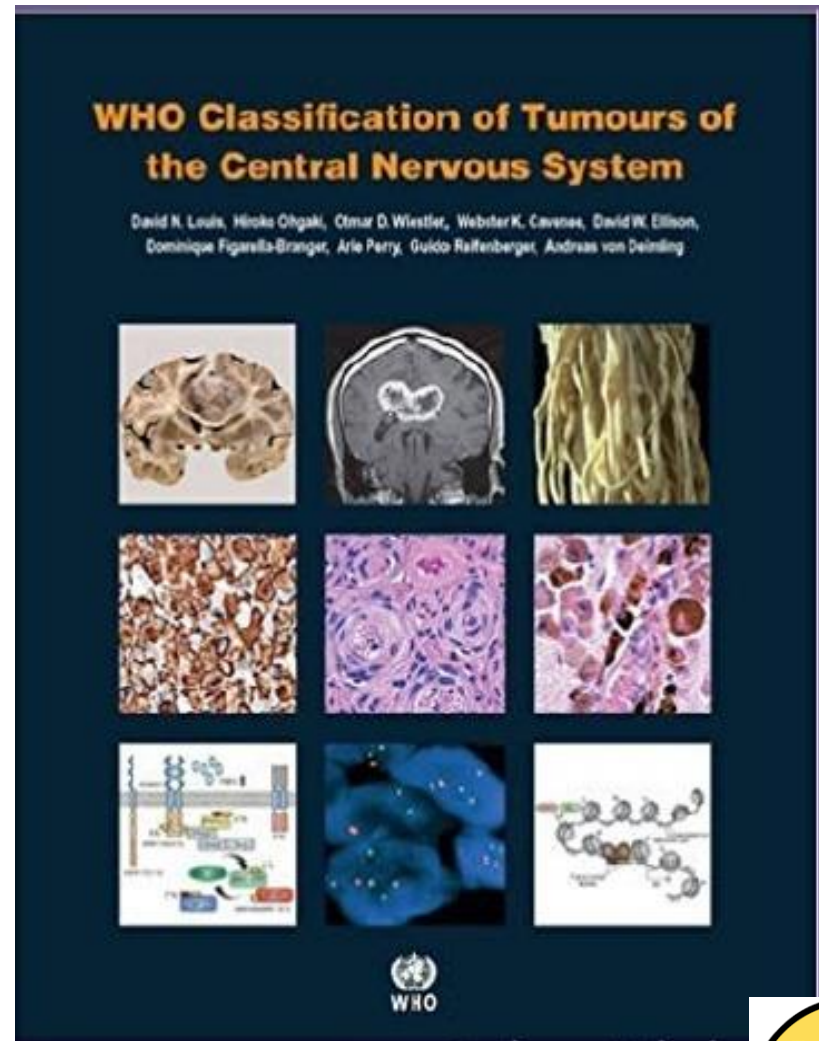
Professor & HOD

Oncopathology dept, GCRI

2007



2016



It took 9yrs for the updates!



Diffuse astrocytic and oligodendroglial tumours

Diffuse astrocytoma, IDH-mutant
Gemistocytic astrocytoma, IDH-mutant
Diffuse astrocytoma, IDH-wildtype
Diffuse astrocytoma, NOS

Anaplastic astrocytoma, IDH-mutant
Anaplastic astrocytoma, IDH-wildtype
Anaplastic astrocytoma, NOS

Glioblastoma, IDH-wildtype
Giant cell glioblastoma
Gliosarcoma
Epithelioid glioblastoma

Glioblastoma, IDH-mutant
Glioblastoma, NOS

Diffuse midline glioma, H3 K27M-mutant

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

Anaplastic oligodendroglioma, IDH-mutant
and 1p/19q-codeleted
Anaplastic oligodendroglioma, NOS

Oligoastrocytoma, NOS
Anaplastic oligoastrocytoma, NOS

Other astrocytic tumours

Pilocytic astrocytoma
Pilomyxoid astrocytoma
Subependymal giant cell astrocytoma
Pleomorphic xanthoastrocytoma
Anaplastic pleomorphic xanthoastrocytoma

Ependymal tumours

Subependymoma
Myxopapillary ependymoma
Ependymoma
Papillary ependymoma
Clear cell ependymoma
Tanycytic ependymoma
Ependymoma, *RELA* fusion-positive
Anaplastic ependymoma

Other gliomas

Chordoid glioma of the third ventricle
Angiocentric glioma
Astroblastoma

Choroid plexus tumours

Choroid plexus papilloma
Atypical choroid plexus papilloma
Choroid plexus carcinoma

Neuronal and mixed neuronal-glial tumours

Dysembryoplastic neuroepithelial tumour
Gangliocytoma
Ganglioglioma
Anaplastic ganglioglioma
Dysplastic cerebellar gangliocytoma
(Lhermitte-Duclos disease)
Desmoplastic infantile astrocytoma and
ganglioglioma
Papillary glioneuronal tumour
Rosette-forming glioneuronal tumour
Diffuse leptomeningeal glioneuronal tumour
Central neurocytoma
Extraventricular neurocytoma
Cerebellar liponeurocytoma
Paraganglioma

Tumours of the pineal region

Pineocytoma
Pineal parenchymal tumour of intermediate
differentiation
Pineoblastoma
Papillary tumour of the pineal region

Embryonal tumours

Medulloblastomas, genetically defined
Medulloblastoma, WNT-activated
Medulloblastoma, SHH-activated and
TP53-mutant
Medulloblastoma, SHH-activated and
TP53- wildtype
Medulloblastoma, non-WNT/non-SHH
Medulloblastoma, group 3
Medulloblastoma, group 4
Medulloblastomas, histologically defined
Medulloblastoma, classic
Medulloblastoma, desmoplastic/nodular
Medulloblastoma with extensive nodularity
Medulloblastoma, large cell / anaplastic
Medulloblastoma, NOS

Embryonal tumour with multilayered rosettes,
C19MC-altered

*Embryonal tumour with multilayered
rosettes, NOS*

Medulloepithelioma
CNS neuroblastoma
CNS ganglioneuroblastoma
CNS embryonal tumour, NOS
Atypical teratoid/rhabdoid tumour
CNS embryonal tumour with rhabdoid features

Tumours of the cranial and paraspinal nerves

Schwannoma
Cellular schwannoma
Plexiform schwannoma

- **In 2014 international society of neuro oncopathology established guideline for incorporating molecular findings in to brain tumor diagnosis .**
- **This lead to major revision of 2007 CNS WHO classification.**
- **2016 CNS WHO classification breaks with the century old principle of diagnosis based entirely on microscopy by incorporating molecular parameters in to the classification of CNS tumor entities.**
- **Now 5th edition of CNS WHO classification is in pipeline.**

Recent updates of CNS tumors

- For the past century, the classification of brain tumors has been based largely on concepts of histogenesis.
 - Light microscopic features in hematoxylin and eosin sections,
 - immunohistochemical expression of proteins and
 - ultrastructural characterization
- Studies over the past two decades have clarified the genetic basis of tumorigenesis in the brain tumor entities

General principles and challenges

- Integrated phenotypic and genotypic parameters for CNS tumor.
- Greater diagnostic accuracy, improved patient management , accurate determinations of prognosis and treatment response.
- Large group of tumors that do not fit into narrowly defined entities they are defined as NOS(not otherwise specified)

- Major example of the diagnostic refinement in new classification is oligoastrocytoma
- Under previous classification, lot of interobserver variability
- In New classification
- Combine genotype and phenotype.
- Astrocytoma (IDH-mutant, *ATRX-mutant*, *1p/19q-intact*)
- Oligodendroglioma (IDH-mutant, *ATRX-wildtype and 1p/19q-codeleted*)

- So the diagnosis of oligoastrocytoma as designated as NOS should be done
 - Only in absence of molecular study “or” if dual tumor population is there.
 - Dual population to be determined by molecular study

- Will genotyping take over histology?
- As of now an integrated approach is recommend by WHO 2016.
- On going research
- Grade based on histology.

- For site lacking any access to molecular diagnostic testing, a diagnostic designation of NOS is permissible
- NOS : either not tested for relevant genetic parameters or the genetic alteration does not fit any known parameter.
- NOS designation tells we do not know enough pathologically, genetically and clinically and which should, therefore, be subject to future study before additional refinements in classification can be made
- WHO grade written in roman numerical
- Italics for specific gene mutation but not for families

Diffuse astrocytoma and anaplastic astrocytoma

- Grade II and grade III astrocytoma has been divided into IDH-mutant, IDH-wildtype and NOS categories.
- IDH wildtype is rare diagnosis to be give with caution
- Protoplasmic and fibrillary astrocytoma removed.

- Only gemistocytic astrocytoma remains as a distinct variant of diffuse astrocytoma, IDH mutant
 - Fibrillary and protoplasmic astrocytomas are deleted
- Gliomatosis cerebri has also been deleted from the 2016 CNS WHO classification as a distinct entity rather being considered a growth pattern

Glioblastomas

- Glioblastoma, IDH-wildtype > 55 yrs age
- Glioblastoma, IDH-mutant secondary to diffuse gliomas
- Glioblastoma, NOS
- Sequencing for IDH differs with age.
 - in younger adults IDH sequencing is highly recommended following negative R132H IDH1 immunohistochemistry,
 - whereas > 55 yr suggests that sequencing may not be needed in the setting of negative R132H IDH1 immunohistochemistry in such patients.

- *Epithelioid glioblastoma* has been added
- IDH-wildtype glioblastoma
 - Giant cell glioblastoma
 - Gliosarcoma
 - Epithelioid glioblastoma

- Glioblastoma with primitive neuronal component was added as a pattern
- Known as glioblastoma with PNET-like component
- Comprised of diffuse astrocytoma(any grade) or rarely oligodendroglioma
- With well demarcated nodules containing primitive cells with neuronal differentiation.
 - Homer Wright rosettes, synaptophysin positivity and loss of GFAP expression
- *MYC or MYCN amplification*

- These tumors have a tendency for craniospinal fluid dissemination
- So on diagnosis warrants a search for craniospinal seeding clinically.
- *Small cell glioblastoma/astrocytoma*
- *granular cell glioblastoma/astrocytoma* remain the same as growth pattern
- Both have poor glioblastoma-like prognosis

Integrated diagnosis of infiltrating gliomas

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graph TD; Root[Integrated diagnosis of infiltrating gliomas] --> IDH_WT[IDH wildtype]; Root --> IDH_Mut[IDH mutation]; Root --> H3K27M_Mut[H3K27M mutation]; IDH_WT --> Box1[Grade 2: Astrocytoma<br/>Grade 3: Anaplastic astrocytoma<br/>Grade 4: Glioblastoma]; IDH_Mut --> 1p19q_Intact[1p/19q intact]; IDH_Mut --> 1p19q_CoDeleted[1p/19q co-deleted]; 1p19q_Intact --> Box2[Grade 2: Astrocytoma<br/>Grade 3: Anaplastic astrocytoma<br/>Grade 4: Glioblastoma]; 1p19q_CoDeleted --> Box3[Grade 2: Oligodendroglioma<br/>Grade 3: Anaplastic oligodendroglioma]; H3K27M_Mut --> Box4[Diffuse midline gliomas];
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IDH wildtype

Grade 2: Astrocytoma
Grade 3: Anaplastic astrocytoma
Grade 4: Glioblastoma

IDH mutation

***H3K27M* mutation**

Diffuse midline gliomas

1p/19q intact

Grade 2: Astrocytoma
Grade 3: Anaplastic astrocytoma
Grade 4: Glioblastoma

1p/19q co-deleted

Grade 2: Oligodendroglioma
Grade 3: Anaplastic oligodendroglioma

	IDH-wildtype glioblastoma	IDH-mutant glioblastoma
Synonym	Primary glioblastoma, IDH-wildtype	Secondary glioblastoma, IDH-mutant
Precursor lesion	Not identifiable; develops de novo	Diffuse astrocytoma Anaplastic astrocytoma
Proportion of glioblastomas	~90%	~10%
Median age at diagnosis	~62 years	~44 years
Male-to-female ratio	1.42:1	1.05:1
Mean length of clinical history	4 months	15 months
Median overall survival		
Surgery + radiotherapy	9.9 months	24 months
Surgery + radiotherapy + chemotherapy	15 months	31 months
Location	Supratentorial	Preferentially frontal
Necrosis	Extensive	Limited
<i>TERT</i> promoter mutations	72%	26%
<i>TP53</i> mutations	27%	81%
<i>ATRX</i> mutations	Exceptional	71%
<i>EGFR</i> amplification	35%	Exceptional
<i>PTEN</i> mutations	24%	Exceptional

Summary of the changes in the 2016 WHO CNS tumors classification

- Diffuse gliomas, separated from the common group of glial tumours, as diffuse astrocytic and oligodendroglial tumours.
- Restructured with incorporation of genetically defined entities.
- Medulloblastomas are restructured with incorporation of genetically defined entities.
- Other embryonal tumors are also restructured, with incorporation of genetically defined entities .
- The term “primitive neuroectodermal tumor” is removed.
- Ependymoma - genetically defined variant of RELA fusion positive incorporated.

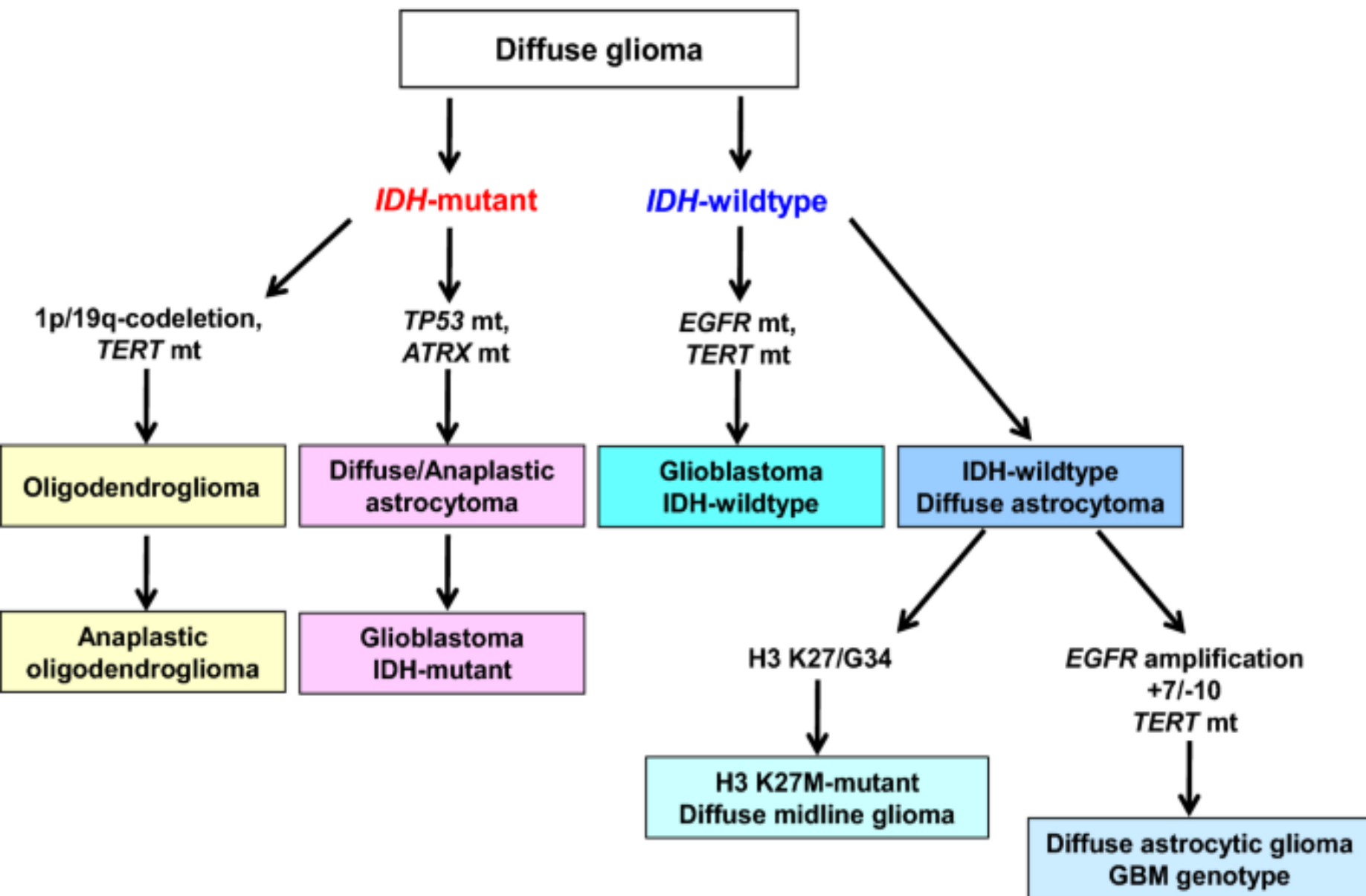
Oligodendrogliomas

- Requires both IDH gene family mutation and combined whole-arm losses of 1p and 19q (1p/19q codeletion).
- In absence of genetic testing -“NOS “ can be given

- Childhood tumors that histologically resemble oligodendroglioma often do not demonstrate IDH gene family mutation and 1p/19q Codeletion
- Until such tumors are better understood at a molecular level
- Should be included in the oligodendroglioma, NOS category

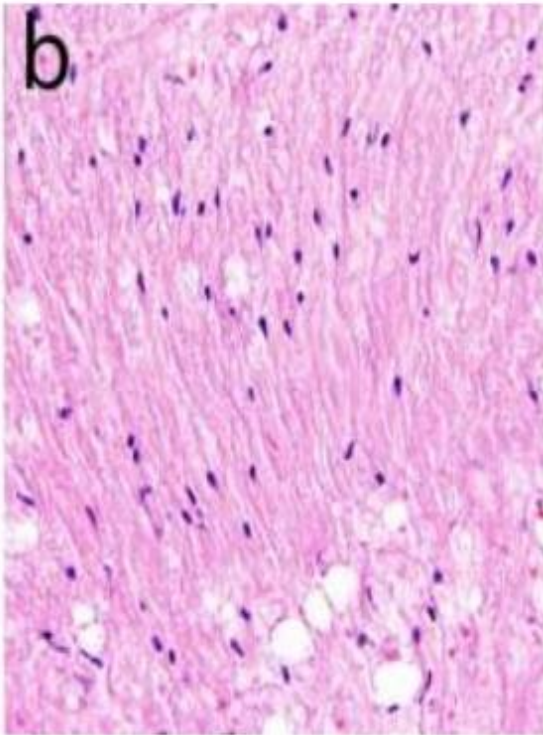
Oligoastrocytomas

- This diagnosis strongly discouraged
- With proper genetic testing can be grouped under astrocytoma or oligodendroglioma
- But can be reported with suffix “NOS “ In absence of genetic testing
- Rare cases of true oligoastrocytoma (genetically, phenotypically) have been reported
- Until further reports confirming such tumors are available for evaluation as part of the next WHO classification, they should be included under the provisional entities of oligoastrocytoma, NOS

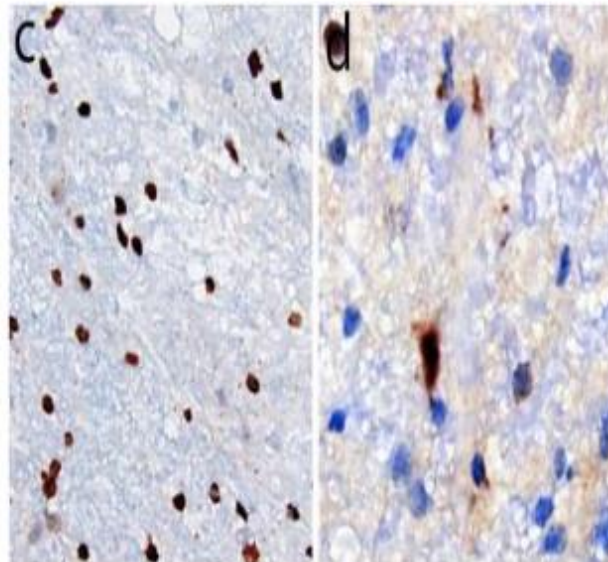


Pediatric diffuse gliomas

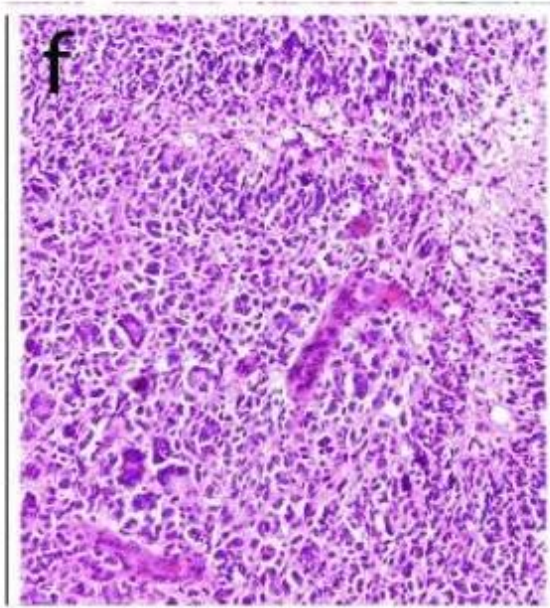
- Pediatric diffuse gliomas were grouped with their adult counterparts
- Information on the distinct underlying genetic abnormalities is emerging
- K27M mutations in the histone H3 gene *H3F3A* and some times *HIST1H3B* gene
- This newly defined entity is termed *diffuse midline glioma, H3 K27M-mutant* - includes tumors previously referred to as diffuse intrinsic pontine glioma (DIPG)



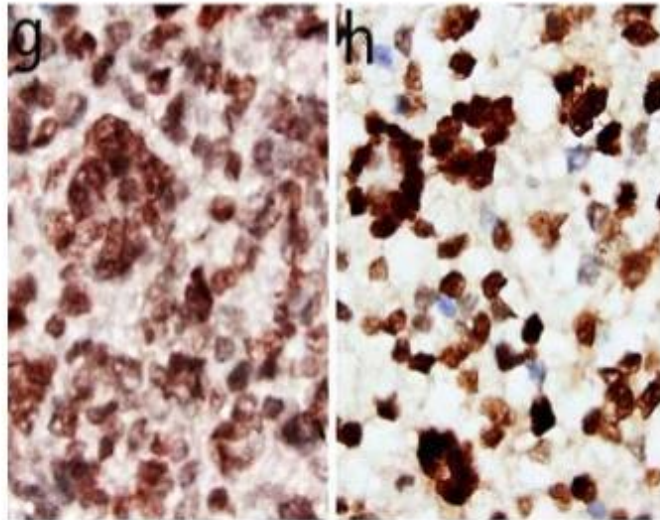
- These tumors involve the brain stem (especially pons), spinal cord, thalamus



- tumor cells strongly expressed the H3 K27M-mutant protein (c)
- (d) showed loss of ATRX expression



- In thalamic mass classic features of glioblastoma with prominent multinucleated giant cell



- In addition to H3 K27M-mutant protein expression (g)
- (h) strong p53 staining

Other astrocytomas

- Anaplastic pleomorphic xanthoastrocytoma, WHO grade III has been added.
- Previously Pleomorphic xanthoastrocytoma with anaplastic features.
- 5 or more mitoses per 10 high-power fields
- Necrosis may be present
- Bad prognosis

- Grading of pilomyxoid astrocytoma has also been changed(earlier grade II)
- Significant similarities between pilocytic and pilomixoid genetic features.
- Further studied needed to clarify behavior
- Till then suppress the grade

Ependymomas

- More prognostic and reproducible classification and grading scheme is yet to be published
- *Ependymoma, RELA fusion-positive*, This variant accounts for the majority of supratentorial tumors in children
- Cellular ependymoma, has been deleted
- More studies needed

Neuronal and mixed neuronal-glial tumours

- Newly recognized entity *diffuse leptomeningeal glioneuronal tumor*
- Present with diffuse leptomeningeal disease
- With or without a recognizable parenchymal component
- Commonly in spinal cord.
- Children and adolescents

Neuronal and mixed neuronal-glial tumours

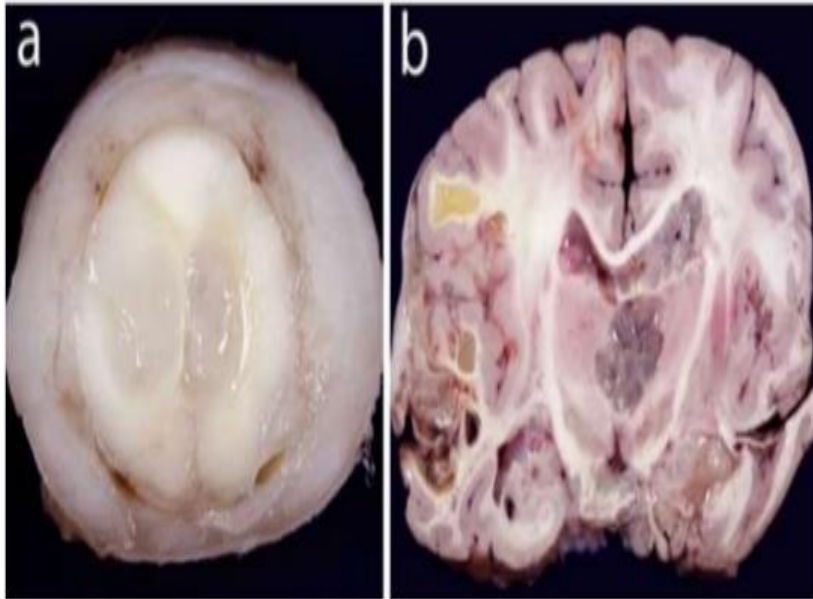
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	9493/0
Desmoplastic infantile astrocytoma/ ganglioglioma	9412/1
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Central neurocytoma	
Extraventricular neurocytoma	
Cerebellar liponeurocytoma	
Papillary glioneuronal tumour	
Rosette-forming glioneuronal tumour of the fourth ventricle	
Paraganglioma	

Neuronal and mixed neuronal-glial tumours

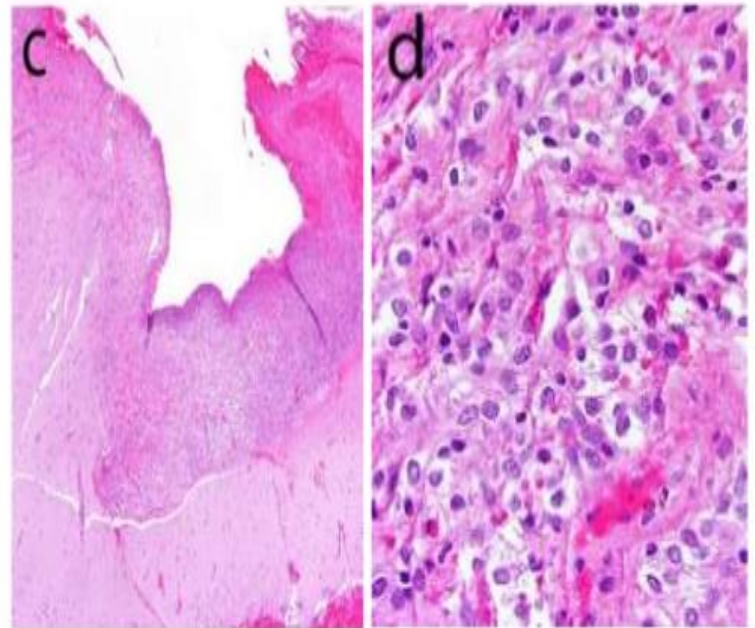
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumour	9509/1
Rosette-forming glioneuronal tumour	9509/1
<i>Diffuse leptomeningeal glioneuronal tumour</i>	
Central neurocytoma	9506/1
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1

Diffuse leptomeningeal glioneuronal tumor

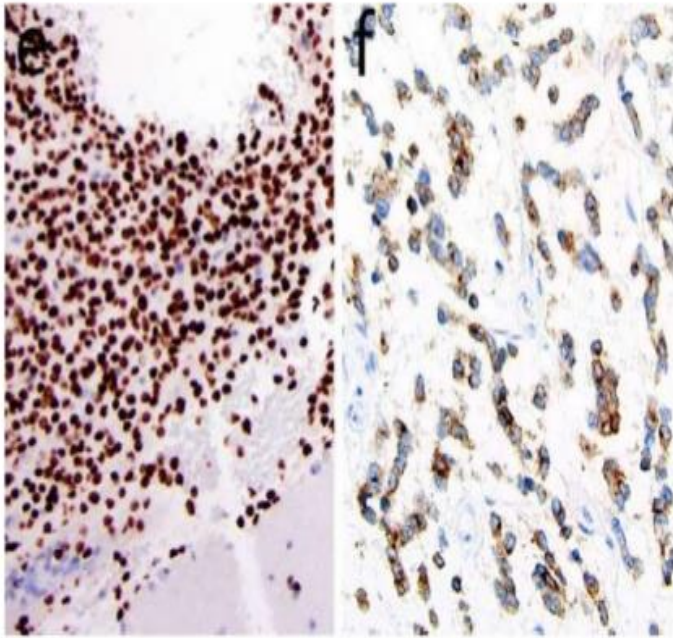
- Monomorphic clear cell glial morphology, reminiscent of oligodendroglioma
- *BRAF fusions, deletions of chromosome arm 1p*, either alone or occasionally combined with 19q
- IDH mutations are absent.
- Nosological position unclear whether to place under gliomas or glioneural tumors
- Prognosis variable



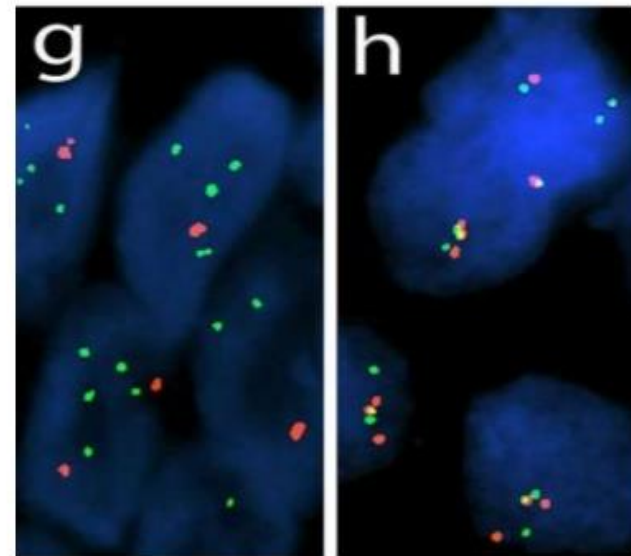
this DLGNT patient had widespread expansion and fibrosis of spinal **(a)** and cerebral **(b)**, along with intraventricular masses and variably cystic, mucoid intraparenchymal extensions



The DLGNT biopsy specimen showed a leptomenigeal infiltrate **(c)** with oligodendroglioma-like cytologic features **(d)**.

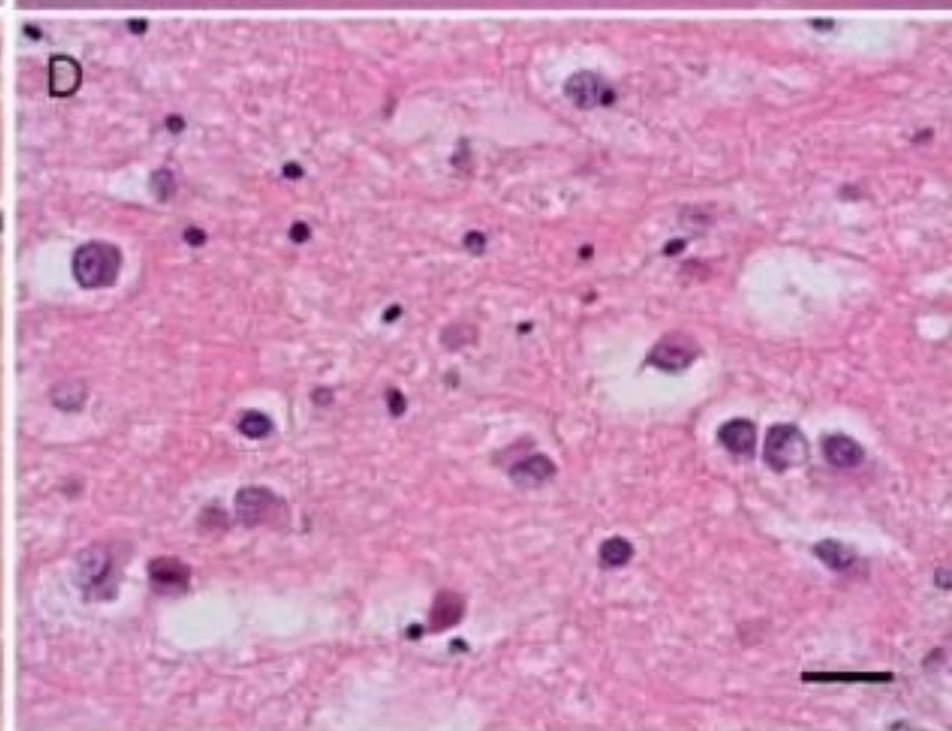
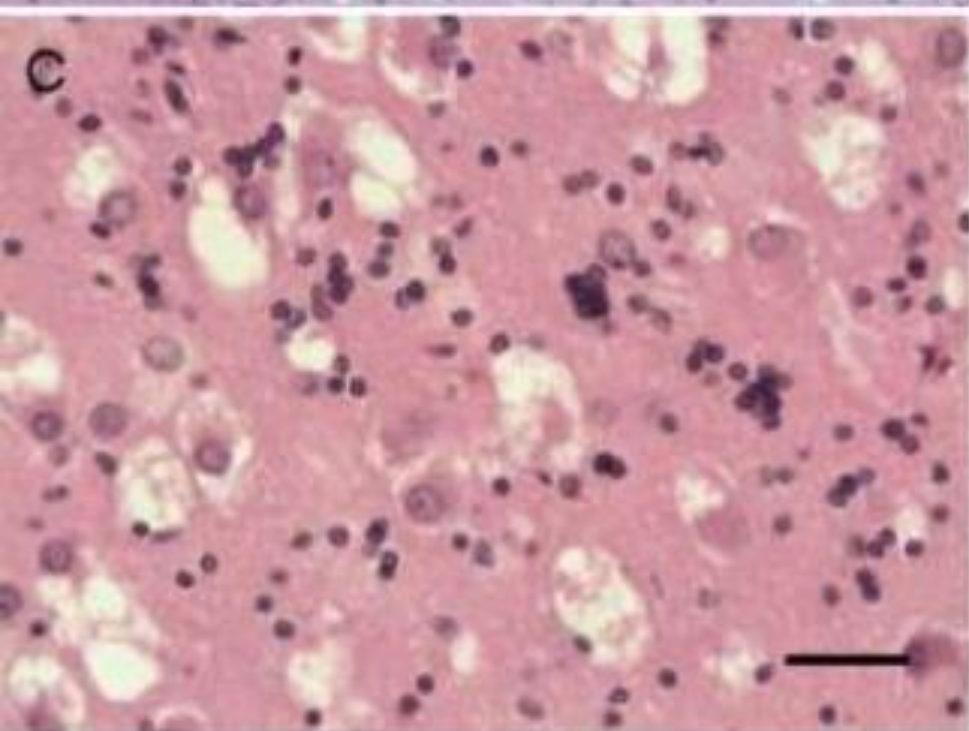
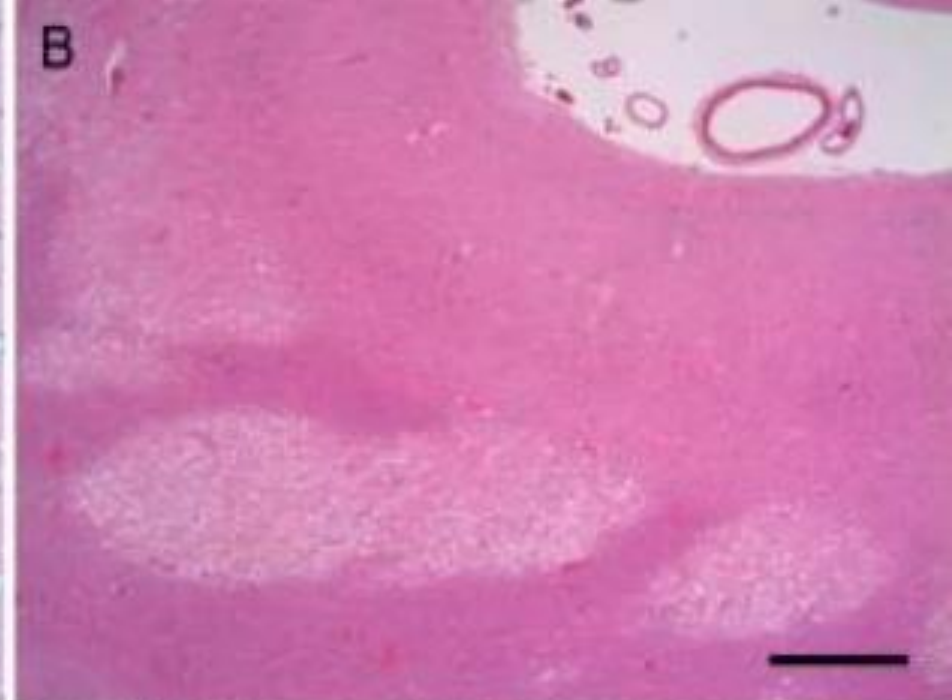
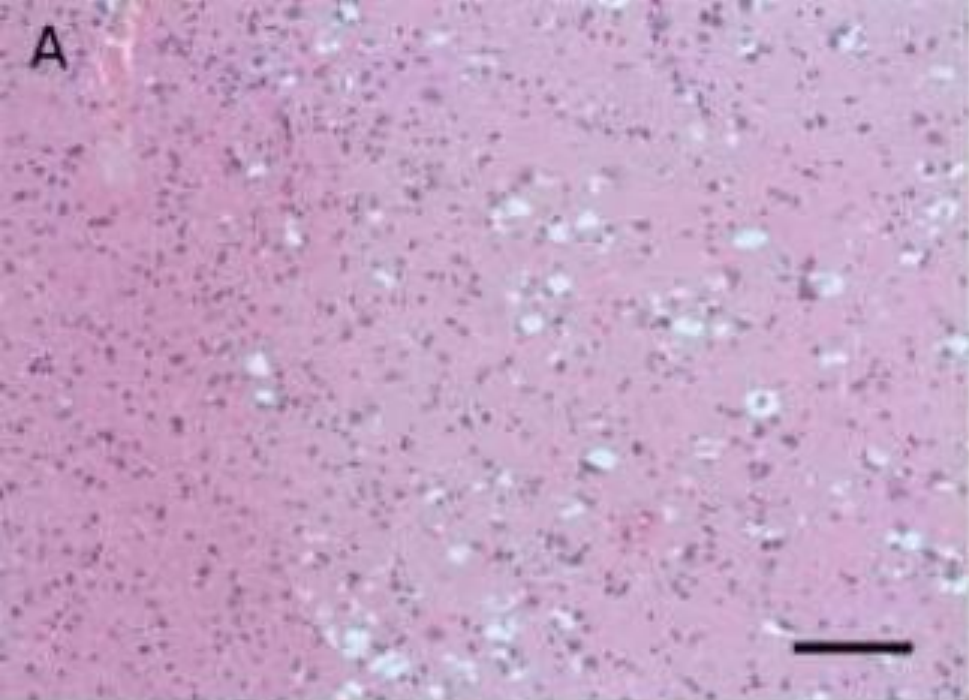


OLIG2-positive (e), variable synaptophysin immunoreactivity(f)



FISH showing chromosome 1p deletion (g; tumor cells showing red as 1p, green as 1q signals)
BRAF fusion/duplication (h; increased red *BRAF* and green *KIAA1549* copy numbers, in addition to yellow fusion signals)

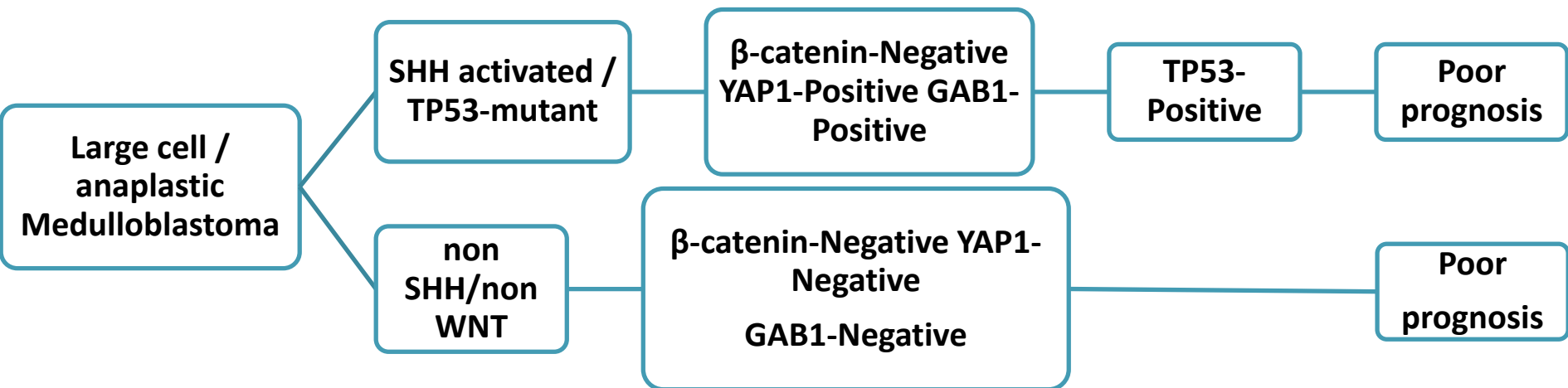
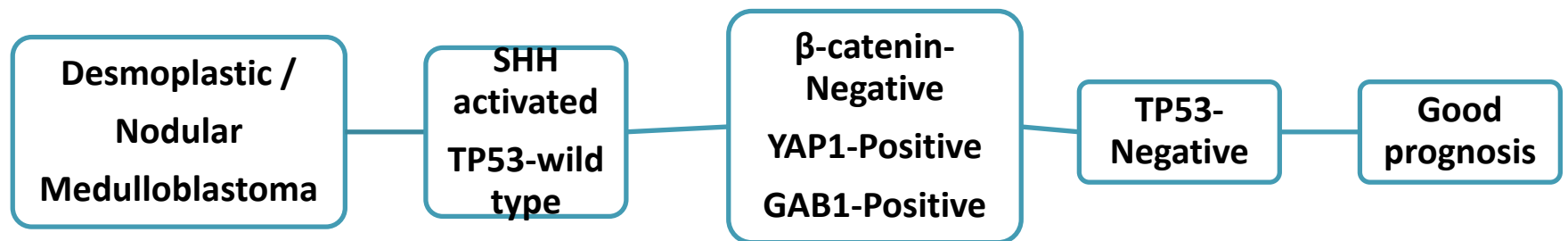
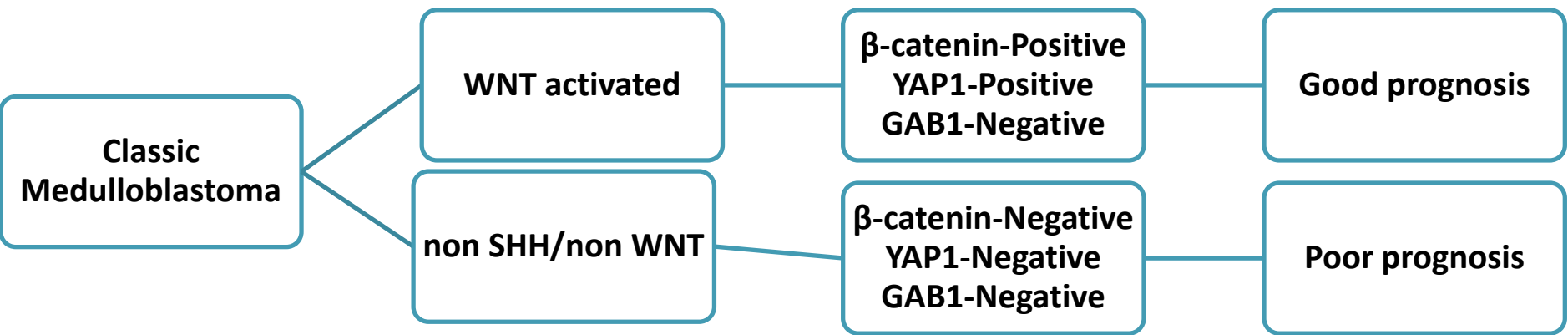
- Newly recognized architectural related to ganglion cell tumors is found, *multinodular and vacuolated pattern*
- Reported as *multinodular and vacuolated tumor of the cerebrum*
- Multiple nodules of tumor with a conspicuous vacuolation. The tumor cells show glial and/or neuronal differentiation



Medulloblastomas

- There are long-established histological variants of medulloblastoma
 - desmoplastic/nodular,
 - medulloblastoma with extensive nodularity,
 - large cell, and
 - Anaplastic , have clinical utility
- widely accepted four genetic (molecular) groups of medulloblastoma
 - WNT activated,
 - SHH-activated,
 - “group 3”
 - “group 4”
- “Genetically defined” and “Histologically defined” variants

- Wingless (Wnt) -family of growth factor receptors involved in embryogenesis and cell–proliferation control mechanisms
- *SHH* – Sonic Hedgehog
- Group 3 – MYC amplification
- Group 4 - Isochromosome 17q
- Integrated diagnosis that includes both the molecular group and histological phenotype



Other embryonal tumors

- Substantial changes
- Removal of the term *primitive neuroectodermal tumor* or *PNET* from the diagnostic lexicon
- Reclassification based on amplification of the C19MC region on chromosome 19

- Amplification of the C19MC seen in
 - Embryonal tumors with multilayered rosettes,
 - Some cases, medulloepithelioma
- Presence of C19MC amplification results in a diagnosis of embryonal tumor with multilayered rosettes (ETMR), C19MC-altered.
- In the absence of C19MC amplification, a tumor with histological features conforming to ETANTR/ ETMR should be diagnosed as embryonal tumor with multilayered rosettes, NOS

- Atypical teratoid/rhabdoid tumor (AT/RT) is now defined by alterations of either INI1 or, very rarely, BRG1
- Histological features of AT/RT but no genetic features then descriptive diagnosis of CNS embryonal tumour with rhabdoid features
- CNS embryonal tumor, NOS that includes tumors previously designated as CNS PNET.

Nerve sheath tumor

Nerve sheath tumors

- Similar to that of the 2007 CNS WHO
- Few changes
- Melanotic schwannoma classified as a distinct entity rather than variant
- Clinically , malignant behavior in a significant subset and genetically, associations with Carney Complex and the *PRKARIA* gene distinct from conventional schwannoma
- Hybrid nerve sheath tumors have been included in the 2016 CNS WHO, recognized in a variety of combinations.
- Two subtypes of Malignant peripheral nerve sheath tumor (MPNST):
 - Epithelioid MPNST and
 - MPNST with perineurial differentiation

Meningioma

Meningiomas

- Classification and grading of meningiomas did not undergo major revisions.
- Introduction for brain invasion as a criteria for atypical meningioma (grade II)
- Previously only considered as staging criteria
- Brain invasion joins a mitotic count of 4 or more as a histological criterion that can suffice for diagnosing an atypical meningioma, WHO grade II.
- Atypical meningioma can also be diagnosed on the basis of the Additive criteria of 3 of the other 5 histological features:
 - Spontaneous necrosis,
 - Sheetting (loss of whorling or fascicular architecture),
 - Prominent nucleoli,
 - High cellularity
 - Small cells (tumor clusters with high nuclear:cytoplasmic ratio).

Solitary fibrous tumor / hemangiopericytoma

- Both solitary fibrous tumors and hemangiopericytomas occur in the neuraxis, share inversions 12q13, fusing the *NAB2* and *STAT6* genes
- Overlapping features if not identical entities
- WHO 2016 combined term *solitary fibrous tumor / hemangiopericytoma*

Three grades

- Grade I
- Grade II
- Grade III

Solitary fibrous tumor / hemangiopericytoma

WHO grade

Three Grade

Grade 1

Grade 2

Grade 3

- Both solitary fibrous tumors and hemangiopericytomas occur in the neuraxis, share inversions 12q13, fusing the *NAB2* and *STAT6* genes
- Overlapping features if not identical entities
- WHO 2016 combined term *solitary fibrous tumor / hemangiopericytoma*

- Some tumors with a histological appearance more similar to traditional solitary fibrous tumor can also display malignant features
- WHO grade III, using the cutoff of 5 or more mitoses per 10 high-power fields.
- Additional Studies will, therefore, be required To fine-tune this grading system.

Report format

Table 2. Report format.

Layer 1: Integrated diagnosis (incorporating all tissue-based information)

Layer 2: Histological classification

Layer 3: WHO grade (reflecting natural history)

Layer 4: Molecular information

Report format

Table 4. Reporting format example: medulloblastoma.

Integrated diagnosis	Medulloblastoma histological subtype and molecular subgroup (eg, Wnt, SHH, non-WNT/non-SHH*), WHO grade IV
Histological classification	Classic, anaplastic, large cell, desmoplastic/nodular, medulloblastoma with extensive nodularity
WHO grade	IV
Molecular information	MYC amp, NMYC amp, TP53 status, CTNNB1 status, SMO status, PTCH status, i17q, monosomy 6**

- ❑ Over the past 4 years, advances in molecular pathology have enhanced our understanding of CNS tumors.
 - ❑ Refine their classification & improve the 2016 WHO.
 - ❑ CIMPACT-NOW was formed in late 2016 .
 - ❑ Group of neuropathology & neuro-oncopathology experts .(Directly involved in establishing 2016 WHO)
 - ❑ Practical recommendations (published as CIMPACT-NOW updates) to improve the diagnosis & classification of CNS tumors.
 - ❑ In advance of the publication of a new WHO Classification of CNS tumors.
- ✓ **This article reviews the content of all the available CIMPACT-NOW updates & discuss the implications.**

CIMPACT-NOW

The Consortium to Inform Molecular and Practical Approaches to CNS Tumour Taxonomy

C	Consortium
I	Inform
M	Molecular
P	Practical
A	Approaches
C	CNS tumour
T	Taxonomy
N	Not
O	Official
W	WHO

Update1: Not Otherwise Specified and Not Elsewhere Classified

Refines the meaning of NOS in diagnosing the cases where

1 Molecular testing is not available

2 If available & tests performed but not yielded adequate results

3 OR testing deliberately not performed *

**IDH status not tested in case of elderly patient with Glioblastoma as there is no therapeutic implication*

But, in cases of young patients (<55 years), the clinicians may want to discuss the need for additional molecular testing

So , update 1 introduces the term “**NOT ELSEWHERE CLASSIFIED**”

To be used when a molecular testing performed

Yielded adequate results

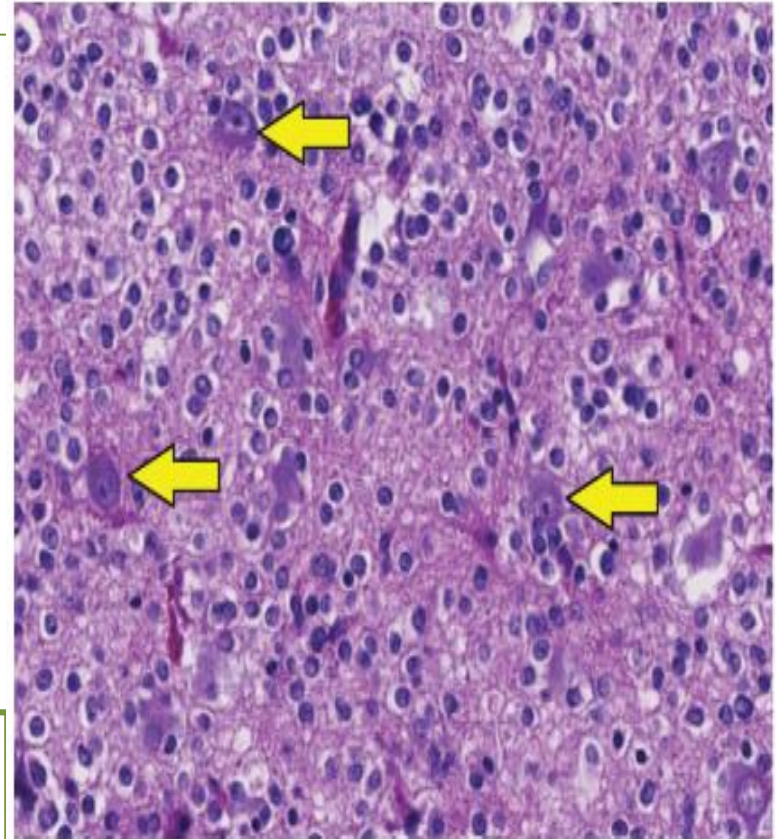
Do not lead to a precise categorization
within the framework of WHO 2016
classification

For e.g:
Patient

With Diffuse glioma IDH wild
type whose histology is
oligodendroglial

And D/D are not fitting either
way....

What to Report



Report it as **Oligodendroglioma NEC**

“To the readers NEC puts a red flag to the report that the diagnosis is not a 2016 WHO mentioned lesion.”

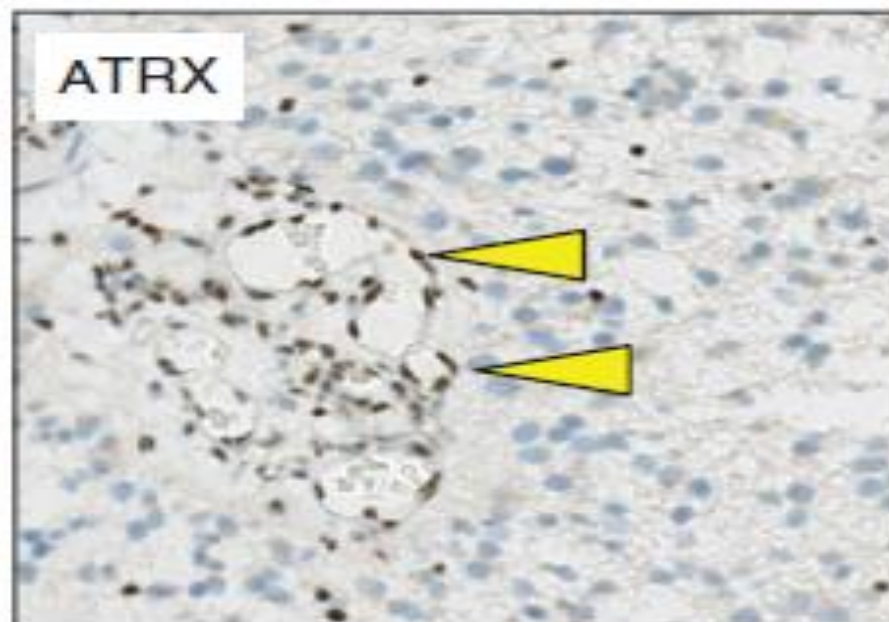
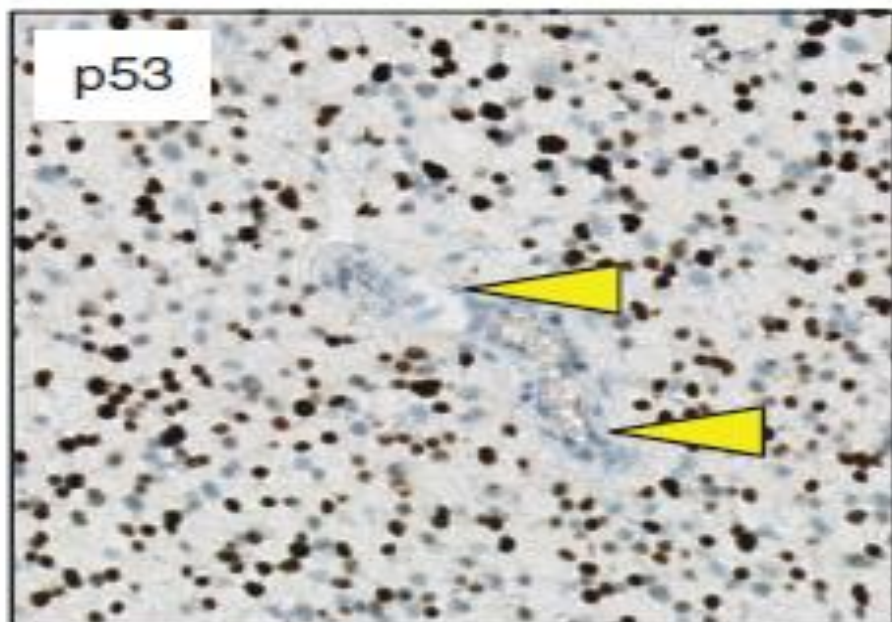
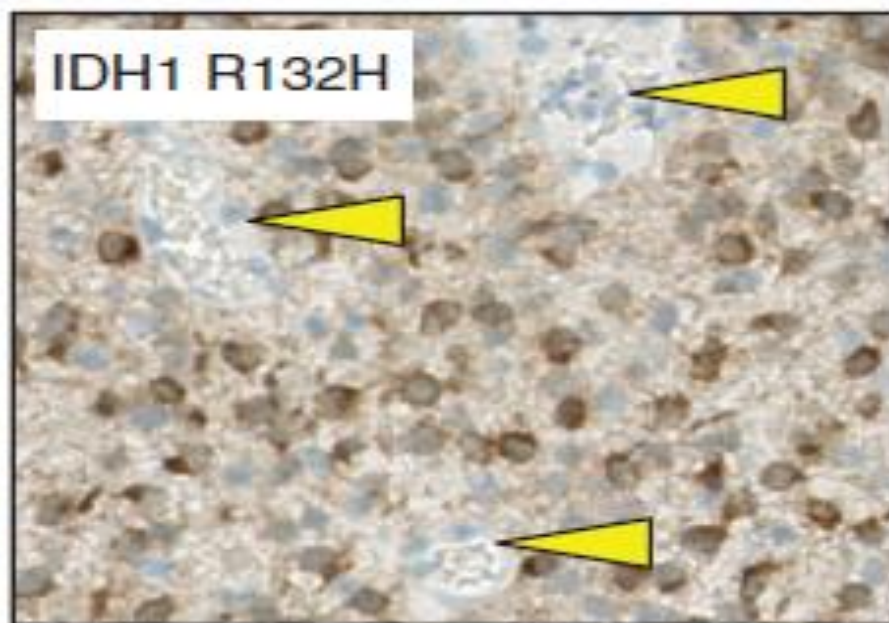
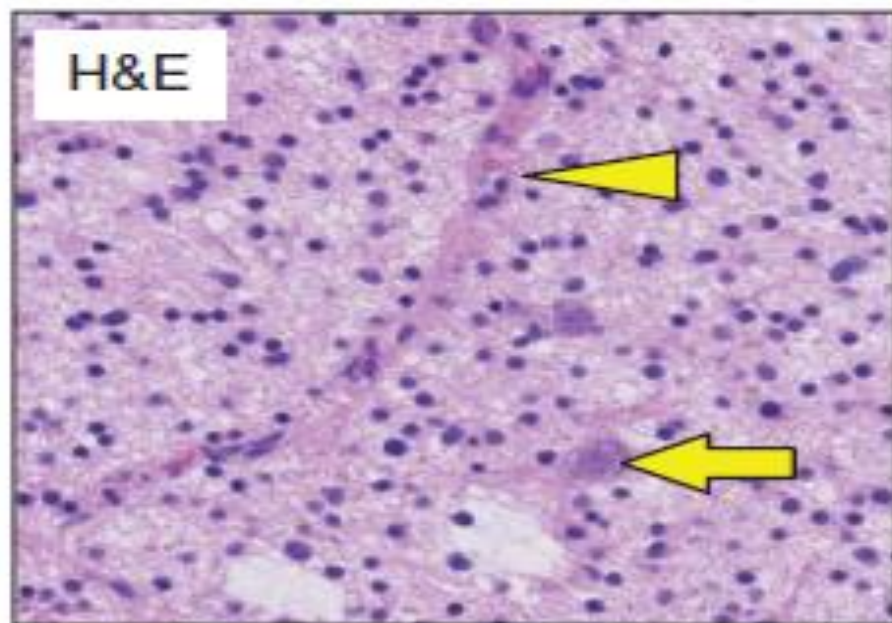
Update2: Clarifying the Diagnosis of Diffuse Midline Glioma, Histone 3K27M-Mutant, and Diffuse Astrocytoma/ Anaplastic Astrocytoma, IDH Mutant

- **1st Issue:** Regarding Diagnosis of Diffuse Midline Glioma, Histone 3K27M-Mutant

<i>Diffuse</i>	<i>Diffuse infiltrative growth</i>
<i>Midline</i>	<i>Tumor affecting “midline” structures (brainstem, thalamus, spinal cord)</i>
<i>Glioma</i>	<i>Glioma type histology</i>
Mandatory for Diagnosis	The above histological aspects + H3K27M mutation
WHY???	Because there are certain other tumors also who show H3K27M mutation but are not midline gliomas (e.g. Pilocytic astrocytoma, ependymoma)

- **2nd Issue:** Regarding Diagnosis of Diffuse Astrocytoma IDH mutant Or Anaplastic Astrocytoma IDH mutant

Earlier	Now
2016 WHO classification says IDH1 <u>or</u> 2 Mutation <u>AND</u> absence of 1p 19q co-deletion is necessary to diagnose	Diagnosis can be made without testing 1p 19q co deletion
HOW??	
	<p>These tumours can be diagnosed if the IHC results show</p> <ul style="list-style-type: none">• loss of ATRX• and or strong & diffuse nuclear staining for p53.



Update3: Molecular Clues for recognizing histologically Lower Grade, Diffuse Astrocytic Gliomas IDH- wild type as Glioblastoma IDH- wild type

WHO GRADE 2 OR 3



WHO GRADE 4 (*a high grade*)

By the presence of

Necrosis & OR microvascular proliferation



we conclude diagnosis of Diffuse astrocytic glioma as glioblastoma



However even if NO necrosis, No microvascular proliferation



Still most histologically Lower grade Diffuse Astrocytic gliomas IDH WT in adults behave as WHO grade 4 lesions

- So update 3 focus on **Molecular criteria**, so that we can upgrade the tumor from 2nd or 3rd grade to grade 4 (high grade lesion)
- (And it has importance with regard to prognosis and treatment)

HOW???

By 3 criteria

1	Gain of whole Chromosome 7 Loss of whole Chromosome 10	(7 +) (10 -)
2	TERT promotor Mutation	
3	EGFR amplification	

- **The presence of 1 or more of the above 3 molecular markers implied/ showed a prognosis consistent with that of glioblastoma.**

Update 5: Improved Grading of Isocitrate Dehydrogenase– Mutant Astrocytomas on the Basis of Cyclin-Dependent Kinase Inhibitor 2A/B Homozygous Deletion Status

- The presence of a homozygous deletion of cyclin-dependent kinase inhibitor 2A/B (*CDKN2A/B*) is now recognized as an **important negative prognostic factor** within the IDH mutant group.
- *IDH*-mutant astrocytomas that harbor homozygous *CDKN2A/B* deletion behave clinically as **high-grade** malignant tumors.

The update 5 recommends grading *IDH*-mutant astrocytomas as -

WHO grade II	in the absence of anaplastic features, significant mitotic activity, and homozygous CDKN2A/B deletion.
WHO grade III	when anaplastic features and significant mitotic activity are present but there is no homozygous deletion of CDKN2A/B.
WHO grade IV	when not only if it shows microvascular proliferation and/or necrosis, but also if molecular analysis reveals the presence of homozygous CDKN2A/B deletion.

Testing for CDKN2A/B deletions is important for optimal counselling.

Homozygous CDKN2A/B deletion in these tumors signifies high-grade malignant behaviour.

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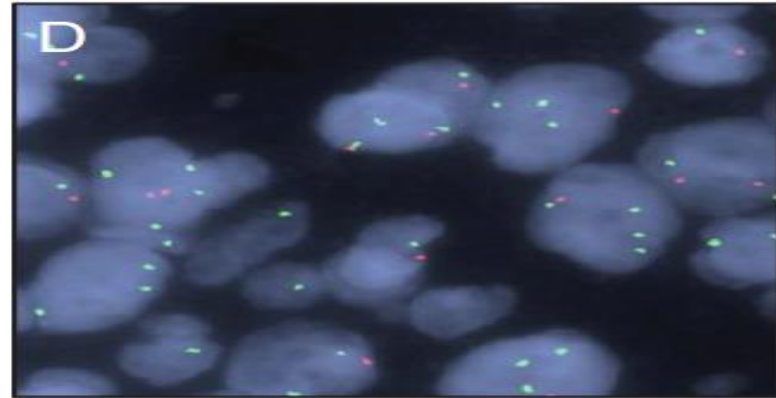
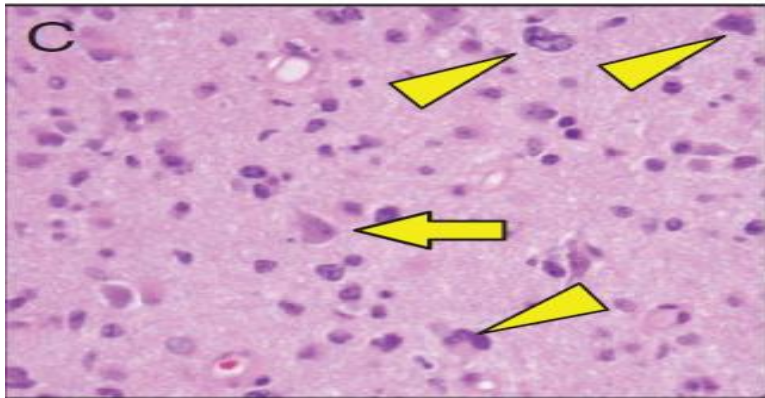
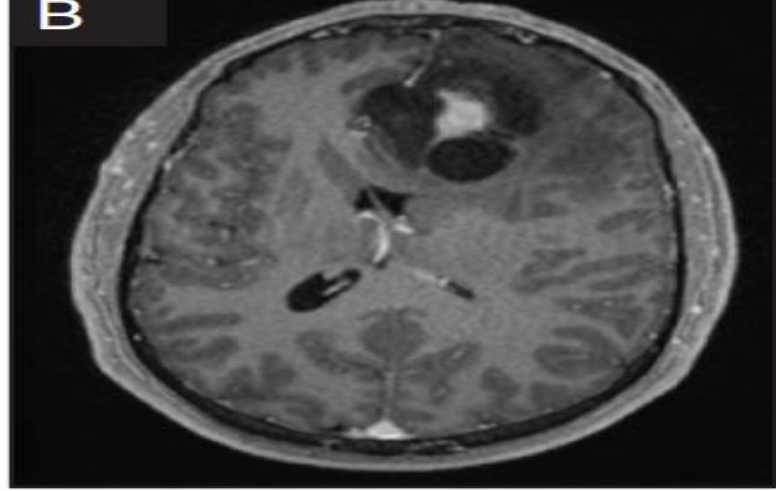


FIGURE-A MRI images of a left frontal Lobe lesion in a 45-year-old ,C- Histology shows infiltrating pleomorphic astrocytic cells with high n:c ratio (arrowheads) and only a few scattered mitoses because necrosis and microvascular proliferation were absent, diagnosis was anaplastic astrocytoma, *IDH*-mutant, grade III. D- FISH assay to analyze *CDKN2A* copy number status demonstrated loss of *CDKN2A* signal and preservation of CEP9 signal in 24 of 50 cells counted, consistent with homozygous deletion of *CDKN2A* and thus reason to upgrade the tumor grade to IV.

Update 4: Classification of “Pediatric-Type” Diffuse Gliomas, Isocitrate Dehydrogenase–Wild-Type, Histone 3–Wild-Type on the Basis of Presence of Myb Proto-Oncogene, Myb Proto-Oncogene Like 1, FGFR1 Alteration, B-Raf Proto-Oncogene, Serine/Threonine Kinase V600E Mutation, or Other Mitogen-Activated Protein Kinase Pathway Alterations

Molecular alterations that are frequently found in histologically low-grade, diffuse gliomas in children.

If such a tumor does not have an

- *IDH* or H3 K27M mutation
- No molecular alterations associated with glioblastoma
- based on its molecular features, the tumor can be diagnosed as-

Diffuse glioma,

- Myb proto-oncogene (*MYB*)-altered,
- Myb proto-oncogene like 1 (*MYBL1*)-altered,
- Fibroblast growth factor receptor 1 (*FGFR1*)-mutant,
- *FGFR1* tyrosine-kinase duplicated,
- Serine/threonine kinase (*BRAF*) V600E–mutant (but not if it has a concurrent deletion in *CDKN2A/B*),
- “Mitogen-Activated Protein Kinase (*MAPK*) pathway-altered.

- Allows for greater precision on prognosis .
- Potential implications for targeted treatment (eg, targeting *BRAF* V600E mutations with *BRAF* inhibitors like dabrafenib) .
- Tumor with a specific alteration that signifies a generally favorable prognosis and could potentially be targeted.

Update 6: Recommendations on Emerging New Entities and Diagnostic Principles for Future CNS Tumor Classification and Grading (cIMPACT-Utrecht meeting report)



- Acknowledges the **utility of methylome profiling for CNS tumor classification and diagnosis.**

To designate

- Diffuse, histologically lower-grade, *IDH*–wild-type astrocytomas with molecular features of glioblastoma directly as “glioblastoma, *IDH*–wild-type”.
- Diffuse astrocytoma *IDH* mutant (homozygous *CDKN2A/B* deletion) as diffuse astrocytoma *IDH* mutant grade 4.
- This eliminates confusion and facilitate inclusion of these patients into clinical trials.
- Definitions and characteristic features for multiple emerging new entities, many of which can be accurately characterized by specific molecular features (eg, diffuse glioma, H3.3 G34-mutant, and spinal ependymoma, *MYCN* protooncogene [*MYCN*]-amplified).

Update 7: Refining the Classification of Ependymomas Using Molecular Features

- This update recommends that ependymomas be classified by both anatomic site and molecular features.
- Supratentorial (ST) ependymomas, when possible, should be classified according to the presence of chromosome 11 open reading frame 95 (*c11orf95*) or yes-associated protein 1 (*YAP1*) gene fusions.
- Based on the degree of histone H3 K27-trimethylation, posterior fossa ependymomas should be classified as
- Type A (PFA) Type B (PFB)

- PFA ependymomas (particularly those with gain of chromosome 1q) are known to have worse prognosis.
- however more survival data need to be collected before a definitive grade.
- Ependymoma of the spinal cord with *MYCN* amplification as a new entity associated with poor clinical outcome .
- Myxopapillary ependymomas of the spinal cord as grade 2 (rather than grade 1) tumors.
- Not awarding the papillary, clear cell, and tanycytic variant of ependymomas with a separate status due to lack of clinical utility.

SUMMARY

cIMPACT-NOW update	Implications
Update 1	<ul style="list-style-type: none">• NOS added to pathological diagnosis: results of molecular testing required for a more precise diagnosis as listed in WHO classification not available; (re-)consider the need and/or possibility for additional molecular testing.• NEC added to pathological diagnosis: indicates a diagnosis that, after adequate (molecular) testing, is not listed as such in most recent WHO classification.
Update 2	<ul style="list-style-type: none">• Not every H3 K27M–mutant tumor is a diffuse midline glioma and carries the same dismal prognosis.• Diffuse (anaplastic) astrocytoma, IDH-mutant can be diagnosed using ATRX and/or p53 expression as immunohistochemical surrogate markers for absence of 1p/19q codeletion

Update 3	<ul style="list-style-type: none"> • Demonstration of +7/−10, <i>EGFR</i> amplification, and/or <i>TERT</i> promoter mutation in WHO grade II or III, IDH–wildtype diffuse gliomas in adult patients allows for the diagnosis glioblastoma, IDH–wild-type
Update 4	<ul style="list-style-type: none"> • IDH– and H3–wild-type diffuse glioma in children that are driven by <i>MYB</i> or <i>MYBL1</i> gene rearrangement, <i>FGFR1</i> mutation, or <i>FGFR1</i> tyrosine kinase domain duplication, BRAF V600E mutation, or by another MAPK pathway alteration generally have favorable prognosis. • Molecular defect in these tumors represents a potential therapeutic target
Update 5	<ul style="list-style-type: none"> • Homozygous <i>CDKN2A/B</i> deletion in IDH-mutant diffuse astrocytoma signifies grade IV malignant behavior
Update 6	<p>Presentation of</p> <ul style="list-style-type: none"> -New general principles for classification of CNS tumors - Suggested revisions of nomenclature for some of these tumors - More recently recognized (sub)types of CNS tumors that appear ready for inclusion in next WHO classification of CNS tumors

Update 7

- Improved classification of ependymomas based on anatomic region and molecular characteristics
 - Supratentorial: classified based on presence of *c11orf95* vs *YAP1* gene fusions (c11orf95 fusion–positive ependymomas largely overlapping with *RELA* fusion-positive ependymomas as described in WHO 2016 classification)
 - PF: PF ependymomas can be classified as type A or type B (PFA or PFB), characterized by respectively absence or presence of H3 K27me3 staining of tumor cell nuclei;
 - gain of Chr. 1q signifies worse prognosis in PFA ependymomas
- Ependymoma of the spinal cord with *MYCN* amplification is a newly recognized entity associated with poor clinical outcome
- Myxopapillary ependymomas of the spinal cord should be considered grade 2 (rather than grade 1) tumors

Conclusion

- Since 2016, cIMPACT-NOW has published several guidelines for improved pathological diagnosis of these neoplasms.
- The cIMPACT-NOW guidelines have important implications for clinical practice and for the **design and interpretation of clinical trials**.
- cIMPACT-NOW recommendations summarized are likely to be incorporated in the new WHO classification
- Because it can be expected that our understanding of the biology of CNS tumors will continue to expand at a rapid pace, continuation of the efforts of cIMPACT-NOW–like consortia may be very helpful for optimal (evidence-based, balanced, rapid) translation of novel insights into clinical diagnostics, with the of providing the best possible care to CNS tumor patients.

THANK YOU