Annals of R.S.C.B., ISSN: 1583-6258, Vol. 25, Issue 5, 2021, Pages. 5046 - 5050

Received 15 May 2021; Accepted 20 May 2021.

Review on Glioma Classification and cIMPACT-NOW updates on WHO 2016 Histological Classification

Priavadhana Rajan Prasaad[1], Vindu Srivastava[2*], Krishna Prasanth.B[3], Abishek Chakkaravarthi.M[4]

[1] Assistant Professor of Pathology, ESIC Medical College and PGIMSR.

[2]Professor of Pathology, Sree Balaji Medical College and Hospital,

Bharath Institute of Higher Education & Research

[3]Epidemiologist & Assistant Professor of Community Medicine,Sree Balaji Medical College and Hospital, Bharath Institute of Higher Education & Research.

[4]Post Graduate Student of Pathology, Sree Balaji Medical College and Hospital,

Bharath Institute of Higher Education & Research

[*]Corresponding author-Dr.Vindu Srivastava MD (Pathology), Professor of Pathology
Sree Balaji Medical college and Hospital, #07 Works road , Chrompet,Chennai-600044,TN, India

Email for Correspondence : vinsripath1@gmail.com

ABSTRACT

Glioma is a term used to refer to neoplastic proliferation of neuroglial structures like astrocytes, oligodendrocytes and ependymal cells. WHO classification of 2000 and 2007 dealt with cytomorphological and histological features alone to determine and diagnose biological behavior of tumors. Histological criteria like anaplasia, mitosis, microvascular proliferation [MVP] and necrosis could not be used to accurately and reproducibly diagnose the new subtypes and hence the revised WHO 2016 criteria which integrates the molecular and histomorphological criteria has become more widely accepted for classification and grading of gliomas. The International Society of Neuropathology established the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) in 2016 to facilitate this attempt. Some of the major changes adapted in WHO 2016 are incorporation of genetically defined entities in diffuse gliomas, incorporation of genetically defined ependymoma variant and identifying IDH-wildtype and mutant glioblastoma entities . This review focuses on the newer subtypes introduced in the WHO 2016 with special emphasis on the molecular and the genetic mutational categories of gliomas.

Keywords-

Glioma, CNS tumor, Taxonomy

INTRODUCTION

Glioma is a term used to refer to neoplastic proliferation of neuroglial structures like astrocytes, oligodendrocytes and ependymal cells. It has been proven that immature, progenitor cells preceeding development of these different lineages acquire genetic and epigenetic alterations in a multistep process and lead to development of astrocytomas, oligodendrogliomas and ependymomas.[13] A majority of CNS tumors are gliomas and a majority of gliomas are primary tumors.[10,11] Gliomas can be infiltrating or localized based on clinical behavior and tumor margin. Adult CNS neoplasms differ from those seen in children. Infiltrating (higher grade) tumors occur in adults while localized (low grade) occur in children. WHO classification of 2000 and 2007 dealt with cytomorphological and histological features alone to determine and diagnose biological behavior of tumor. The discovery of IDH mutations in adult diffuse astrocytomas and oligodendrogliomas among other new mutations lead to a difficulty in including these new

Annals of R.S.C.B., ISSN: 1583-6258, Vol. 25, Issue 5, 2021, Pages. 5046 - 5050

Received 15 May 2021; Accepted 20 May 2021.

molecular subtypes in the existing grading systems. Histological criteria like anaplasia, mitosis, microvascular proliferation [MVP] and necrosis could not be used to accurately and reproducibly diagnose these new subtypes and new grading criteria for differentiation were not reported to be able to replace the WHO 2016 criteria.[10,11,13] In light of identification of various genetic mutations in different subtypes by NGS, and the increasing positive results with correlation of histopathological and molecular features, WHO 2016 was sought to be amended, including them both, to direct clinical treatment and prognosis, referred to as "integrated diagnosis".[1,10,11,13] The International Society of Neuropathology established the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) in 2016 to facilitate this attempt.[1] Under the 2016 classification of glial tumors, new molecular subtypes representing the genotypic features are included - IDH-wildtype and glioblastoma, IDH-mutant; diffuse midline glioma, H3 K27M–mutant; RELA fusion–positive ependymoma, in addition to the other older histological subtypes.[2,11,14]

Summary of the major changes in the 2016 CNS WHO with respect to gliomas:[2,10,11]

- Incorporation of genetically defined entities in diffuse gliomas
- Incorporation of genetically defined ependymoma variant
- Diffuse gliomas (both astrocytomas and oligodendrogliomas) are grouped together according to phenotypic, genotypic and prognostic factors. Localized circumscribed gliomas are grouped separately.
- Addition of newly recognized entities, variants and patterns
  - IDH-wildtype and mutant glioblastoma entities
  - Diffuse midline glioma, H3 K27M–mutant
  - RELA fusion–positive supratentorial ependymomas
  - Anaplastic pleomorphic xanthoastrocytoma
  - Epithelioid variant of glioblastoma
  - Glioblastoma with primitive neuronal component
  - Gliomatosis cerebri
  - Protoplasmic and fibrillary astrocytoma variants
  - Cellular variant of ependymoma

WHO also suggests standardized nomenclature:[2,10,11]

- Histopathological name followed by genetic features, ex: *Diffuse astrocytoma, IDH-mutant.*
- More than one genetic determinant, ex: *Oligodendroglioma, IDH-mutant* and *1p/19q-codeleted*.
- If lacking a genetic mutation, *wildtype* is used, ex: *Glioblastoma, IDH-wildtype*.
- If tumor is lacking a diagnostic mutation, or there is no appropriate resource leading to insufficient information to assign a more specific code: *NOS*.
- If specific genetic alteration is present or absent, *positive* is used, ex: *Ependymoma, RELA fusion–positive*.
- Italics are used for specific gene symbols (e.g., *ATRX*) but not for gene families (e.g., IDH, H3).
- WHO grades are written in Roman numerals (e.g., I, II, III and IV; not 1, 2, 3 and 4).

The new classification, upon retrospection also poses some difficulties. Economical feasibility of different labs in both developing and advanced countries is a concern.[3] Some tumor types cannot be included in the new classification, for example, Infiltrating gliomas with IDH wildtype but 1p/19q co-deletion and classic oligodendroglioma without these genetic mutations.[3] There is variability in adaptation of new subtypes in various labs because of lack of real-time consensus and feedback under the new WHO system.[3,10] WHO classification is the accepted international standard by which brain tumors are diagnosed, treated, and investigated. While from a purely pathological and research point of view, a purely genetic division of the subtypes is preferred to delineate tumors according to their discrete prognoses. This results in a lack of clinical utility of the new system.[3,10] The debate over keeping the present genetic-histologic classification or replacing it with purely genetic classification (which is more accurate) might only be answered by time, by testing the pathologic and clinical utility.[3,10] Another issue is the discordance in reporting mitotic activity and PI among many observers in the II and III grades, for which pHH3 immunostaining can be used. This is due to a lack of cutoff values standardized in the WHO system.[1,10,11]

The new WHO system is mainly focused on adult diffuse type gliomas, while a lack of evidence prevented classification of pediatric type gliomas.[4] pDG tend to be more localized and circumscribed, have prolonged clinical course with long histories of drug resistant epilepsy (LEATS-long term epilepsy associated tumors). Genetic alterations associated with pDG also show overlap across all gliomas, for instance, the BRAF V600E mutation.[4]

Annals of R.S.C.B., ISSN: 1583-6258, Vol. 25, Issue 5, 2021, Pages. 5046 - 5050

Received 15 May 2021; Accepted 20 May 2021.

pDG also manifests in adults making diagnosis more difficult.[4] pDG also lacks IDH mutations and 1p/19q codeletions like in high grade adult diffuse type gliomas, but have RAS/MAPK mutations in low grade and H3 K27 mutations, NTRK mutations or wildtype variants in high grade neoplasms.[4] CDKN2A/B deletions with or without necrosis has been found to be a determinant of prognosis in grades III and IV. Presence of CDKN2A/B deletions indicates a worse prognosis. Other mutations like RB genes, PIK3CA or PIK3R1 mutations, PDGFRA amplification, MYCNamplification, TERT, ATRX, CIC, FGFR1, EGFR mutations, genomic instability and reduced global DNA methylation are seen in III and IV grades but not seen in grade II.[12,17,18,19] These have not been included in the new WHO system or the recent Rounds (1 & 2) updates of the Consortium, because of lack of evidence.[20] Hopefully, classification based on these genotypic markers can be included in future revised classifications. Emerging entities like H3K27 mutations and RELA-fusion positive mutations are seen in diffuse midline gliomas and supratentorial gliomas respectively.[5] KIAA1549-BRAF fusion and CIC, FUBP1 mutations are seen in pilocytic astrocytomas and oligodendrogliomas respectively.[5] Present grading approach is useful for IDH-wildtype but not IDH-mutant gliomas, also for low and high grade oligodendrogliomas. Such variations in the prognoses between different genotypic subtypes cannot be classified under current system and has to revised after conducting further studies.[1,14,18]

Glioblastomas were the first tumors for which an epigenetic biomarker was initiated. Measurement of promoter hypermethylation of MGMT gene is useful to assess response to temozolomide therapy. Emerging entities include high grade IDH wildtype gliomas with H3 G34/35 mutations in cerebral gliomas of childhood and young adults. Another is the same subtype with piloid features that occurs commonly in posterior fossa. Yes-associated protein 1 gene (YAP1) fusion-positive supratentorial ependymomas are seen in children. These have yet to be enveloped into the present classification system.[9]

cIMPACT-NOW updates from Rounds 1 & 2 with respect to gliomas:[8,10,11,15,16]

- Update 1 - use of term like NOS (Not Otherwise Specified) and proposed use of NEC (Not Elsewhere Classified). Under NOS, diagnostic information (histologic and genetic) is not available, while under NEC, diagnostic information is available but does not conform to a 2016 WHO diagnosis. Emerging entities come under this group.[6]
- Update 2 - *Diffuse Midline Glioma, H3 K27M-mutant* and *Diffuse Astrocytoma/Anaplastic Astrocytoma, IDH-mutant*. The former is not reserved other tumors (ependymomas) with H3K27-mutant genotype, while the latter is associated with loss of ATRX nuclear expression and diffuse p53 positivity. H3K27 mutations were found in other tumors, necessitating the use of this terminology. 1p/19q co deletion testing may not be available in many labs, which was why ATRX and p53 mutations are used to diagnose grade III IDH-mutant astrocytomas.[6]
- Update 3 - proposed molecular criteria to correlate similarity in biological behavior of grades III and IV. They include: EGFR amplification and/or whole chromosome 7 gain and 10 loss (+7/-10) and/or TERT promoter mutations.[6,9]
- Update 4 - *IDH-wildtype/H3-wildtype diffuse gliomas* are to be designated as: Diffuse glioma, *MYB*-altered; Diffuse glioma, *MYBL1*-altered; Diffuse glioma, *FGFR1* TKD-duplicated; Diffuse glioma, *FGFR1*-mutant; Diffuse glioma, *BRAF* V600E-mutant (but without *CDKN2A/B* deletion); Diffuse glioma, other MAPK pathway alteration. This was done to better represent these neoplasms presenting in childhood and young adulthood, as some have better and some, worse prognosis.[6]
- Update 5 – It is now understood that IDH-wildtype and IDH-mutant tumors are distinct clinical and genetic entities (CDKN2A/B deletions, RB genes, PIK3CA or PIK3R1 mutations, PDGFRA amplification, MYCNamplification, genomic instability and reduced global DNA methylation)[12] and cannot be represented by WHO terms like diffuse, anaplastic astrocytomas and glioblastomas. It is proposed that the term glioblastoma be reserved for IDH-wildtype tumors with clinical, histologic and genetically aggressive behavior of grade IV, while IDH-mutant be termed based on grade II, III or IV criteria:[7,16]

1. Astrocytoma, IDH-mutant, grade 2: diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation, well differentiated, lacks anaplasia, low/absent mitotic activity, absence of microvascular proliferation, necrosis and *CDKN2A/B* homozygous deletions.

2. Astrocytoma, IDH-mutant, grade 3: diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation, with anaplasia, some mitotic activity, absence of microvascular proliferation, necrosis and *CDKN2A/B* homozygous deletions.
3. Astrocytoma, IDH-mutant, grade 4: diffusely infiltrative astrocytic glioma with an *IDH1* or *IDH2* mutation, combination of microvascular proliferation or necrosis or *CDKN2A/B* homozygous deletion.

- Update 6 – "Entities/variants" were suggested to be replaced with "types/subtypes" respectively.
  Histolgically and genetically definite lists of glial tumors were suggested to be created for the purposes of classification, which will later be used for "integrated diagnosis".
  Ependymomas were suggested to include anatomic site in nomenclature.
  Chordoid glioma was not suggested to include site in nomenclature with respect to gliomas.
  Methylome profiling has been suggested to identify different types and subtypes.
  Arabic numerals will replace Roman numerals in the 5th edition of WHO.[8]
- Update 7 – Ependymomas were suggested to include both molecular features and anatomic site in nomenclature, for example: Supratentorial (ST) ependymomas includes chromosome 11 open reading frame 95 (*c11orf95*) or yes-associated protein 1 (*YAP1*) gene fusions.[15]

REFERENCES

[1] Komori T. Updating the grading criteria for adult diffuse gliomas: beyond the WHO2016CNS classification. Brain Tumor Pathol. 2020 Jan;37(1):1-4. doi: 10.1007/s10014-020-00358-y. PMID: 32060660.

[2] Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016 Jun;131(6):803-20. doi: 10.1007/s00401-016-1545-1. Epub 2016 May 9. PMID: 27157931.

[3] Komori T. Updated 2016 WHO classification of tumors of the CNS: turning the corner where molecule meets pathology. Brain Tumor Pathol. 2017 Oct;34(4):139-140. doi: 10.1007/s10014-017-0299-3. PMID: 28840403.

[4] Komori T. The molecular framework of pediatric-type diffuse gliomas: shifting toward the revision of the WHO classification of tumors of the central nervous system. Brain Tumor Pathol. 2021 Jan;38(1):1-3. doi: 10.1007/s10014-020-00392-w. PMID: 33398472.

[5] Kristensen BW, Priesterbach-Ackley LP, Petersen JK, Wesseling P. Molecular pathology of tumors of the central nervous system. Ann Oncol. 2019 Aug 1;30(8):1265-1278. doi: 10.1093/annonc/mdz164. PMID: 31124566; PMCID: PMC6683853.

[6] Louis DN, Ellison DW, Brat DJ, Aldape K, Capper D, Hawkins C, Paulus W, Perry A, Reifenberger G, Figarella-Branger D, von Deimling A, Wesseling P. cIMPACT-NOW: a practical summary of diagnostic points from Round 1 updates. Brain Pathol. 2019 Jul;29(4):469-472. doi: 10.1111/bpa.12732. Epub 2019 May 22. PMID: 31038238.

[7] Brat DJ, Aldape K, Colman H, Figrarella-Branger D, Fuller GN, Giannini C, Holland EC, Jenkins RB, Kleinschmidt-DeMasters B, Komori T, Kros JM, Louis DN, McLean C, Perry A, Reifenberger G, Sarkar C, Stupp R, van den Bent MJ, von Deimling A, Weller M. cIMPACT-NOW update 5: recommended grading criteria and terminologies for IDH-mutant astrocytomas. Acta Neuropathol. 2020 Mar;139(3):603-608. doi: 10.1007/s00401-020-02127-9. Epub 2020 Jan 29. PMID: 31996992.

[8] Louis DN, Wesseling P, Aldape K, Brat DJ, Capper D, Cree IA, Eberhart C, Figarella-Branger D, Fouladi M, Fuller GN, Giannini C, Haberler C, Hawkins C, Komori T, Kros JM, Ng HK, Orr BA, Park SH, Paulus W, Perry A, Pietsch T, Reifenberger G, Rosenblum M, Rous B, Sahm F, Sarkar C, Solomon DA, Tabori U, van den Bent MJ, von Deimling A, Weller M, White VA, Ellison DW. cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. Brain Pathol. 2020 Jul;30(4):844-856. doi: 10.1111/bpa.12832. Epub 2020 Apr 19. PMID: 32307792.

[9] Brat DJ, Aldape K, Colman H, Holland EC, Louis DN, Jenkins RB, Kleinschmidt-DeMasters BK, Perry A, Reifenberger G, Stupp R, von Deimling A, Weller M. cIMPACT-NOW update 3: recommended diagnostic criteria for "Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV". Acta Neuropathol. 2018 Nov;136(5):805-810. doi: 10.1007/s00401-018-1913-0. Epub 2018 Sep 26. PMID: 30259105; PMCID: PMC6204285.

Received 15 May 2021; Accepted 20 May 2021.

[10] Lee SC. Diffuse Gliomas for Nonneuropathologists: The New Integrated Molecular Diagnostics. Arch Pathol Lab Med. 2018 Jul;142(7):804-814. doi: 10.5858/arpa.2017-0449-RA. Epub 2018 May 18. PMID: 29775073.

[11] Pisapia DJ. The Updated World Health Organization Glioma Classification: Cellular and Molecular Origins of Adult Infiltrating Gliomas. Arch Pathol Lab Med. 2017 Dec;141(12):1633-1645. doi: 10.5858/arpa.2016-0493-RA. PMID: 29189064.

[12] Kam KL, Appin CL, Mao Q, Ikegami S, Lukas RV, Nikiforova MN, Roy S, Brat DJ, Horbinski C. Is Next-Generation Sequencing Alone Sufficient to Reliably Diagnose Gliomas? J Neuropathol Exp Neurol. 2020 Jul 1;79(7):763-766. doi: 10.1093/jnen/nlaa044. PMID: 32483596; PMCID: PMC7304984.

[13] Lenting K, Verhaak R, Ter Laan M, Wesseling P, Leenders W. Glioma: experimental models and reality. Acta Neuropathol. 2017 Feb;133(2):263-282. doi: 10.1007/s00401-017-1671-4. Epub 2017 Jan 10. PMID: 28074274; PMCID: PMC5250671.

[14] Schwartzbaum JA, Fisher JL, Aldape KD, Wrensch M. Epidemiology and molecular pathology of glioma. Nat Clin Pract Neurol. 2006 Sep;2(9):494-503; quiz 1 p following 516. doi: 10.1038/ncpneuro0289. PMID: 16932614.

[15] Gonzalez Castro LN, Wesseling P. The cIMPACT-NOW updates and their significance to current neuro-oncology practice. Neurooncol Pract. 2020 Aug 29;8(1):4-10. doi: 10.1093/nop/npaa055. PMID: 33664964; PMCID: PMC7906262.

[16] Yeaney GA, Brat DJ. What Every Neuropathologist Needs to Know: Update on cIMPACT-NOW. J Neuropathol Exp Neurol. 2019 Apr 1;78(4):294-296. doi: 10.1093/jnen/nlz012. PMID: 30830209.

[17] Masui K, Kato Y, Sawada T, Mischel PS, Shibata N. Molecular and Genetic Determinants of Glioma Cell Invasion. Int J Mol Sci. 2017 Dec 4;18(12):2609. doi: 10.3390/ijms18122609. PMID: 29207533; PMCID: PMC5751212.

[18] Jiang T, Mao Y, Ma W, Mao Q, You Y, Yang X, Jiang C, Kang C, Li X, Chen L, Qiu X, Wang W, Li W, Yao Y, Li S, Li S, Wu A, Sai K, Bai H, Li G, Chen B, Yao K, Wei X, Liu X, Zhang Z, Dai Y, Lv S, Wang L, Lin Z, Dong J, Xu G, Ma X, Cai J, Zhang W, Wang H, Chen L, Zhang C, Yang P, Yan W, Liu Z, Hu H, Chen J, Liu Y, Yang Y, Wang Z, Wang Z, Wang Y, You G, Han L, Bao Z, Liu Y, Wang Y, Fan X, Liu S, Liu X, Wang Y, Wang Q; Chinese Glioma Cooperative Group (CGCG). CGCG clinical practice guidelines for the management of adult diffuse gliomas. Cancer Lett. 2016 Jun 1;375(2):263-273. doi: 10.1016/j.canlet.2016.01.024. Epub 2016 Mar 7. PMID: 26966000.

[19] Masui K, Onizuka H, Cavenee WK, Mischel PS, Shibata N. Metabolic reprogramming in the pathogenesis of glioma: Update. Neuropathology. 2019 Feb;39(1):3-13. doi: 10.1111/neup.12535. Epub 2019 Jan 4. PMID: 30609184.

[20] Wood MD, Halfpenny AM, Moore SR. Applications of molecular neuro-oncology - a review of diffuse glioma integrated diagnosis and emerging molecular entities. Diagn Pathol. 2019 Apr 9;14(1):29. doi: 10.1186/s13000-019-0802-8. PMID: 30967140; PMCID: PMC6457044.