Content available at: https://www.ipinnovative.com/open-access-journals

IP Archives of Cytology and Histopathology Research

Journal homepage: https://www.achr.co.in/

Review Article

WHO CNS 5 and meningiomas: What's new?

Indranil Chakrabarti[1]*, **Sujaya Mazumder**[1]

[1] *Dept. of Pathology and Laboratory Medicine, All India Institute of Medical Sciences, Kalyani, West Bengal, India*

ARTICLE INFO

Article history:
Received 25-05-2024
Accepted 15-06-2024
Available online 16-07-2024

Keywords:
Meningiomas
WHO CNS 5
Molecular markers

ABSTRACT

Meningiomas are the most common primary intracranial tumors in adults comprising about one-third of cases. Most of them are slow-growing and follow a benign course. However, some may behave aggressively with recurrence and even metastasis. Histopathological features have long been regarded as the gold standard for diagnosis, grading, and prognostication. Advances in genomics and molecular characteristics of meningiomas have uncovered the potential use of many biomarkers for more accurate grading and prediction of prognosis and recurrence. Precision clinical trials are needed to utilize these biomarkers for targeted therapy. The present review is a snapshot of some of these important updates in meningioma as per the 2021 WHO Classification of Tumors of the Central Nervous System (WHO CNS5).

1. Introduction

Meningiomas are the most common primary intracranial tumors in adults accounting for 37.6% of all primary brain and central nervous system (CNS) tumors.[1] These tumors arise from the meningothelial (arachnoid) cells of the arachnoid mater and are typically found along the meningeal surfaces of the calvarium, spinal canal, and orbit. Many of these slow-growing tumors are discovered incidentally. Some cases may manifest with neurological deficits that vary according to tumor location and compression of adjacent structures. Patients commonly present with headaches, weakness, and seizures while higher-grade tumors behave more aggressively, often with extracranial metastasis.[2]

The meningiomas were traditionally graded according to the histological criteria which was believed to predict these tumors' biological course. However, the 2021 WHO Classification of Tumors of the Central Nervous System (WHO CNS5), has incorporated some major changes in the diagnostic criteria based on the growing understanding of the various biological pathways underlying meningiomas from diverse bioinformatic studies.[3]

2. Discussion

The fifth edition of the WHO Classification of Tumors of the Central Nervous System (WHO CNS5), published in 2021, is the sixth version of the international standard for diagnosing CNS tumors. Based on the updates of the consortium to inform molecular and practical approaches to CNS tumor taxonomy (cIMPACT-NOW) which was created in 2016 under the sponsorship of the International Society of Neuropathology (ISN), the WHO CNS5 had continued the trend of incorporating the molecular characteristics of tumors into the histological and immunohistochemical findings. Meningiomas, which constitute about one-third of the primary brain tumors, are no exception. The WHO has laid down the essential and desirable criteria for diagnosis which include molecular alterations along with the histologic criteria. (Table 1)

* *Corresponding author*.
E-mail address: drinch@rediffmail.com (I. Chakrabarti).

https://doi.org/10.18231/j.achr.2024.015

2.1. Imaging

These tumors can be picked up on Magnetic Resonance Imaging (MRI) as characteristic isodense, uniformly contrast-enhancing dural masses while calcification is best visualized on Computed tomography (CT).[2] Certain histologic subtypes show peritumoral edema and some may show cyst formation within or at the periphery.[2] Gadolinium-enhanced MRI with the help of qualitative and quantitative radiographic features can even provide clues to the histological grade of meningiomas, local failure, and patient outcomes.[2,4,5] However, histopathological examination has been the gold standard of diagnosis, grading, and prognostication.

2.2. General changes in CNS5 classification

One of the general changes made in the taxonomy of tumors in CNS5 is that "type" has now replaced "entity" and "subtype" has replaced the "variant" in line with the changes made in the classification of tumors of other organ systems. Again, only the types are listed in the main WHO classification, while subtypes are mentioned under the individual type of tumors e.g. the type meningioma is mentioned in the main classification while the subtypes of meningioma i.e. Meningothelial meningioma, Fibrous meningioma, Transitional meningioma, atypical meningioma, anaplastic (malignant) meningioma, etc. are mentioned in the chapter on meningioma.

As far as the grading goes, the Roman numerals have now been replaced with Arabic numerals i.e. Grade II meningiomas (atypical meningiomas) are now referred to as Grade 2 meningiomas (atypical meningiomas).

2.3. The etiopathogenesis of meningiomas

Exposure to ionizing radiation (particularly in childhood) and endogenous or exogenous hormones, etc. have been linked to an increased risk for the development of meningiomas.[2]

Among the germline mutations and familial syndromes predisposing to the development of meningiomas, Type 2 neurofibromatosis (NF2) is most common. Patients suffering from NF2 have a greater tendency to develop grade 2 and 3 or multiple meningiomas.[6] Other familial syndromes associated with meningiomas include Gorlin syndrome (Nevoid basal cell carcinoma syndrome), BAP1 tumor predisposition syndrome (BAP1-TPDS), Familial schwannomatosis, multiple endocrine neoplasia 1 (MEN1), Cowden syndrome, Werner syndrome, Rubinstein-Taybi syndrome, Familial multiple meningiomas etc.[7]

In meningiomas, monosomy of chromosome 22 is the most frequently reported genetic abnormality, with 60-70% of tumors showing allelic losses in 22q12.2, the region encoding the NF2 gene.[2,7] The frequency of this abnormality increases with tumor grade, occurring in 50% of benign and 75-85% of atypical (Grade 2) or anaplastic (Grade 3) meningiomas.[7] Other causes of NF2 gene deficiency include promoter methylation, epigenetic inactivation, and somatic mutations.[8]

Higher-grade meningiomas (Grade 2 and 3) are associated with complex genetic changes, such as:[2]

1. Losses on 1p, 6p/q, 10q, 14q, and 18p/q.
2. Less frequent losses on 2p/q, 3p, 4p/q, 7p, and 8p/q.
3. Heterozygous or homozygous deletions of tumor suppressor genes CDKN2A, p14ARF, and/or CDKN2B located on chromosome 9p.

Genomic sequencing has identified two subsets of meningiomas:[2]

1. NF2-mutant meningiomas: Defined by NF2 mutations and/or loss of chromosome 22.
2. NF2-wildtype meningiomas: Harbor mutations in genes such as AKT Serine/Threonine Kinase 1/Protein Kinase B (AKT1), tumor necrosis factor receptor-associated factor 7 (TRAF7), Smoothened Frizzled Class Receptor (SMO), and/or Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (PIK3CA).

The first subset i.e. with NF2 mutation and/or loss of chromosome 22q, may go on to accumulate additional copy-number losses, genomic instability, mutations in the promoter region of the telomerase reverse transcriptase (TERTp) gene, etc. while the NF2-wild subset with AKT1, KLF4, SMO, PIK3CA, and/or TRAF7 mutations show balanced copy-number profiles.[2]

Interestingly, the localization of meningiomas often indicates the underlying mutations.[9]

For example

1. Convexity and the majority of spinal meningiomas often carry NF2 mutation and/or loss of chromosome 22q
2. Skull base meningiomas mostly harbor mutations in AKT1, TRAF7, SMO, and/or PIK3CA.

2.4. Histopathological subtypes and molecular associations

The WHO classification system presently describes 15 different meningioma subtypes which are as follows:

1. Meningothelial meningioma
2. Fibrous meningioma
3. Transitional meningioma
4. Psammomatous meningioma
5. Angiomatous meningioma
6. Microcystic meningioma

7. Secretory meningioma
8. Lymphoplasmacyte-rich meningioma
9. Metaplastic meningioma
10. Chordoid meningioma
11. Clear cell meningioma
12. Rhabdoid meningioma
13. Papillary meningioma
14. Atypical meningioma
15. Anaplastic (malignant) meningioma

The chapter on meningioma in the CNS5 describes in detail the morphologic features of each subtype. The WHO CNS grading criteria have been laid down for all meningiomas (Table 2) and are to be applied across all these histologic subtypes.

It must be noted that similar to the previous edition, clear cell and chordoid meningiomas are assigned CNS Grade 2 based on morphological diagnosis alone. For a diagnosis of atypical meningioma, CNS Grade 2 criteria must be met.

Papillary and rhabdoid meningiomas were previously considered Grade 3 meningiomas. However, as per the new CNS tumor classification, they are now assigned CNS Grade 3 only if they meet the criteria of CNS Grade 3 meningiomas.[2] (Table 2)

Invasion of dura, bone, or soft tissue or the presence of pleomorphic/atypical nuclei do not affect the CNS grading. However, bone invasion has been associated with a worse prognosis in atypical meningiomas.[2,10]

In the new version of the classification, molecular markers are introduced as diagnostic criteria for selected subtypes and the application of WHO CNS grading. For example:

1. The secretory subtype of meningioma is diagnosed by characteristic morphologic features and/or combined KLF4 and TRAF7 mutations.[2,11]
2. Any meningioma with a TERTp mutation and/or CDKN2A/B homozygous deletion is now assigned WHO CNS Grade 3, irrespective of histological diagnosis or criteria of anaplasia.[2]

Additionally, several characteristic mutations and copy number variations (CNVs) have been identified in various subtypes of meningiomas. However, these findings require more extensive studies to fully characterize their independent prognostic value and to establish their potential as targets for therapeutic interventions.[11] (Table 3)

AKT1 p.E17K mutations combined frequently with TRAF7 mutations or SMO and PIK3CA mutations are exclusively seen in meningothelial meningiomas. In contrast, 22q deletion and mutation of the retained NF2 allele are noted in fibrous, transitional, and psammomatous meningiomas.[2] Psammomatous meningiomas which usually occur in the region of the thoracic spine in middle-aged or elderly women, may additionally show epigenetic changes.[2] Metaplastic, microcystic, and angiomatous meningiomas all show a high frequency of chromosome 5 gain.[12] Deletion of Chromosome 2p has been reported in chordoid meningiomas while the vast majority of clear cell meningiomas harbor SMARCE1 mutations, which can be either germline or somatic.[2,11]

The majority of atypical meningiomas exhibit loss of NF2 combined with either genome instability (large-scale chromosomal alterations) or loss of SMARCB1.[13] Recurrent losses of chromosome 1p, 6q, 14q,18q and gain of 1q are indicators of poor prognosis.[14] TERTp mutation and homozygous deletion of CDKN2A and/or CDKN2B are associated with CNS WHO Grade 3 meningiomas, which have a high risk of recurrence and a short interval to progression.[2]

Papillary meningiomas are often associated with PBRM1 mutation/deletion, while rhabdoid meningiomas are linked to mutations in BRCA1-associated protein-1 (BAP1). Loss of H3 p.K28me3 (K27me3), seen in about 10–20% of anaplastic meningiomas, is associated with aggressive behavior, recurrence, and shorter overall survival.[2] In pediatric meningiomas, YAP1 fusions have been identified as a potential NF2-independent oncogenic driver.[15]

2.5. Integrated diagnosis and layered reporting- the way forward

In addition to the light microscopic features, immunohistochemical stains for Somatostatin receptor 2a (SSTR2a), Epithelial membrane antigen (EMA), progesterone receptor (PR), and Ki 67 are used for the diagnosis of meningiomas.

Molecular methods like in-situ hybridization, RNA sequencing, and high-throughput DNA sequencing are increasingly being used to detect various molecular alterations. Some surrogate IHC stains are also used as an alternative to DNA-based molecular methods e.g. loss of SMARCE1 and BAP1 can be detected by IHC in clear cell meningiomas and rhabdoid meningiomas respectively. Loss of H3 p.K28me3 (K27me3), which is indicative of aggressive behavior of meningiomas, can also be detected by IHC.[2]

Methylome profiling can determine the DNA methylation patterns, and separate subgroups of meningiomas, including those with a higher risk of recurrence.[2]

The integrated diagnosis of meningiomas incorporates all these information by combining the histological diagnosis with the findings of molecular studies. The layered reporting of meningiomas uses the integrated diagnosis (combined histological and molecular diagnosis), followed by histopathological classification, CNS WHO Grade, and molecular information. This not only provides a structured and informative diagnosis to the treating clinicians but also sets a trend of mentioning the molecular markers that may

Table 1: Diagnostic criteria formeningiomas as per CNS 5[2]

Essential criteria (Any one of the following)	Classic histopathological features matching at least one of the meningioma subtypes (mentioned in text)
	Suggestive histopathological features along with biallelic inactivation of NF2 or other classic drivers of conventional meningioma (TRAF7, AKT1, KLF4, SMO, PIK3CA), clear cell meningioma (SMARCE1), or rhabdoid meningioma (BAP1)
	Suggestive histopathological features combined with one of the defined DNA methylation classes of meningioma
Desirable criteria	Meningeal localization
	Immunoreactivity for EMA
	Strong and diffuse immunoreactivity for Somatostatin receptor 2a (SSTR2A)
	Classic copy-number alterations (CNAs) of NF2-mutant meningioma, such as monosomy 22/22q in lower-grade meningiomas, with additional losses of 1p, 6, 10q, 14q, and/or 18 in higher-grade meningiomas

Table 2: CNS WHO Grading ofmeningiomas and recurrence rates:[2]

CNS WHO Grade 1	**CNS WHO Grade 2**	**CNS WHO Grade 3**
Low grade meningioma	Intermediate-grade meningioma/Atypical meningioma	High-grade meningioma/ Anaplastic (malignant) meningioma
Meningiomas as diagnosed by the diagnostic criteria of meningiomas (Table 1) but not meeting the criteria of WHO CNS grade 2 or 3	Meningioma fulfilling **either 1 of 3 following criteria** • 4 to 19 mitotic figures in 10 consecutive HPF of each 0.16 mm^2 ($\geq$ 2.5/mm^2) • Unequivocal brain invasion (not only perivascular spread or indentation of the brain without pial breach) • Specific morphological subtype (chordoid or clear cell)	Meningioma fulfilling **any one** of the following criteria • Frank anaplasia resembling carcinoma, high-grade sarcoma, or melanoma • Markedly elevated mitotic activity : $\geq$ 20 mitoses in 10 consecutive HPF of each 0.16 mm^2 ($\geq$ 12.5 mitoses/mm^2) • Any meningioma with TERTp mutation, irrespective of histological criteria of anaplasia
	Meningioma fulfilling **3 of the following 5 criteria** • Increased cellularity • Small cells with high N:C ratio • Large and prominent nucleoli • Uninterrupted patternless or sheet-like growth (loss of lobular architecture) • Foci of spontaneous necrosis (non-iatrogenic)	• Any meningioma with CDKN2A/B homozygous deletion, irrespective of histological criteria of anaplasia
Recurrence rates of about 7–25%	Recurrence rates of about 9- 52%	Recurrence rates of about 50-94%

Table 3: Molecular characteristics of various subtypes of meningioma[2,11]

Histologic Subtypes	**Mutations**	**Copy Number Variations**
Meningothelial	AKT1 p.E17K mutations combined frequently with TRAF7 mutations or SMO and PIK3CA mutations	None
Secretory	Combined KLF4 p.K409Q and TRAF7 mutations.; some cases show isolated KLF4 mutations	None
Fibroblastic	Mutation of the retained NF2 allele	del 22q
Transitional	Mutation of the retained NF2 allele	del 22q
Psammomatous	Mutation of the retained NF2 allele; epigenetic changes	del 22q
Metaplastic	Mutation of the retained NF2 allele	gain 5
Microcystic	Mutation of the retained NF2 allele	gain 5
Angiomatous	Mutation of the retained NF2 allele	gain 5
Atypical	Mutation of the retained NF2 allele	del 1p, del 22q
Chordoid	Mutation of the retained NF2 allele	del 2p
Clear cell	SMARCE1 (germline and somatic)	None
Anaplastic	NF2, TERTp	del 1p, 10, 22q, homozygous deletion of CDKN2A/B
Rhabdoid	BAP1	BAP1 locus
Papillary	PBRM1 mutation/deletion	Not specific

be therapeutically targeted for precision oncology.

3. Conclusion

The recent World Health Organization (WHO) classification has incorporated molecular information to guide the integrated diagnosis and management of meningiomas. The inclusion of CDKN 2A/B and TERTp mutations into the new classification, and the increasing use of molecular diagnostics have paved the way for the emergence of potential therapeutically targetable biomarkers which may lead to effective targeted therapy, based on the results of precision medicine trials.

4. Conflict of Interest

None.

5. Source of Funding

None.

References

1. Ostrom QT, Gittleman H, Liao P, Vecchione-Koval T, Wolinsky Y, Kruchko C, et al. CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010-2014. *Neuro Oncol*. 2017;19(Suppl 5):1–88.
2. Louis DN, Sahm F, Perry A, Deimling AV, Claus E, Meningiomas MC, et al.. WHO Classification of Tumours Editorial Board. Central nervous system tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2021 [cited 2024-06-12]. (WHO classification of tumours series, 5th ed.; vol. 6). . Available from: https://tumourclassification.iarc.who.int/chaptercontent/45/91.
3. Chen WC, Choudhury A, Youngblood MW, Polley MC, Lucas CG, Mirchia K, et al. Targeted gene expression profiling predicts meningioma outcomes and radiotherapy responses. *Nat Med*. 2009;29(12):3067–76.
4. Coroller TP, Bi WL, Huynh E, Abedalthagafi M, Aizer AA, Greenwald NF, et al. Radiographic prediction of meningioma grade by semantic and radiomic features. *PLoS One*. 2017;12(11):e0187908. doi:10.1371/journal.pone.0187908.
5. Morin O, Chen WC, Nassiri F, Susko M, Magill ST, Vasudevan HN, et al. Integrated models incorporating radiologic and radiomic features predict meningioma grade, local failure, and overall survival. *Neurooncol Adv*. 2019;1(1):vdz011. doi:10.1093/noajnl/vdz011.
6. Jaoude SA, Peyre M, Degos V, Goutagny S, Parfait B, Kalamarides M, et al. Validation of a scoring system to evaluate the risk of rapid growth of intracranial meningiomas in neurofibromatosis type 2 patients. *J Neurosurg*. 2020;134(5):1377–85.
7. Lee YS, Lee YS. Molecular Characteristics of Meningiomas. *J Pathol Transl Med*. 2020;54(1):45–63.
8. Moussalem C, Massaad E, Minassian GB, Ftouni L, Bsat S, Houshiemy MNE, et al. Omeis, I. Meningioma genomics: A therapeutic challenge for clinicians. *J Integr Neurosci*. 2021;20(2):463–9.
9. Soni N, Ora M, Bathla G, Szekeres D, Desai A, Pillai J, et al. Molecular Updates from the 2021 WHO Classification of CNS Tumors and Imaging Correlates. *AJNR Am J Neuroradiol*. 2024;p. ajnr.A8368. doi:10.3174/ajnr.A8368.
10. Gabeau-Lacet D, Aghi M, Betensky RA, Barker FG, Loeffler JS, Louis DN, et al. Bone involvement predicts poor outcome in atypical meningioma. *J Neurosurg*. 2009;111(3):464–71.
11. Goldbrunner R, Stavrinou P, Jenkinson MD, Sahm F, Mawrin C, Weber C, et al. EANO guideline on the diagnosis and management of meningiomas. *Neuro Oncol*. 2021;23(11):1821–34.
12. Abedalthagafi MS, Merrill PH, Bi WL, Jones RT, Listewnik ML, Ramkissoon H, et al. Angiomatous meningiomas have a distinct genetic profile with multiple chromosomal polysomies including polysomy of chromosome 5. *Oncotarget*. 2014;5(21):10596–606.
13. Harmancı AS, Youngblood MW, Clark VE, Coşkun S, Henegariu O, Duran D, et al. Integrated genomic analyses of de novo pathways underlying atypical meningiomas. *Nat Commun*. 2017;8:16215. doi:10.1038/ncomms16215.
14. Olar A, Wani KM, Wilson CD, Zadeh G, Demonte F, Jones DT, et al. Global epigenetic profiling identifies methylation subgroups associated with recurrence-free survival in meningioma. *Acta Neuropathol*. 2017;133(3):431–44.
15. Sievers P, Chiang J, Schrimpf D. YAP1-fusions in pediatric NF2-wildtype meningioma. *Acta Neuropathol*. 2020;139(1):215–8.

Author biography

Indranil Chakrabarti, Additional Professor https://orcid.org/0000-0002-3651-2986

Sujaya Mazumder, Assistant Professor

Cite this article: Chakrabarti I, Mazumder S. WHO CNS 5 and meningiomas: What's new?. *IP Arch Cytol Histopathology Res* 2024;9(2):67-71.