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Commentary

The selection of articles for this edition of literature highlights are all somewhat specialised but also relevant to general radiologists as they reflect a fundamental shift in how we manage brain tumours.

The 2016 WHO classification of brain tumours included references to genetic alterations in the brain tumours that were increasingly being recognised as determinants of the biological behaviour of these lesions. Isocitrate Dehydrogenase (IDH) mutation status is of many such mutations. Neuroradiologists realised that they will need to up their game to try and identify these variations using imaging biomarkers. The initial observations were facilataed by the use of various databases such as The Cancer Genome Atlas and The Cancer Imaging Archive which led to the initial recognition of the T2 FLAIR mismatch sign as a marker of IDH mutant 1p-19q non co deleted status. This has proven to be highly specific but not particularly sensitive for the IDHm status. Addition of machine learning algorithms although promise to improve the performance of imaging surrogates.

Although the 2021 WHO classification has not been officially published as yet the previews indicate that there is a fundamental change in the way the gliomas are classified. The changes are most profound for paediatric age lesions but impact adult gliomas as well.

The most important implications for the adult gliomas include IDH mutated lesions with features of GBM no longer classified as GBM. IDH wild type lesion with features of low /intermediate gliomas may be considered GBMs if carry TERT promoter mutation, EGFR amplification or +7/-10 chromosome pattern. IDH mutant diffuse gliomas are all considered a single type.1p/19q codeletion marker for Oligodendroglioma.

The most important changes in paediatric gliomas is their separation from adult lesions. The additional require a more detailed appreciation and are beyond the scope of this commentary.

In summary the 2021 WHO classification of brain tumours will emphasise their genetic and molecular variations and use these variations to classify these lesions. Our ability to predict these variations using imaging is still imprecise but is likely to benefit greatly by implementation of artificial intelligence and machine learning algorithms which allow analysis of scores of apparently disparate but eventually linked features in real time.

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Characterisation of isocitrate dehydrogenase gene mutant WHO grade 2 and 3 gliomas: MRI predictors of 1p/19q co-deletion and tumour grade

AIM: To identify imaging predictors of molecular subtype and tumour grade in patients with isocitrate dehydrogenase (IDH) gene mutant (IDH_{mut}) World Health Organization (WHO) grade 2 or 3 gliomas.

MATERIALS AND METHODS: Patients with histologically confirmed WHO grade 2 or 3 IDH_{mut} gliomas between 2016 and 2019 were included in the study. Magnetic resonance imaging (MRI) images

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were evaluated for the presence or absence of potential imaging predictors of tumour subtype, such as T2/fluid attenuated inversion recovery (FLAIR) signal match, and these factors were examined using regression analysis. On perfusion imaging, the maximum relative cerebral blood volume ($rCBV_{max}$) was evaluated as a potential predictor of tumour grade. The performance of two experienced neuroradiologists in correctly predicting tumour type on MRI was evaluated.

RESULTS: Eighty-five patients were included in the study. The presence of T2/FLAIR signal match >50% of tumour volume ($p<0.01$) and intratumoural susceptibility ($p=0.02$) were independent predictors of 1p/19q co-deletion. Mean $rCBV_{max}$ was significantly higher in WHO grade 3 astrocytomas ($p=0.04$) than WHO grade 2 astrocytomas. The consensus prediction of 1p/19q co-deletion status by two neuroradiologists of tumour was 95% sensitive and 86% specific.

CONCLUSION: The presence of matched T2/FLAIR signal could be used to identify tumour subtype when biopsy is inconclusive or genetic analysis is unavailable. $rCBV_{max}$ predicted astrocytoma grade. Experienced neuroradiologists predict tumour subtype with good sensitivity and specificity.

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C.J. Park, K. Han, H. Kim, S.S. Ahn, D. Choi, Y.W. Park, J.H. Chang, S.H. Kim, S. Cha, S.-K. Lee

MRI Features May Predict Molecular Features of Glioblastoma in Isocitrate Dehydrogenase Wild-Type Lower- Grade Gliomas

BACKGROUND AND PURPOSE: Isocitrate dehydrogenase (IDH) wild-type lower-grade gliomas (histologic grades II and III) with epi- dermal growth factor receptor (EGFR) amplification or telomerase reverse transcriptase (TERT) promoter mutation are reported to behave similar to glioblastoma. We aimed to evaluate whether MR imaging features could identify a subset of IDH wild-type lower-grade gliomas that carry molecular features of glioblastoma.

MATERIALS AND METHODS: In this multi-institutional retrospective study, pathologically confirmed IDH wild-type lower-grade glio- mas from 2 tertiary institutions and The Cancer Genome Atlas constituted the training set (institution 1 and The Cancer Genome Atlas, 64 patients) and the independent test set (institution 2, 57 patients). Preoperative MRIs were analyzed using the Visually AcceSAble Rembrandt Images and radiomics. The molecular glioblastoma status was determined on the basis of the presence of EGFR amplification and TERT promoter mutation. Molecular glioblastoma was present in 73.4% and 56.1% in the training and test sets, respectively. Models using clinical, Visually AcceSAble Rembrandt Images, and radiomic features were built to predict the mo- lecular glioblastoma status in the training set; then they were validated in the test set.

RESULTS: In the test set, a model using both Visually AcceSAble Rembrandt Images and radiomic features showed superior predic- tive performance (area under the curve 1/4 0.854) than that with only clinical features or Visually AcceSAble Rembrandt Images (areas under the curve 1/4 0.514 and 0.648, respectively; P , . 001, both). When both Visually AcceSAble Rembrandt Images and radio- mics were added to clinical features, the predictive performance significantly increased (areas under the curve 1/4 0.514 versus 0.863, P , .001).

CONCLUSIONS: MR imaging features integrated with machine learning classifiers may predict a subset of IDH wild-type lower- grade gliomas that carry molecular features of glioblastoma.

Neuro-Oncology 2021; 23(8): 1231-51

David N. Louis, Arie Perry, Pieter Wesseling , Daniel J. Brat , Ian A. Cree, Dominique Figarella-Branger, Cynthia Hawkins, H. K. Ng, Stefan M. Pfister, Guido Reifenberger, Riccardo Soffietti, Andreas von Deimling, and David W. Ellison

The 2021 WHO Classification of Tumors of the Central Nervous System: A summary

The fifth edition of the WHO Classification of Tumors of the Central Nervous System (CNS), published in 2021, is the sixth version of the international standard for the classification of brain and spinal cord tumors. Building on the 2016 updated fourth edition and the work of the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy, the 2021 fifth edition introduces major changes that advance the role of molecular diagnostics in CNS tumor classification. At the same time, it remains wedded to other established approaches to tumor diagnosis such as histology and immunohistochemistry. In doing so, the fifth edition establishes some different approaches to both CNS tumor nomenclature and grading and it emphasizes the importance of integrated diagnoses and layered reports. New tumor types and subtypes are introduced, some based on novel diagnostic technologies such as DNA methylome profiling.The present review summarizes the major general changes in the 2021 fifth edition classification and the specific changes in each taxonomic category. It is hoped that this summary provides an overview to facilitate more in-depth exploration of the entire fifth edition of theWHO Classification ofTumors of the Central Nervous System.

Clin Cancer Res 2017; 23: 6078-85

Sohil H. Patel, Laila M. Poisson, Daniel J. Brat, Yueren Zhou, Lee Cooper, Matija Snuderl, Cheddhi Thomas, Ana M. Franceschi, Brent Griffith, Adam E. Flanders, John G. Golfinos, Andrew S. Chi, Rajan Jain

T2–FLAIR Mismatch, an Imaging Biomarker for IDH and 1p/19q Status in Lower-grade Gliomas: A TCGA/TCIA Project

PURPOSE: Lower-grade gliomas (WHO grade II/III) have been classified into clinically relevant molecular sub- types based on IDH and 1p/19q mutation status. The purpose was to investigate whether T2/FLAIR MRI features could distinguish between lower-grade glioma molecular subtypes.

EXPERIMENTAL DESIGN: MRI scans from the TCGA/TCIA low- er grade glioma database (n 1/4 125) were evaluated by two independent neuroradiologists to assess (i) presence/absence of homogenous signal on T2WI; (ii) presence/absence of "T2–FLAIR mismatch" sign; (iii) sharp or indistinct lesion margins; and (iv) presence/absence of peritumoraledema. Metrics with moderate - substantial agreement underwent consensus review and were correlated with glioma molecular subtypes. Somatic mutation, DNA copy number, DNA methylation, gene expression, and protein array data from the TCGA lower-grade glioma database were analyzed for molecular–radiographic associations. A separate institutional cohort (n 1/4 82) was analyzed to validate the T2–FLAIR mismatch sign.

RESULTS: Among TCGA/TCIA cases, interreader agreement was calculated for lesion homogeneity [k 1/4 0.234 (0.111–0.358)], T2–FLAIR mismatch sign [k 1/4 0.728 (0.538–0.918)], lesion margins [k 1/4 0.292 (0.135–0.449)], and peritumoraledema [k 1/4 0.173 (0.096–0.250)]. All 15 cases that were positive for the T2–FLAIR mismatch sign were IDH-mutant, 1p/19q non- codeletedtumors (P < 0.0001; PPV 1/4 100%, NPV 1/4 54%). Analysis of the validation cohort demonstrated substantial interreader agreement for the T2–FLAIR mismatch sign [k 1/4 0.747 (0.536-0.958)]; all 10 cases positive for the T2–FLAIR mismatch sign were IDH-mutant, 1p/19q non-codeletedtumors (P < 0.00001; PPV 1/4 100%, NPV 1/4 76%).

CONCLUSIONS: Among lower-grade gliomas, T2–FLAIR mis- match sign represents a highly specific imaging biomarker for the IDH-mutant, 1p/19q non-codeleted molecular subtype.