Standard Treatments And Subclassification Of Low Grade Gliomas Considering TERT Promoter Mutation And ATRX Loss: Beyond The 2016 WHO Classification

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Background:
Grade II glioma is a heterogeneous group of various pathologies. 2016 WHO classification defined subgroups of Grade II gliomas based on isocitrate dehydrogenase (IDH) mutation and 1p/19q codeletion status. However, implications of telomerase reverse transcriptase promoter (TERTp) mutation and alpha-thalassemia/mental retardation syndrome X-linked (ATRX) loss are not considered in the classification.

Methods:
Patients (n = 191) who underwent surgery and pathologically proven for supratentorial newly diagnosed low-grade glioma (WHO grade II) were included this study. Molecular diagnoses including IDH1/2 mutation, 1p/19q codeletion, TERTp mutation, ATRX expression, O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status was evaluated. The overall survival according to TERTp mutation and ATRX loss in each 2016 WHO class were compared.

Results:
There were 34 (17.8%) IDH-wildtype astrocytomas, 81 (42.4%) IDH-mutant astrocytomas, and 76 (39.8%) IDH-mutant and 1p/19q-codeleted oligodendrogliomas. The median overall survival (OS) of each group were 3.9, 10.4, and 18.7 years, respectively. TERTp mutation had negative impact for survival in IDH-wildtype astrocytomas (HR = 5.458, 95% confidence interval [CI] 1.771-16.826), while no significant differences were observed regarding TERTp mutation in IDH-mutant astrocytomas and oligodendrogliomas. Among IDH-wildtype/TERTp-mutant astrocytomas, ATRX loss was significantly correlated with poor outcome (2.1 vs 3.0 years, p=0.033).

Conclusions:
Molecular status of TERTp mutation and ATRX expression can help stratifying IDH-wildtype astrocytomas. IDH-wildtype astrocytomas which harbor TERTp mutation only without ATRX loss showed the worst outcome. Further study is needed to verify the role of TERTp mutation and ATRX in gliomas.