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Intrinsic Gene Expression Profiles of Gliomas Are a Better Predictor of Survival than Histology.

Gravendeel LA, Kouwenhoven MC, Gevaert O, de Rooi JJ, Stubbs AP, Duijm JE, Daemen A, Bleeker FE, Bralten LB, Kloosterhof NK, De Moor B, Eilers PH, van der Spek PJ, Kros JM, Sillevius Smitt PA, van den Bent MJ, French PJ.

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Gliomas are the most common primary brain tumors with heterogeneous morphology and variable prognosis. Treatment decisions in patients rely mainly on histologic classification and clinical parameters. However, differences between histologic subclasses and grades are subtle, and classifying gliomas is subject to a large interobserver variability. To improve current classification standards, we have performed gene expression profiling on a large cohort of glioma samples of all histologic subtypes and grades. We identified seven distinct molecular subgroups that correlate with survival. These include two favorable prognostic subgroups (median survival, >4.7 years), two with intermediate prognosis (median survival, 1-4 years), two with poor prognosis (median survival, <1 year), and one control group. The intrinsic molecular subtypes of glioma are different from histologic subgroups and correlate better to patient survival. The prognostic value of molecular subgroups was validated on five independent sample cohorts (The Cancer Genome Atlas, Repository for Molecular Brain Neoplasia Data, GSE12907, GSE4271, and Li and colleagues). The power of intrinsic subtyping is shown by its ability to identify a subset of prognostically favorable tumors within an external data set that contains only histologically confirmed glioblastomas (GBM). Specific genetic changes (epidermal growth factor receptor amplification, IDH1 mutation, and 1p/19q loss of heterozygosity) segregate in distinct molecular subgroups. We identified a subgroup with molecular features associated with secondary GBM, suggesting that different genetic changes drive gene expression profiles. Finally, we assessed response to treatment in molecular subgroups. Our data provide compelling evidence that expression profiling is a more accurate and objective method to classify gliomas than histologic classification. Molecular classification therefore may aid diagnosis and can guide clinical decision making. [Cancer Res 2009;69(23):9065-72].

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