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Radiomic magnetic resonance imaging signature reveals three distinct subtypes of glioblastoma with different clinical and molecular characteristics, offering prognostic value beyond IDH1 mutation status

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Despite variable proliferation and significant molecular, histological and imaging heterogeneity across and within patients, the standard-of-care for glioblastoma patients is notably uniform. Non-invasive characterization of this heterogeneity may be useful in personalized treatment planning. We hypothesized that pattern analysis methods applied to clinically-acquired multi-parametric magnetic resonance imaging (mpMRI) sequences would be able to identify complex and otherwise visually not easily appreciable imaging subtypes of glioblastoma that relate to prognosis and underlying molecular characteristics of the tumor. The imaging profiles of preoperative mpMRIs (T1, T1-Gd, T2, T2-FLAIR, DSC, DTI) of de novo glioblastoma patients were summarized by advanced radiomic features, including volumetric, shape, texture, statistical and histogram features. A completely unsupervised clustering method of K-Means was employed to dissect phenotypic heterogeneity, without any a-priori knowledge or target of molecular and clinical characteristics. The model was developed/cross-validated in a discovery cohort (n=208) and subsequently evaluated in a replication cohort (n=53), for which IDH1 mutation and MGMT methylation status were known. Clustering revealed three distinct/reproducible radiographic subtypes of glioblastoma, with the differential clinical outcome, tumors' spatial distribution, radiological measures of cell-density, vascularization, infiltration and extent of the tumor and underlying molecular characteristics, including IDH1, MGMT, EGFRvIII and transcriptomic subtype composition. The hazard ratio using a Cox proportional hazard model was 3.74 (95% CI:3.01-4.65) among subtypes. The combination of subtype information with IDH1 status provided superior survival prediction accuracy (c-index=0.75) than that by IDH1 status alone (c-index=0.56), thereby highlighting the synergistic consideration of molecular and imaging measures for prognostication. The discovered subtypes and their clinical and molecular correlates provide an in vivo portrait of informative phenotypic heterogeneity in glioblastoma and may potentially assist in precision diagnostics, homogeneous patient selection into clinical trials and tailoring therapeutic options based on patient's subtype. Further, the imaging characteristics suggest that subtype-specific treatment of peritumoral infiltrated tissue might be more effective than current uniform standard-of-care.

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