Title

Non-invasive *in vivo* biomarker of EGFR pathway activation alterations in glioblastoma, from clinically-acquired dynamic susceptibility contrast magnetic resonance imaging: the 'ϕ' index.

Authors

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Abstract

Glioblastoma, the most common adult primary malignant brain tumor, has a grim prognosis and a large degree of inter- and intratumoral radiologic, histologic, and molecular heterogeneity. Spatial and temporal heterogeneity are considered the primary drivers of treatment resistance. Spatial heterogeneity renders molecular target determination prone to sampling error, since currently it is based on single tissue specimen analysis. Changes of molecular target status over time (during therapy), complicates the evaluation of GBM even further, potentially calling for adaptive therapy protocols. While various genes are commonly mutated in glioblastoma, the spread of point-mutations within those genes is quite diverse. Epidermal growth factor receptor (EGFR), is found to be mutated or amplified in approximately 60% of glioblastomas, and exhibits a spread of extracellular domain missense mutations accompanying amplification and the EGFR splice variant III (EGFRvIII). EGFRvIII has been shown to increase tumor invasiveness through several downstream pathways, including Akt and Ras/Raf/MAPK. Similar downstream pathway activation has been found in wild-type EGFR amplification in glioblastomas, suggesting a common underlying mechanism for the increased invasion seen in EGFR-activating alterations. This study reports the development of a clinically significant radio-phenotypic biomarker associated with the activation of the EGFR pathway in *de novo* glioblastoma, irrespective of whether it is through amplification of wild-type EGFR or expression of EGFRvIII or other known activating EGFR missense mutations. This non-invasive robust *in vivo* biomarker is based on a quantitative peritumoral heterogeneity index (PHI/ϕ-index), obtained by comparing the peritumoral perfusion signal in the proximal and distal tissue, relative to the tumor core. PHI is derived from routine clinical magnetic resonance imaging (MRI) protocols and describes self-normalized within-scan perfusion heterogeneity measures for individual patients, instead of population-based statistics, hence is likely to be robust to variations across scanners, thereby enabling its replication to other centers. A retrospective analysis was conducted on a single-institutional cohort from the University of Pennsylvania with various EGFR alterations and available pre-operative standard and advanced MRI. EGFR alterations included tumors with EGFRvIII (n=42), wild-type EGFR amplification (n=6), and the most common EGFR missense mutations (n=25) (i.e. A289D/T/V, R108K, G598V). Lower PHI values, consistent with uniformly aggressively infiltrating tumors throughout the peritumoral edema, was found on tumors with EGFR alterations compared to EGFR non-mutated and non-amplified control cases (n=100). The resulted MRI biomarker of this study, suggestive of increased tumor invasiveness, matched the anticipated biological impact of the EGFR alterations and represents a marker of EGFR pathway activation in glioblastoma, potentially useful for monitoring targeted treatment-response along this pathway.