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Three-dimensional nuclear telomere architecture is associated with differential time to progression and overall survival in glioblastoma patients.

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The absence of biological markers allowing for the assessment of the evolution and prognosis of glioblastoma (GBM) is a major impediment to the clinical management of GBM patients. The observed variability in patients' treatment responses and in outcomes implies biological heterogeneity and the existence of unidentified patient categories. Here, we define for the first time three GBM patient categories with distinct and clinically predictive three-dimensional nuclear-telomeric architecture defined by telomere number, size, and frequency of telomeric aggregates. GBM patient samples were examined by three-dimensional fluorescent in situ hybridization of telomeres using two independent three-dimensional telomere-measurement tools (TeloView program [P(1)] and SpotScan system [P(2)]). These measurements identified three patients categories (categories 1-3), displaying significant differences in telomere numbers/nucleus ($P(1) = .0275$; $P(2) \leq .0001$), telomere length ($P(1)$ and $P(2) = .0275$), and number of telomeric aggregates ($P(1) = .0464$; $P(2) \leq .0001$). These categories corresponded to patients with long-term, intermediate, and short-term survival, respectively ($P = .0393$). The time to progression analyses showed significant differences between the three categories ($P = .0167$). There was a correlation between time to progression, median survival, and nuclear telomere architecture. Our study suggests a link between patient outcome and three-dimensional nuclear-telomere organization and highlights the potential clinical power of telomere signatures as a new prognostic, predictive, and potentially pharmacodynamic biomarker in GBM. Furthermore, novel automated three-dimensional high-throughput scanning as developed here permits to obtain data from 300 nuclei in 20 minutes. This method is applicable to any cell type and scanning application.

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