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Study advises treating glioblastoma brain tumors based on complexity

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Survival for patients with glioblastoma, an aggressive and deadly brain cancer, could be determined by the complexity of their tumor, according to researchers at the Translational Genomics Research Institute (TGen).

The findings from a recent study suggest—to the researchers' surprise—that the survival of those patients whose cancer cells exhibit a complex genomic landscape on average exceeded those patients with a less complex tumor structure. The published results appear today in the scientific journal Neuro-Oncology.

Current standard-of-care treatment involves surgical removal of as much tumor as possible without destroying normal brain tissue, coupled with radiation and oral chemotherapy with temozolomide (TMZ). This regimen typically extends median survival to 14.7 months.

The researchers found that standard-of-care worked best for patients with complex, though fragile tumor genomes, defined as those with more abnormal genomic events, such as mutations, rearrangements, or amplifications. The more abnormal the tumor genome, the more likely the therapy was to improve patient survival.

By studying those patients at the extreme ends of the survival timeline, the "outliers," the researchers hoped to identify the role tumor complexity plays in treatment outcomes.

"It's kind of like the game Jenga. What are the key blocks that, if you

take them out, the tower of cancer comes tumbling down," said Dr. Michael Berens, Professor and Director of TGen's Cancer and Cell Biology Division, and the study's senior author.

Conversely, those patients with simple, but robust, cancer genomes had shorter survival. The current standard-of-care therapies found few ways to thwart the cancer. This surprised the researchers, because the more complex cancers with multiple mutations often evade targeted therapies while the simple tumors either shrink or disappear.

"The typical approach to discovering the genomic drivers of human cancers is to find and understand a pivotal mechanism," said Dr. Sen Peng, TGen bioinformatician and the paper's lead author. "In our 'outliers' study, we discovered instead that the broader genomic landscape was far more telling of which patients may best respond to standard care, information that one day may determine if patients would be best served by conventional or experimental therapy."

First of its kind for glioblastoma

This was the first genomic study that comprehensively examined GBM outliers in the survival spectrum.

The researchers used deep genomic sequencing to examine 18 glioblastoma multiforme (GBM) tumor samples from deceased patients who were part of the Ohio Brain Tumor Study (OBTS), including 10 short-term survivors (average survival of 7 months), and 8 long-term survivors (average survival 33 months). Each group of "outliers" represented the shortest and longest quartile of the study's overall patient survival distribution.

"This study categorizes those patients who should receive standard-of-care therapies, and those who should be prioritized to receive potential

benefit from a new, more innovative regimen," Dr. Berens said. "In particular, those with likely short-term-survival may benefit from molecular profiling of targetable mutations and gene pathways."

This study also highlights a number of genetic features that could indicate targetable mutations that could hold promise for better clinical outcomes, thereby enabling a more precise treatment plan.

"The result would be more effective therapy directed to identified features in profiled patient cancer specimens, as opposed to subjecting all patients to chemotherapy in hopes of a positive response," said Dr. Berens.

"The Ivy Foundation is dedicated to lengthening the survival of patients with glioblastoma," said Catherine (Bracken) Ivy, founder and president of the Arizona-based Ben & Catherine Ivy Foundation. "The 'outlier' study by TGen offers a basis for better understanding which patients will benefit most from current therapy to extend good quality of life."

Dr. Andrew Sloan, Director of the Brain Tumor and Neuro-Oncology Center for University Hospitals in Cleveland, Ohio, said, "This study raises the prospect that doctors may have an additional resource to better align patients to a beneficial current therapy, or to recommend entry to a clinical trial."

Dr. Sloan assisted the study in the collection of tissues from the Ohio Brain Tumor Study patients used in this *Neuro-Oncology* paper, "Integrated Genomic Analysis of Survival Outliers in Glioblastoma."

More information: Integrated genomic analysis of survival outliers in glioblastoma. DOI: 10.1158/1538-7445.AM2016-129